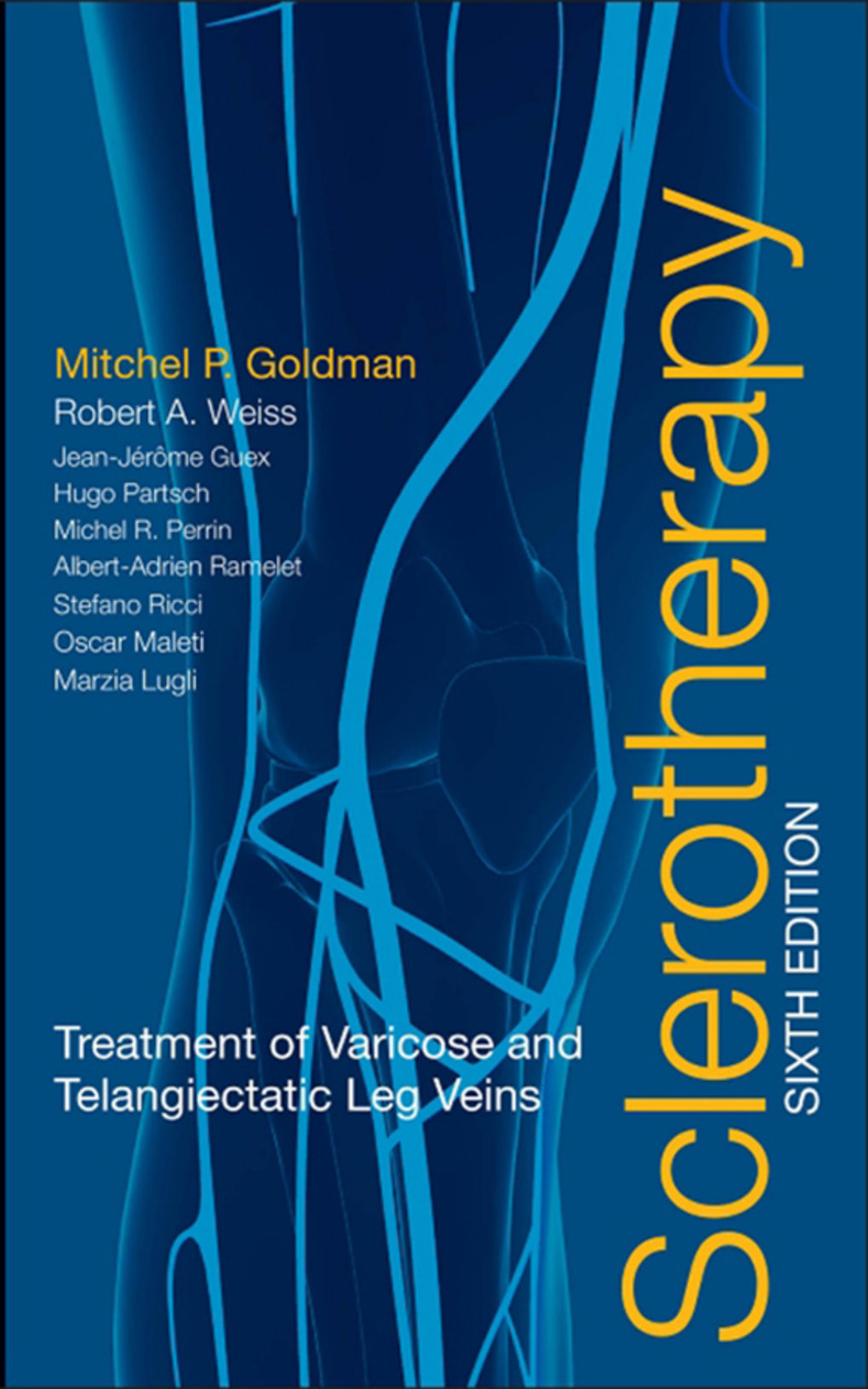

Sclerotherapy

SIXTH EDITION

Treatment of Varicose and Telangiectatic Leg Veins

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SCLEROTHERAPY

TREATMENT OF VARICOSE AND TELANGIECTATIC LEG VEINS

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SCLEROTHERAPY

Sixth Edition

TREATMENT OF VARICOSE AND TELANGIECTATIC LEG VEINS

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Preface

The first edition of this text was written over 30 years ago at the beginning of my medical career. Although it was thought of as an authoritative text, it merely represented a review of the world's literature on sclerotherapy and actually served to teach me the basics of phlebology. The second edition, written five years later, expanded on the theme of an encyclopedic review of the literature and included practical information gained through my early experience in phlebology. The third edition, written five years later, brought my co-author, friend and teacher John Bergan who added his incredible depth of knowledge and expertise in venous disease and vascular surgery. The third edition again continued in the spirit of an encyclopedic dissertation with more practical information and case reports. The fourth edition brought another co-editor, JJ Guex, who added a European perspective to the text. In addition, Professor Hugo Partsch, the world's leading authority on compression therapy re-wrote the Compression chapter and Albert-Adrien Ramelet, MD, added a new chapter on Veno-Active Drugs. The fifth edition brought a new co-editor to the textbook, Robert Weiss, who updated many chapters as well as developed a new video section. Stefano Ricci, MD, a world class historian, anatomist and phlebologist, updated the anatomy chapter, with the surgical chapter rewritten by Dr Michel Perrin, an internationally respected vascular surgeon and phlebologist. The addition of these international leaders and outstanding teachers and clinicians from France and Italy further broadened the scope of this text.

The sixth edition updates each chapter with new scientific and clinical discoveries and improved practical teaching. Robert Weiss, MD, has updated the videos to aid physicians applying the knowledge of this text to their patient practice. The surgical chapter has been updated by two outstanding vascular surgeons, Oscar Maleti and Marzia Lugli; and Hugo Partsch, Stefano Ricci and AA Ramelet have updated their respective chapters. A major new theme, however, has been the contribution of several dermatology residents and dermatologic surgery fellows to the text. These young physicianas have brought a fresh perspective to the chapters they have worked on. Doctors Douglas Wu, Joanna Bolton, Lisa Zaleski-Larsen, Cindy Chambers, Monique Vanaman Wilson, and Misha Heller have my personal thanks and appreciation for their outstanding work.

The success of the combined efforts of the new chapter editors and young phlebologists is represented by many new references, 17 new illustrations,16 new tables and 5 new videos, all of which should increase the practicality of the sixth edition while maintaining its encyclopedic nature.

Phlebology and the treatment of varicose and telangiectatic leg veins continues to evolve significantly with the addition of endovenous laser and radiofrequency techniques as well as tissue glue, newer forms of foaming detergent solutions as well as mechical ablation of the vascular endothelia for treating the great and small saphenous veins as well as perforator and tributary veins.

The world continues to shrink, with the International Union of Phlebology bringing physicians from all nations together every two years to share their experiences. The aim is to enhance patient care, evidenced by an increase in successful treatment, while minimizing adverse events but it these joint efforts have led to an increasing body of knowledge that deserves to be organized in one source.

I thank the world phlebological community for sharing the combined expertise of thousands of physicians in such a selfless manner under the encouragement of the International Union and each country's phlebological society.

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Founder and Editor-in-Chief

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Introduction

A significant percentage of the species *Homo sapiens* is known to develop varicose veins, whereas the condition is rare in four-legged animals (Butie A, personal communication, 1989) (Fig. A). This suggests that the erect stance is of significant importance in the development of varicose veins. Why, then, do other erect species fail to develop them? The answer is probably related to anatomic differences. Taller mammals, such as giraffes and those that walk upright (similar to humans), have relatively thick fascial layers enclosing the deep venous system; humans and shorter mammals, such as rabbits and rats, do not.[1] Physiologic studies demonstrate that giraffe capillaries are highly impermeable to plasma proteins. In addition, their tight skin and fascial layers provide a functional 'antigravity suit' to prevent venous hypertension. Finally, a prominent lymphatic system and precapillary vasoconstriction propel blood and lymphatic fluid against gravity. Therefore, with a disturbance in this complex system, in humans, the transmission of high venous pressure to superficial veins, which are not designed to contain that pressure, results in dilation; that is, varicose veins. So the development of varicose veins is but one manifestation of 'venous insufficiency'.

As discussed in detail later in this introduction and in Chapter 2, varicose veins should be thought of as one clinical manifestation of venous hypertension. This, when chronic, causes a sequence of cutaneous complications: edema, cutaneous pigmentation, venous/stasis dermatitis, atrophie blanche, cutaneous ulceration and malignant degeneration. Varicose veins alone may also be complicated by hemorrhage, thrombophlebitis and pain.

The primary therapeutic procedure for all stasis complications, except malignant degeneration, is to normalize the underlying pathologic physiology that gives rise to cuticular venous hypertension (which is characterized by increased interstitial fluid and resultant reduced oxygenation and defective nutrition of the skin). This may be accomplished through the treatment of the superficial and/or deep venous systems and their conduits (perforator veins).

Deep venous hypertension is usually managed with conservative compression therapy. In selected patients, vein valve transplantation or repair can also be efficacious. However, surgeons are understandably loath to operate through eczematous skin that may be contaminated with bacteria. Thus, dermatologic treatment is extremely important in providing the optimal operative field. Alternatively, direct sclerotherapy of an underlying incompetent perforating vein through the ulcer may be performed. Sclerotherapy in this setting has been shown to markedly enhance ulcer healing.[2,3] Newer surgical techniques of perforating vein interruption using endoscopic visualization or thermocoagulation via intravascular radiofrequency or lasers, or duplex-guided foam sclerotherapy, can also normalize venous hypertension. Finally, it is becoming more apparent that treating the incompetent superficial venous system with either surgical intervention or sclerotherapy is also beneficial in restoring and/or improving competence of the deep venous system.[4–9]

HISTORICAL ASPECTS OF TREATMENT

Varicose veins have obviously been a problem for a long time. Egyptian papyrus scrolls have been found that contain instructions for the treatment of leg disorders, and Ebers, in his papyrus of 1550 BC, advised that surgery should not be performed on varicose veins.[10] The earliest method of treating varicose veins, in common with most physical diseases, consisted of making offerings to the gods for help, and this continued for centuries, as can be seen in a votive relief from around 400 BC found at the Greek Temple of Asklepios (Asclepius; Latin: Aesculapius) (Fig. B). Physicians, however, attempted to formulate more terrestrial treatments.

Hippocrates observed the association between varicose veins and leg ulceration more than 2000 years ago.[11] His humoral theory dictated bloodletting as a form of treatment for varicose veins, and this remained the treatment of choice into the Middle Ages. The first description of medical treatment appears in the writings of Hippocrates in the fourth century BC. He describes treating varicose veins by traumatizing them with 'a slender instrument of iron' to cause thrombosis.[12] Surgeons, too, were developing various treatments for varicose veins. Plutarch described the first varicectomy without anesthesia on the Roman Consul Gaius Marius (157–86 BC). According to Dryden's translation:[13]

For having, as it seems, both his legs full of great tumours, and disliking the deformity, he determined to put himself into the hands of an operator, when, without being tied, he stretched out one of his legs, and slightly, without changing countenance, endured most excessive torments in the cutting, never either flinching or complaining; but when the surgeon went to the other, he declined to have it done, saying, 'I see the cure is not worth the pain.'

Stripping and cauterization were practiced by Celsus (30 BC to AD 30). Antillus was the first to mention ligation of the vessels, and, in the second century AD, Galen recommended that varicose veins be torn out with a hook. Paulus of Aegina (circa AD 660 in Alexandria) performed ligation and stripping of the segments of the varicosity. However, after William Harvey's discovery of the true nature of circulation, surgical removal of the affected veins was rejected because the procedure could cause complications that were more dangerous than the disease itself. The modern history of surgical

Figure A Brahma bull with a varicose vein on the right posterior medial leg. (Courtesy A. Butie, MD)

Figure B According to the inscription, this tablet found on the west side of the Acropolis in Athens was dedicated to Dr Amynos by Lysimachidis of Archarnes. This represents the earliest known depiction of varicose veins, from the end of the fourth century BC. (From National Archaeological Museum of Greece.)

treatment began after the introduction of anesthesia and sterile techniques in the late nineteenth century. This is reviewed in Chapter 10.

Compression therapy was recognized very early as an effective form of treatment (see Chapter 6). Roman soldiers wrapped their legs in leather straps to minimize leg fatigue during long marches. Marianus Sanctus Barolitanus (1555), Pare Johnson (1678) and de Marque (1618) recommended the use of plaster bandages. Firm support was not widely used until Wiseman (1676) introduced the laced leather stocking for treating ulcers associated with varicose veins.[14] Although compression therapy may be quite effective for patients with limited venous disease,[15] when used alone it is associated with a high rate of ulcer recurrence.[16] This association may be related to the expertise of the medical practitioner applying compression and to the materials used. To be effective, a compression bandage must generate 40 to 70 mmHg.[17] This means that the toes of a correctly bandaged leg must become slightly cyanotic when the leg is horizontal and return to a pink color on standing. Obviously, skill and experience are a prerequisite for proper compression treatment (see Chapter 6).

The first use of an intravenous injection in humans is attributed to Sigismund Eisholtz (1623–1688). He used an enema syringe to inject distilled plantain water into a branch of the crural vein to irrigate an ulcer with a small siphon.[18] In 1682, D. Zollikofer of St. Gallen, Switzerland, reported on the injection of an acid into a vein to create a thrombus.[18] This was the first attempt at 'sclerotherapy', a term derived from the Greek word for 'hard', and made popular by H.I. Biegeleisen in 1937.[19]

Extravascular sclerotherapy of a hemangioma was first reported in 1836. The surgeon, Mr Lloyd, injected from three to six drops of nitric acid dissolved in a drachm of water. This solution was 'thrown into the tumour by means of a syringe through a minute puncture at its base'.[20] No mention was made of the outcome of this treatment, but the next reported case was instantly fatal.[21]

Intravascular sclerotherapy of an arterial malformation to produce a clot was first performed in 1840, on animals, by Pravaz with a solution of absolute alcohol.[22] In 1851, a solution of ferric chloride was used to sclerose varicose veins.[23] This was made possible through modification of the syringe with the invention of a sharpened hollow needle capable of direct venous puncture.[24] In 1854, Desgranges reported the cure of 16 cases of varicose veins with the injection of a mixture of 5 g iodine and 45 g tannin in 50 mL of water.[25] Desgranges noted that this solution produced far fewer local reactions than did ferric chloride. His patients were kept in bed for 10 to 12 days. Unfortunately, extended use of this solution and technique produced septic complications.

These intravascular sclerotherapy treatments were stimulated by Rynd's introduction of the hypodermic syringe in 1845.[26,27] Both the syringe of Rynd, an elaborate trocar and cannula, and the subsequently modified syringe of Pravaz were modifications of the lacrimal syringe developed by Anel in 1713.[28] It is interesting that the apparatus manufactured for Pravaz was unsatisfactory, because when blood and coagulant–sclerosant mixed after the trocar had been withdrawn and the syringe was screwed on, blood clotted within the lumen of the cannula.[29] It was not until Wulfing Luer in Germany adopted the hollow needle onto a Ferguson

syringe that a device approaching the modern syringe was used.

Between 1904 and 1910, Scharf used sublimate on himself and 90 patients with varicose veins.[30] Nathan Brann, founder of the first phlebology society, also recommended vein sclerosis with sublimate, which produced firm thrombosis of varicose veins.[31]

The foundation of modern sclerotherapy treatment of varicose veins began in 1916 when Linser reported many successful treatments using perchloride of mercury with an intravascular technique.[32] He emphasized ambulatory treatments limiting the maximal dose of sublimate to 1–2 mL per treatment session. He also inadvertently encouraged walking after treatment, noting that many 'women had to walk for longer periods to their houses after treatment.'[33] However, 1% to 3% of patients developed mercury intoxication with nephritis, stomatitis and enteritis, and again the procedure was abandoned.[34] In 1916, Sicard noticed the sclerosing effect of Luargol solution used in the treatment of syphilis.[35] He reported his first series of cases in 1920 on the use of carbonate of soda but later found that salicylate of soda was best for sclerosing varicose veins.[36]

Genevrier, a military physician in 1918 who used intravenous quinine to treat malaria, often injected varicose veins in the same patients, thereby treating both the malaria and the varicosities.[37]

The first pharmaceutically manufactured sclerosing solution was a mixture of saline and procaine. Thereafter, multiple solutions were produced by the German pharmaceutical industry. This stimulated research on both sides of the Atlantic for an ideal sclerosing solution and many different compounds were tried (Box 1). These included the following: 50% grape sugar,[38] mercury bi-iodide,[39] 20% and 30% sodium salicylate,[40,41] sodium citrate,[42] 20–30% sodium chloride,[42] 1% bichloride of mercury,[43] 50–60% calorose (75% invert sugar with 5% saccharose),[44] and 12% quinine sulfate with 6% urethane.[44] These substances were used widely but caused unacceptable levels of allergic reactions, necrosis, pain and even fatalities.[45–47] (A complete discussion of the development and properties of modern sclerosing solutions is found in Chapter 7.)

Tournay was instrumental in developing a school of sclerotherapy in France and refined the injection technique to include drainage of intravascular thrombi. McAusland[48] popularized the technique in the United States in 1939 with his report of the successful treatment of 10,000 patients. He promoted injection into empty veins to limit the degree of thrombosis, treatment of the incompetent saphenofemoral junction before sclerosing distal varices, the use of postsclerotherapy compression, and the use of minimal sclerosant concentrations (in the form of sodium morrhuate froth) for sclerosing telangiectasia. Brunstein[49] further popularized injection into empty veins and the use of postsclerotherapy compression to produce cosmetic, painless, efficient sclerosis. The advent of synthetic sclerosing agents in 1946 firmly established sclerotherapy (primarily in Europe) as a viable form of treatment for varicose veins. Still, many physicians perceived clinical results of sclerotherapy treatment to be less optimal than those obtained with surgical approaches.

Although the use of compression therapy for treatment of venous disease is mentioned in the Old Testament and was performed by Hippocrates in the fourth century BC, it has been used in sclerosing treatment of varicose veins only within the past 50 years.[50] Postsclerosis compression, initially described by Brunstein[49] in the 1940s, Sigg[51] and Orbach[52] in the 1950s and Fegan[53] in the 1960s, is perhaps the most important advance in sclerotherapy treatment of varicose veins since the introduction of relatively safe synthetic sclerosing agents in the 1940s. With the advent of 'compression' sclerotherapy, clinical results equal to surgical procedures are now being reported.

In Europe, sclerotherapy has been fully accepted by the medical community since the 1960s and exists as a separate specialty (phlebology and/or angiology).[54] Even today, however, American physicians do not understand the technique or its indications, safety and efficacy. Eighty-two percent of gynecologists surveyed did not have enough knowledge to advise patients who requested information on the treatment of varicose and telangiectatic leg veins. In fact the gynecologists incorrectly perceived that sclerotherapy produced indiscriminate venous destruction; had a high risk of venous thrombosis and allergic reactions; caused permanent pigmentation or scarring; necessitated prolonged, repetitive, painful treatments; and had a low percentage of improvement.[55]

Box 1 Historical Introduction of Sclerosing Agents

1840	Absolute alcohol (Monteggio, Leroy D'Etiolles)
1851–1853	Ferric chloride (Pravaz)
1855	Iodo tannic liquor (Desgranges)
1880	'Chloral' (Negretti)
1904	5% Phenol solution (Tavel)
1906	Potassium iodo-iodine (Tavel)
1910	'Sublime' (Scharf)
1917	Hypertonic glucose/50–60% calorose (Kausch)
1919	30% Sodium salicylate (Sicard and Gaugier)
1919	Sodium bicarbonate (Sicard and Gaugier)
1920	1% Bichloride of mercury (Wolf)
1922	12% Quinine sulfate with 6% urethane (Genevrier)
1922	Bi-iodine of mercury (Lacroix, Bazelis)
1926	Hypertonic saline with procaine (Linser)
1927	50% Grape sugar (Doerffel)
1929	Sodium citrate (Kern and Angel)
1929	20–30% Hypertonic saline (Kern and Angel)
1930	Sodium morrhuate (Higgins and Kittel)
1933	Chromated glycerin (Scleremo) (Jausion)
1937	Ethanolamine oleate (Biegeleisen)
1946	Sodium tetradecyl sulfate (Sotradecol) (Reiner)
1949	Phenolated mercury and ammonium (Tournay and Wallois)
1959	Stabilized polyiodinated ions (Variglobin) (Imhoff and Sigg)
1966	Polidocanol (Aethoxysklerol) (Henschel and Eichenberg)
1969	Hypertonic saline/dextrose (Sclerodex)

Modified from Goldman MP, Bennett R. J Am Acad Dermatol 1987;17:167.

REASONS FOR TREATMENT

Patients seek therapy for telangiectasias or varicose veins principally because of their unsightly appearance. A survey has shown that American women are more concerned with lower extremity telangiectasia than with almost any other cosmetic problem.[56] However, proper treatment is frequently difficult to obtain because correct surgical intervention and sclerotherapy are not often taught in medical schools or residency programs. Frequently, patients with telangiectasias of the legs are told that they must live with the problem. Treatment options, including sclerotherapy, are either mentioned disparagingly or not discussed at all. However, available evidence indicates that safe, effective forms of treatment other than surgery are possible and quite successful.

In addition to the cosmetic benefits of sclerotherapy, studies have demonstrated that sclerotherapy treatment of incompetent perforating veins increases the efficacy of the calf muscle pump, resulting in an improved clearance of extravascular fluid.[57] Lymphangiography of patients with chronic venous insufficiency who are treated with sclerotherapy also demonstrates normalization of lymphatic drainage, in addition to improvements in venous hemodynamics.[58,59] Also, a significant percentage of patients (28–85%) with chronic venous insufficiency have superficial venous insufficiency alone or in combination with deep venous system abnormalities.[60–62] These patients show greater improvement with sclerotherapy or surgical treatment of the superficial veins combined with compression therapy than with compression therapy alone.[63] In addition, whereas the symptoms of heaviness and aching of the legs are often relieved by wearing a graduated compression stocking,[64] patients prefer to be rid of the veins altogether because wearing a compression stocking (which may be difficult to apply) is unsightly, and uncomfortable in warm, humid climates.

Hobbs,[2] Lofgren,[65] and Beninson and Livingood[66] have pointed out that the treatment of varicosities per se may have no effect on alleviating superficial venous pressure. It is the treatment of the underlying communicating or perforating veins draining the gaiter area that is important.[2,16,18,67,68] These vessels may be either surgically ligated[16,18,67,68] or sclerosed.[2] Only then can the retrograde flow under high pressure through the calf muscle pump be diverted upstream and away from the skin. This succeeds in lowering the cuticular venous pressure with decreased capillary permeability and edema, thus increasing tissue oxygenation and nutrition. Wilson and Browse[56] estimate that 40–50% of patients with venous ulceration have nonthrombotic or perforating vein incompetence that can be treated successfully with interruption of the abnormal veins, either through superficial ligation or sclerotherapy.

PRESENT DAY TREATMENT

A common misconception among physicians is that knowledge of or dexterity in venipuncture confers expertise in sclerotherapy. True expertise in sclerotherapy, like all specializations in medicine and surgery, comes only after extensive postgraduate education, the observation of trained physicians using meticulous technique, and subsequent (preferably supervised) practice. Fortunately, physicians who specialize in the treatment of venous disease (phlebologists, dermatologists and vascular surgeons) now can offer relatively simple treatments for this widespread medical ailment.

Sclerotherapy, as practiced today, has been shown to be better than placebo in the treatment of varicose and telangiectatic leg veins.[69] Sclerotherapy is also as effective as comparable surgical procedures (ligation and stripping) in long-term follow-up studies of most types of varicose veins, excluding those with significant saphenofemoral incompetence.[70–73]

As discussed in Chapter 9, new methods of sclerosing varicose veins with reflux at the saphenofemoral junction (SFJ reflux) by using sclerosant foam under duplex control may also increase the safety and efficacy of sclerotherapy in patients with that particular condition, and is becoming as effective as surgical and intravascular laser and radiofrequency (RF) treatment. The older recommendation of Wallois, who used a liquid sclerosing solution in nonsurgical patients,[74] is to treat these patients once or twice a year to maintain effective sclerosis of the varicose great saphenous vein (GSV). Although this method (with nonfoamed sclerosing solutions) does not produce a cure, it maintains both cosmetic and symptomatic improvement. Finally, as discussed further in Chapter 10, sclerotherapy can also complement surgical and/or intravascular laser/RF treatment, especially for varicose or perforating veins, and can prevent recurrences.[75]

Modern sclerotherapy has been demonstrated to result in a relief of symptoms in up to 85% of patients with both varicose[3] and telangiectatic veins.[76] In addition, sclerotherapy treatment has been demonstrated to be a more physiologic approach to eliminating abnormal varicose veins. One study of dissected cadaver legs demonstrated that more than 50% of the patients with significant varicose veins had a normal great saphenous system, suggesting that vein stripping may be an inappropriate procedure in a significant percentage of patients.[77] This is especially important regarding use of the GSV as a conduit for myocardial revascularization. Although the internal mammary artery is a better conduit for coronary artery bypass grafting, the GSV is still necessary in a significant number of patients.[78] Most patients require multiple grafts, and the internal mammary artery can accommodate only one or two graft segments.

Sclerotherapy of 'varicose' (abnormal) veins does not impede the vascular vein surgeon from harvesting appropriate conduits for coronary artery bypass. The structural quality of vein grafts is of decisive importance for the maintenance of patency. Patency half-life with a good-to-excellent graft is 10.5 years, versus 0.5 years when fair- and poor-quality grafts (including those taken from varicose veins) are used.[79] A more recent study cites an incidence of graft failure at 30 months of 68% in patients grafted with diseased veins, versus 27% when healthy veins were used.[80] Most importantly, treatment of 'early' varicose veins is thought to halt their progression into larger, more severe varices.[81,82] Early treatment may prevent the development of valvular incompetence. Therefore, not only is sclerotherapy not detrimental to coronary bypass grafts but it may help in providing better conduits for this procedure should the need arise.

Perhaps more significant in this age of cost control, sclerotherapy has been demonstrated to be much less costly than surgical procedures in the treatment of varicose veins.[83–86] In lieu of the inpatient hospital ligation and stripping operation, sclerotherapy treatment is performed on an outpatient basis, permitting patients to return to work immediately after the procedure. Newer surgical techniques practiced in ambulatory surgical centers allow SFJ ligation, or radiofrequency or endoluminal laser closure of the GSV to be performed without general anesthesia. In this setting, the traditional expense of surgical procedures is lessened. However, even with the most modern surgical treatments, the morbidity and cost of surgery is greater than that of sclerotherapy.

However, when SFJ incompetence is present, a limited ligation and stripping procedure, or endovenous RF or laser closure followed by immediate ambulatory phlebectomy with sclerotherapy 3 to 6 weeks later, may be necessary. Because of the 'limited' nature of the procedure (as described in Chapter 10), hospitalization is not required and the procedure is performed under local anesthesia in an outpatient surgical facility. The patient is ambulatory and leaves after the hour or so procedure, resuming normal activities within 24 hours. In addition to cost savings, patients' preference for outpatient sclerotherapy has been a major reason for the modernization of varicose vein treatment.[83] This preference has occurred despite the recurrence of varicose veins (usually to a minor degree) in 88% of patients who were treated with sclerotherapy alone.[83]

Unfortunately, the straightforwardness of sclerotherapy—performed with a simple syringe and sclerosing solution in an awake patient with rapid recuperation—is thought by those without an adequate knowledge of phlebology to be entirely cosmetic in nature. This has led to medical reimbursement in the United States being withheld or trivialized by medical insurance companies. Some have even suggested changing the name of sclerotherapy to 'endovenous chemical ablation' which appears to have a more formidable name.[87] We believe that it is best not to try and change a name to 'mislead' but to educate.

In summary, the presence of varicose and telangiectatic veins is not a normal physical finding but a medical disease deserving of treatment. Varicose and telangiectatic veins may be symptomatic, representing an obvious manifestation of venous disease with its resultant complications, and may pose medical risks and complications in and of themselves. According to Hippocrates, the only advantages of having varicose veins are that 'the bald are not subject to varicose veins; but should they occur, the hairs are reproduced', and 'if varicose veins or hemorrhoids occur during mania, the mania is cured'.[88]

Fortunately, the majority of patients with varicose and telangiectatic veins do not have a life-threatening problem. Therefore, treatment should be as simple as possible, with the least risk of significant side effects. Modern sclerotherapy treatment has been demonstrated to fulfill these requirements with efficacy that is comparable with operative procedures. This textbook examines the pathophysiology and practical application of sclerotherapy treatment for varicose veins and telangiectasias through a review of the world literature, presentation of experimental studies and recommendations derived from the practices of the contributing authors.

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1 Anatomy

Stefano Ricci

INTRODUCTION

The anatomy chapter in a modern text devoted to sclerotherapy is traditionally not the most fascinating aspect, as the anatomy rarely changes and is very similar to that described in older texts. Anatomy chapters are rarely consulted because readers believe they know the basics of venous anatomy, but they should be reviewed regularly, and as one uses duplex ultrasound, the importance of understanding anatomy increases greatly. While this chapter reports on the images and the concepts of the classic anatomy texts that we used during our university medical studies, it is clear from our experience with duplex ultrasound observations that a 'déjà vu' sensation to anatomy is not entirely correct and anatomy is more than a fixed science—new understanding has been added.

Dissection anatomy, indeed, had its fullest expression from the late eighteenth to the early twentieth century (Mascagni, Gray, Sobotha, Testut, etc.) when all the aspects of dissection anatomy were definitively studied (Fig. 1.1). In the past 50 years, anatomical dissection has been little used to investigate venous anatomy, probably because of the assumption that there is nothing new to discover (but also because it is more and more difficult to find cadavers for this purpose). Meanwhile, most anatomical, clinical and surgical textbooks describe the superficial veins of the lower limb as a simple 'tree' formed by a few constant and recognizable veins, though clinical experience often shows anomalies and variations with respect to the classical anatomical description or even the complete absence of some of these veins. Furthermore, studies in the field of limb veins usually concern subjects with varicose pathology and rarely subjects with a normal venous system.

Confirming this, the official Anatomical Terminology (*Nomina Anatomica*)[1] includes only a limited number of veins and does not take into account their numerous variations. Inadequacy of official anatomy has caused many authors to name single veins independently or even after the author's name, which, in the absence of an accepted interpretation frame, has added some confusion. The nomenclature consensus statement of 2001 at the Rome UIP World Congress was organized with the purpose of solving this problem (see Table 1.1).[2]

Contrast phlebography, until recently the 'gold standard' for venous investigation, has the major drawback of being practically never complete, but rather showing only the veins filled by contrast media. Furthermore, it focuses mainly on deep veins and in pathologic conditions, and thus has not contributed much to the understanding of normal vein anatomy.

Understanding of vein anatomy did not progress much until ultrasound imaging (USI), specifically duplex scanning (DS), became an established technique for clinical investigation of patients with venous diseases. Technology simplifications and low costs have allowed its widespread use.

Ultrasound imaging makes it easy to observe the veins of the lower limb, unlike anatomical dissection and phlebography. Examination is noninvasive, repeatable and relatively low in cost. Veins can be observed at full distention, with the patient in a standing position, so that, unlike with anatomical dissection, their real volumetric relationship with the surrounding tissue is readily appreciated. Ultrasound images show not only the veins (as contrast phlebography does), but their relation to surrounding anatomical structures, in particular muscle and fascial layers. This allows precise anatomical identification of the observed veins (Fig. 1.2). Therefore, USI is a unique tool for the study of vein anatomy [ultrasound (US) dissection] and makes it possible to verify data obtained from anatomical dissections. In addition, DS allows the detection of blood flow in the observed veins with assessment of their function and involvement in venous pathology. Interestingly, USI was first employed for the clinical identification of pathologically changed veins. Later it was used for collecting data on normal vein anatomy.[3]

In this chapter vein anatomy is first described from the traditional point of view, and successively as observed by USI with special reference to the superficial veins of the lower limb in relation to varicose vein disease and sclerotherapy. For this purpose an interpretation key is emphasized, which makes it possible to categorize the extreme variability of the superficial veins of the lower limb into a limited number of specific anatomical and varicose patterns.

NOMENCLATURE

Nomenclature used throughout the textbook conforms to that developed at the Venous Consensus Conference Classification in 1994.[4] In addition, the newest revisions of nomenclature and definitions are used, which were developed at the Nomenclature Congress in Rome in 2001 (Table 1.1).[2,5] The long saphenous vein is referred to by the English-Latin term great (GSV). The short saphenous vein is referred to using the English-Latin translation small (SSV), avoiding the term 'lesser' as the L could be confused with the term 'long'. Veins that 'perforate' the fascia are termed perforator veins. Veins that connect to other veins within a fascial

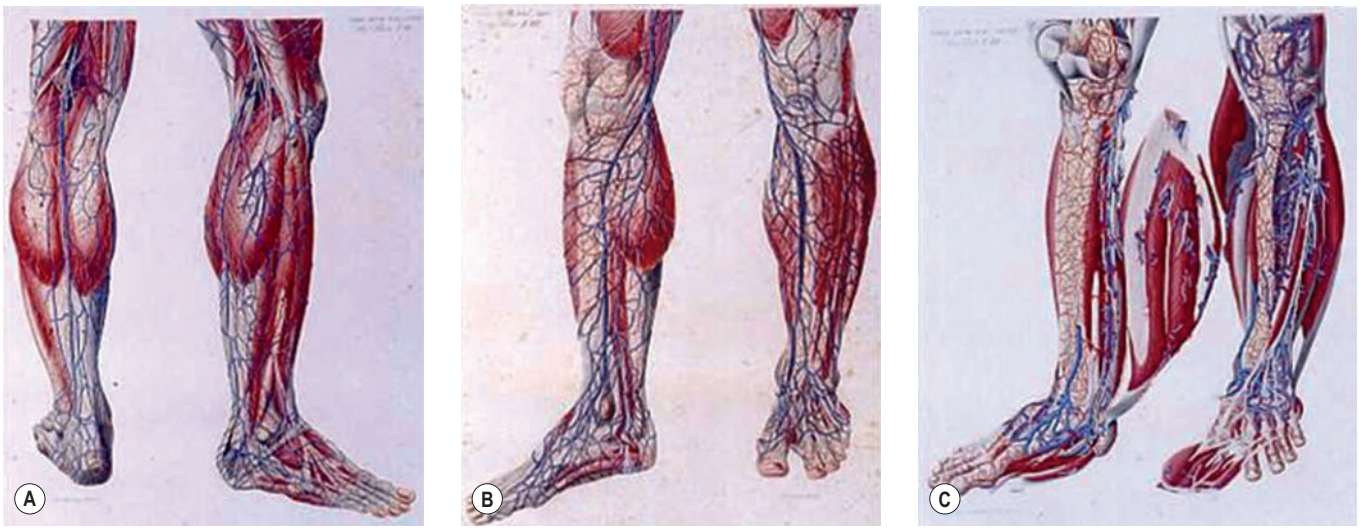

Figure 1.1 Three plates from the *Piccola Anatomia*, which was published in a reduced size because of the high printing costs of the time, are shown here. These demonstrate that anatomical knowledge was already complete 200 years ago. (The *Grande Anatomia* of Paolo Mascagni was published between 1823 and 1831 by Nicolò Capurro in Pisa).

Table 1.1 Summary of Important Changes in Nomenclature of Lower Extremity Veins

Old Terminology	New Terminology
Femoral vein	Common femoral vein
Superficial femoral vein	Femoral vein
Sural veins	Sural veins
	Soleal veins
	Gastrocnemius veins (medial and lateral)
Hunterian perforator	Mid-thigh perforator
Cockett perforators	Paratibial perforator
	Posterior tibial perforators
May perforator	Ankle lateral and medial perforators
Gastrocnemius point	Intergemellar perforator

Modified from Sherman RS. Ann Surg 1949;130:218.

plane are referred to as communicating veins. The principal deep vein of the thigh is termed the superficial femoral vein, now properly called the femoral vein. The superficial femoral vein actually has turned out to be a potentially lethal misnomer. It has been found that the use of this term is hazardous to patients suspected of having deep venous thrombosis. Many primary care physicians have not been taught and are not aware of the fact that the superficial femoral vein is actually a deep vein of the thigh and that acute thrombosis in this vessel is potentially life threatening.[6]

GENERAL CONSIDERATIONS

The veins of the lower limbs are traditionally described as consisting of two systems: one within the muscular compartment and its fascia, the deep system, and one superficial to the deep fascia, the superficial compartment (Fig. 1.3).

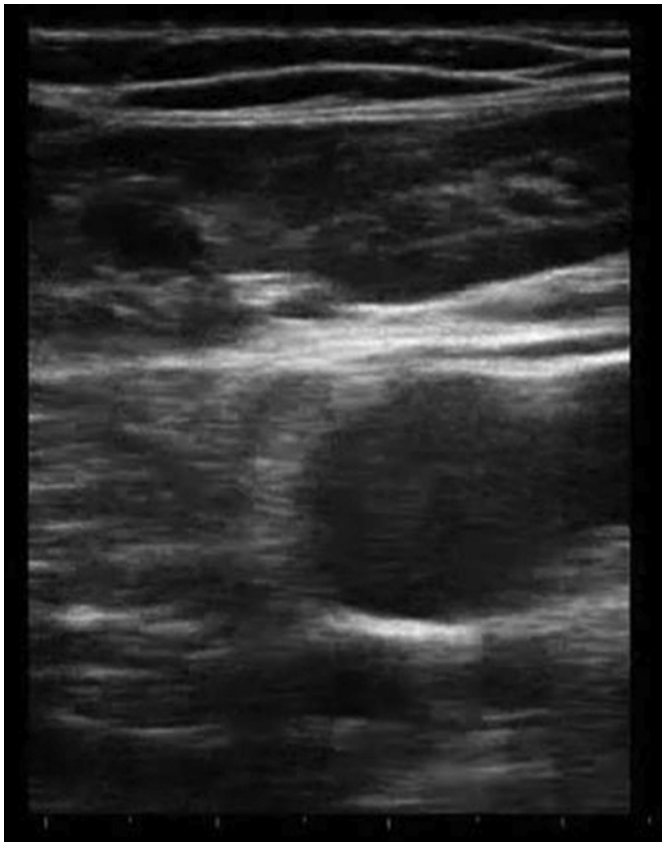

Figure 1.2 Ultrasound imaging shows the veins and their relationship to the surrounding anatomical structures, in particular other vessels, lymph nodes, bones, muscles and fascial layers. This allows precise anatomical identification of the observed veins.

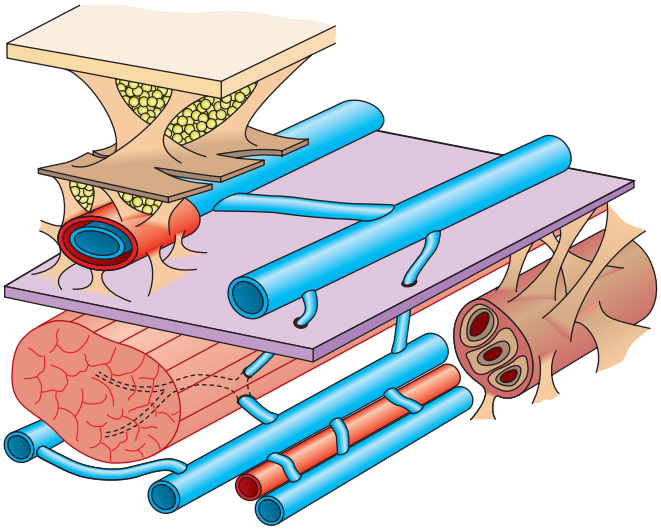

Figure 1.3 According to traditional description, superficial veins are separated from deep veins by muscular fascia. (Adapted from Kubik S. Das Venensystem der unteren Extremitat. Der informierte Artz 1985;4:31.)

The lower limb deep venous system is found inside the muscles within the muscular fascia. This allows it to feel the effects of the tonus variations during contraction–relaxation, being the only structure able to vary its volume.[7] The superficial veins are in an extrafascial position with respect to the muscles, although the most important (i.e., saphenous veins) are found with superficial fascia duplication.

The deep venous system of the lower legs cannot be seen as an independent entity, separated from the superficial veins. The first purpose of venous function is to organize the antigravity blood backflow to the right heart, taking advantage of its volume capacity (three times as much as in arteries), its low pressure and its compliance, so that the reservoir (the interstitium, depending on lymphatics) may not be involved.[7] Other primary important functions, although more localized, are tissue drainage and thermoregulation. These three functions are assured in all different body positions and activities, otherwise 'venous insufficiency' occurs.[8]

Tissue drainage and the maintenance of volume flow are based on valvular and, more importantly, muscle function. Both systems strictly integrate with the venous reservoir function, the respiratory function and the filling 'vis-a-tergo' because of the capillary network.[7]

Venous backflow represents about 10% of the total flow at rest, but increases heavily during dynamic conditions because of the physiologic alternate contraction–relaxation of the flexor–extensor muscles. These act as a peristaltic pump and as a dynamic reservoir, conditioning either the squeezing (contraction) or the distention (relaxation) of the deep veins (with action on the venous sole of the foot and, above all, ankle joint movement of particular amplitude conditioning the most important calf pump (Fig. 1.4).

Deep vein communications, mutual or with superficial veins, are extremely frequent so that the postural and the rest phases may address the venous backflow through less resistant pathways, typically the deep veins in the physiologic situation.[7]

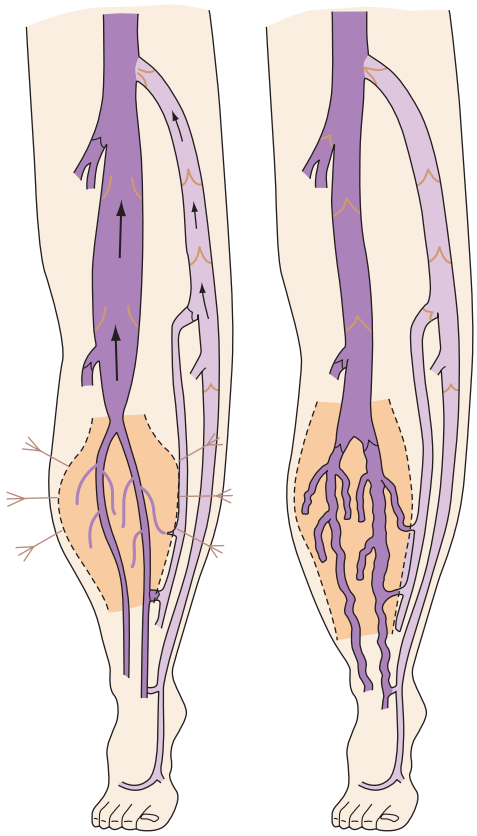

Figure 1.4 Physiologically, alternate contraction–relaxation of the flexor–extensor muscles acts as a peristaltic pump and as a dynamic reservoir, conditioning either the squeezing (contraction) or the distention (relaxation) of the deep veins and the normal emptying of the superficial veins, provided there is normal valvular function. (Adapted from: Tibbs DJ, Sabiston DC, Davies MG, et al. Varicose veins, venous disorders, and lymphatic problems in the lower limbs. Oxford University Press; 1997.)

DEEP VENOUS SYSTEM

The structure of the deep venous system is shown in Figure 1.5.[9] There are at least two deep veins for each of the three arteries (anterior and posterior tibial arteries and peroneal artery), mutually communicating by transverse bridges (like a ladder). The extremely rich muscular plexus (also connected to the superficial veins) drains into these axial veins placed parallel to arteries. At the foot, axial veins are prevalent in the plantar region, where the first pump mechanism is present (Léjars sole) (Fig. 1.6).[10–12]

At the soleus and gastrocnemius sites the veins are even larger in number and arranged in a spiral shape, because of the longitudinal excursion amplitude of the muscles between contraction and relaxation. This creates a volume reservoir (pump chamber), and the relative muscles (soleus and gastrocnemius) are responsible for both movement/standing position as well as pump function (the second and most important pump). This system is correctly termed the calf muscle pump or peripheral heart (see Fig. 1.4).[12]

In contrast, posterior deep compartment veins (posterior tibial and peroneal) and anteroexternal compartment veins (anterior tibial) are rectilinear, as the surrounding muscles

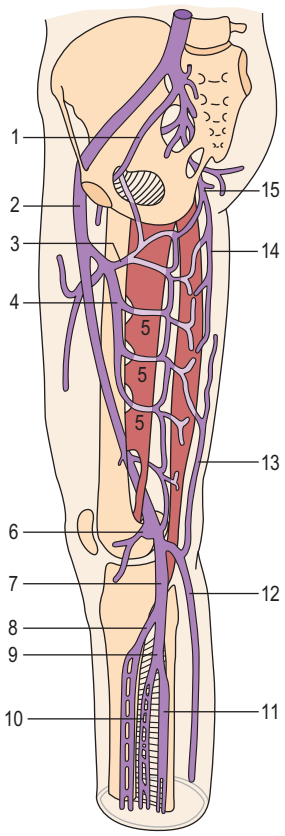

Figure 1.5 In the leg, two deep veins for each of the three arteries communicate by means of transverse bridges. At the knee and thigh, deep veins flow into the collecting system 'popliteal–femoral veins'. Several other secondary veins are present that can ensure a natural bypass when obstruction occurs to the femoral vein. *1,* Obturator vein; *2,* common femoral vein; *3,* medial circumflex femoral vein; *4,* profunda femoris vein; *5,* perforating veins; *6,* descending genicular vein; *7,* popliteal vein; *8,* posterior tibial vein; *9,* proximal portion of the posterior tibial venous axis (common trunk); *10,* posterior tibial veins; *11,* peroneal (interosseous veins); *12,* short saphenous vein; *13,* posterior subcutaneous femoral vein; *14,* ischial vein; *15,* inferior gluteal vein. (Adapted from Kubik S. Das Vevensystem der unteren Extremitat. Der informierte Artz 1985;4:31–38.)

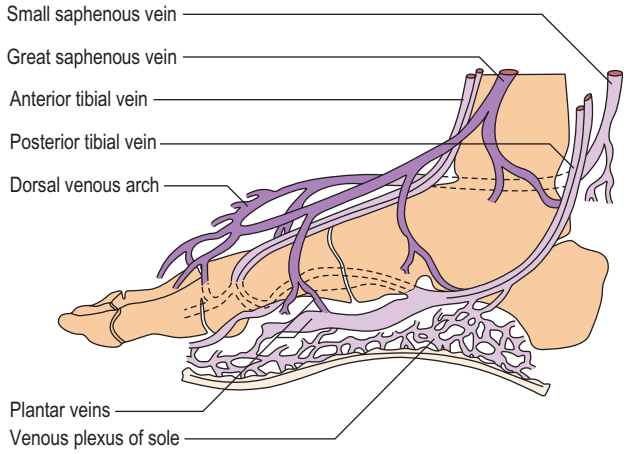

Figure 1.6 At the foot, axial veins are prevalent in the plantar region, where the first pump (although not the most important) mechanism is present (Léjars sole). (Adapted from: Tibbs DJ, Sabiston DC, Davies MG, et al. Varicose veins, venous disorders, and lymphatic problems in the lower limbs. Oxford University Press; 1997.)

lean against the bones and have a limited shortening during contraction.[7]

At the knee and thigh, deep leg veins flow into the collecting system (popliteal–femoral veins). They run in the popliteal crease and adductors canal, and are not enwrapped by a muscular layer as the blood flow to the abdominal cavity has not been held back by compression.[7] The other thigh veins (profunda femoris and circumflex) are still deep intramuscular veins. The popliteal vein is also connected by anonymous muscular veins to the profunda femoris and the sciatic nerve vein, creating a natural bypass when obstruction occurs to the femoral vein (thrombosis, extrinsic compression, bone fracture).[13] Thanks to this autonomy, the femoral vein is used as an alternative conduit when other more accessible superficial veins are unavailable (see Fig. 1.5).[9]

The common femoral vein collects the backflow of the lower limb and sends it to the pelvis (iliac veins and inferior vena cava), where aspiration pleurodiaphragmatic forces prevail, together with vis-a-tergo of the renal veins. The common femoral vein in particular receives the GSV below the inguinal ligament where it becomes the external iliac vein. A potential alternative way of discharge in this area is the obturator vein (normally draining part of the muscles of the medial thigh) and the sciatic vein, often not macroscopically evident (first embryonic vein, secondarily replaced by the femoropopliteal axis, which can be activated in certain conditions). Together with the superficial veins they can contribute to limb drainage in case of femoral thrombosis by their connection to the hypogastric vein (see Fig. 1.5). However, the same system may be the cause of varices when endopelvic hypertension is transmitted to the superficial limb veins. The sciatic vein may also be involved in congenital venous malformations, typically Klippel–Trenaunay syndrome.[13]

ANATOMY OF THE SUPERFICIAL VEINS

The most important superficial veins are the GSV and the SSV. It is generally thought that the term saphenous is derived from the Greek word *saphenes*, meaning evident, but it could also come from the Arabic words *el safin*, which mean hidden or concealed.[14] Of course, these terms were important in the practice of blood letting.

GREAT SAPHENOUS VEIN

This vein begins on the dorsum of the foot as a dorsal venous arch and internal marginal vein. It passes anterior (10–15 mm) to the medial malleolus, crosses the tibia at the distal third and runs along the tibial internal edge. At the knee the vein bends posteriorly, running around the condylus femoralis, in contact with the anterior edge of the sartorius muscle, then ascends in the anteromedial thigh, crosses the sartorius and adductor brevis and enters the Scarpa triangle to empty into the common femoral vein (Fig. 1.7).[9,15] This termination point is referred to as the saphenofemoral junction (SFJ), but is also known as the *crosse*, which is the French description for its appearance as a shepherd's crook. The average diameter of a normal GSV is 3.5–4.5 mm (range 1–7 mm).[16]

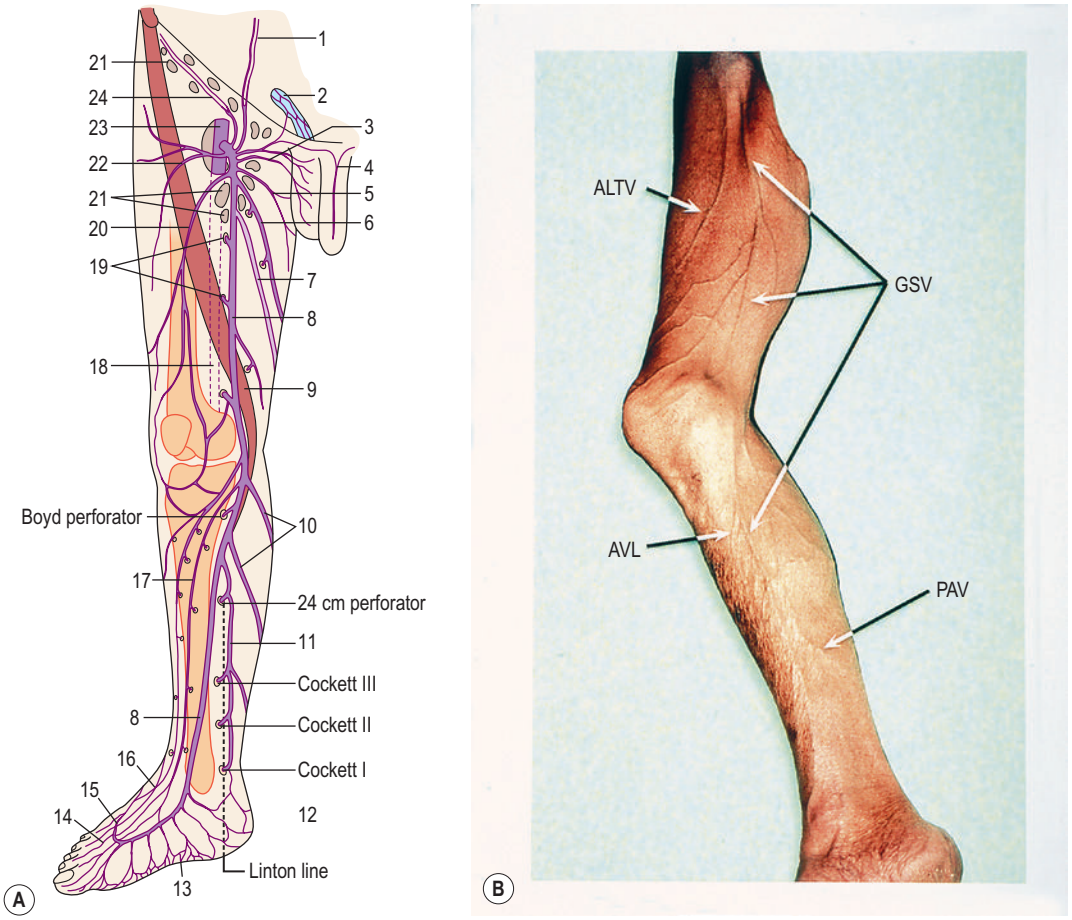

Figure 1.7 **A,** Traditional anatomical terms for the lower limb, medial aspect. *1,* Superficial epigastric vein; *2,* pampiniform plexus; *3,* external pudendal vein; *4,* superficial dorsal vein of the penis; *5,* superficial medial circumflex femoral vein; *6,* accessory posterior saphenous vein of the thigh; *7,* femoropopliteal vein; *8,* great saphenous vein; *9,* sartorius muscle; *10,* anastomoses between the great and small saphenous veins; *11,* posterior arcuate vein (posterior saphenous vein of the leg or vein of Leonardo); *12,* medial marginal communicating veins; *13,* plantar sole; *14,* superficial dorsal metatarsal veins; *15,* superficial dorsal venous arch of the foot; *16,* venous plexus of the dorsal surface of the foot; *17,* anterior vein branch (anterior saphenous vein of the leg); *18,* superficial femoral vein; *19,* perforating veins of Dodd; *20,* accessory small saphenous vein (anterior accessory saphenous vein); *21,* superficial inguinal lymph nodes; *22,* superficial lateral circumflex femoral vein; *23,* common femoral vein; *24,* superficial circumflex iliac veins. **B,** The great saphenous vein (GSV) and its tributaries are occasionally well displayed on thin legs. *ALTV,* Anterolateral thigh vein; *AVL,* anterior vein of the leg (accessory saphenous vein); *PAV,* posterior arch vein. (B, Adapted from Somjen GM. Dermatol Surg 1995;21:35.)

The GSV receives multiple tributaries along its course. These usually lie in a less supported, more superficial plane above the membranous fascia. The posterior arch vein, the anterior superficial tibial vein and the medial superficial pedal vein join the GSV in the lower leg. The posterior arch vein (known as the vein of Leonardo, but now classified as the posterior accessory saphenous vein) is a major tributary to the GSV. It enters the GSV below the knee and otherwise communicates with the deep venous system through multiple perforating veins. These are, in ascending order: the Cockett I, Cockett II and Cockett III perforators and the 24-cm perforating vein, now called the upper, middle and lower posterior tibial perforators.

In the thigh, two main clusters of perforating veins connect the saphenous vein to the deep system. Just above the knee, there is the Dodd group, and in the mid-thigh, the Hunterian perforators (now called mid-thigh perforators).

Two large tributaries in the upper third of the thigh—the posteromedial and anterolateral tributaries—join the GSV proximally. These veins usually enter the GSV before it dives posteriorly to penetrate the deep fascia at the fossa ovalis. Both the medial and lateral superficial thigh veins may be so large that they are mistaken for the GSV itself.[17] A variable number of perforators connect the GSV to the femoral, posterior tibial, gastrocnemius and soleal veins.[18]

SMALL SAPHENOUS VEIN

The SSV is the most prominent and physiologically important superficial vein below the knee (Fig. 1.8).[9] Like the GSV, the SSV has a thick wall and usually measures 3 mm in diameter when normal.[19] It begins at the lateral aspect of the foot and ascends posterior to the lateral malleolus as a continuation of the dorsal venous arch. It continues up the calf between the gastrocnemius heads to the popliteal fossa, where it usually enters the popliteal vein.

The termination of the SSV is quite variable, usually occurring in the popliteal vein, as stated before. However, in 27% to 33% of the population, it terminates above the

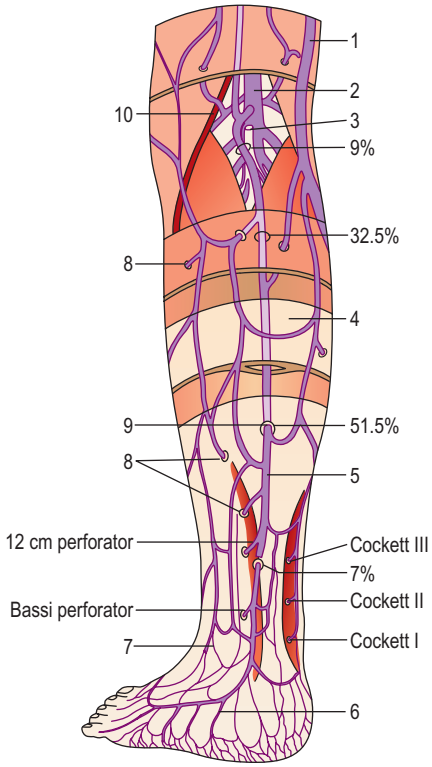

Figure 1.8 Traditional anatomical terms for the lower limb, posterior aspect. *1,* Great saphenous vein; *2,* popliteal vein; *3,* tibial nerve; *4,* deep fascia; *5,* small saphenous vein; *6,* lateral marginal communicating veins; *7,* lateral malleolus; *8,* perforating veins; *9,* gastrocnemius point; *10,* common peroneal nerve.

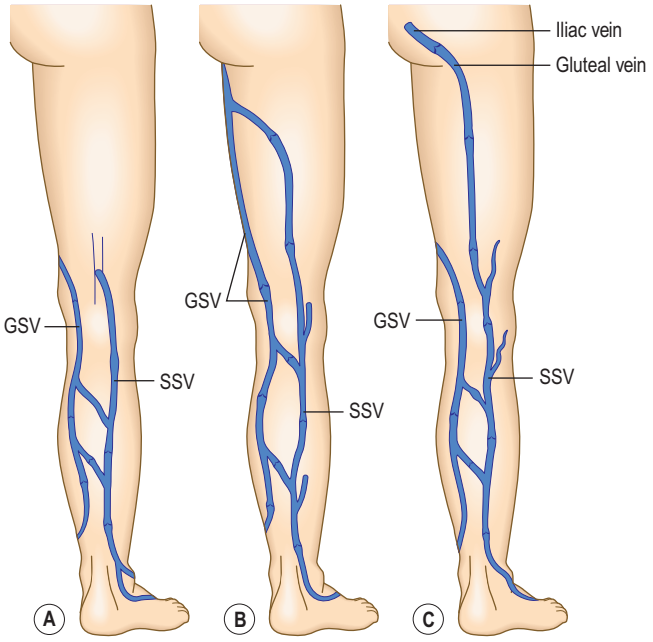

Figure 1.9 Variations in the termination of the small saphenous vein (SSV). **A,** Termination into the saphenopopliteal junction; **B,** termination into the great saphenous vein (GSV); **C,** termination into the gluteal vein.

level of the popliteal fossae, either directly into the GSV or into other deep veins. In 15.3% of patients, the SSV communicates with the popliteal vein, then continues terminating in the GSV. In 9% to 10%, the SSV empties into the GSV or the deep veins below the popliteal fossae.[9,20] The SSV may also join the GSV in the thigh through an oblique epifascial vein (the Giacomini vein), or it may continue up under the membranous fascia of the thigh as the femoropopliteal vein, joining the deep veins in the thigh at various locations (Fig. 1.9).[21–23]

Like the GSV, the SSV runs on or within the deep fascia, usually piercing the deep fascia just below the flexor crease of the knee as it passes into the popliteal fossa.[24] Gross incompetence of the SSV usually occurs only in areas where the SSV and its tributaries are superficial to the deep fascia, on the lateral calf and lower third of the leg behind the lateral malleolus. The SSV often receives substantial tributaries from the medial aspect of the ankle, thereby communicating with the medial ankle perforators. The SSV may also receive a lateral arch vein that courses along the lateral calf to terminate in the SSV distal to the popliteal fossa. It may also connect directly with the GSV.

OTHER SUPERFICIAL VEINS AND COLLATERAL VEINS

The superficial collateral or communicating venous network consists of many longitudinally, transversely and obliquely oriented veins. These originate in the superficial dermis, where they drain cuticular venules. These veins are normally of lesser diameter, but when varicose they can dilate to more than 1 cm. They are thin walled and are more superficial than the superficial fascia that covers the saphenous trunks. They drain into deep veins through the saphenous veins, directly through perforating veins or through anastomotic veins in the abdominal, perineal and gluteal areas.[25] Therefore, collateral veins may become varicose either in combination with truncal varicose veins or independently (Fig. 1.10).[15]

Although many collateral veins are unnamed, some prominent or consistent superficial veins are; for example, the Giacomini vein, which connects the proximal GSV to the SSV. This vein has been found by duplex examination in 70% of limbs with chronic venous insufficiency.[26] Other examples include the lateral anterior accessory saphenous vein (AASV), which runs from the lateral knee to the SFJ; the anterior crural veins, which run from the lower lateral calf to the medial knee, and the infragenicular vein, which drains the skin around the knee. Geniculate perforators, although small, may contribute significant reflux (see Figs 1.7, 1.8).

A lateral subdermal plexus of reticular veins, first described by Albanese et al,[27] has its origin through perforating veins at the lateral epicondyle of the knee (Fig. 1.11). It has been speculated that it represents a remnant of the embryonic superficial venous system that fails to involute. This system of veins has its importance in the development of telangiectasia. These veins may become varicose even in the absence of truncal varicosities.

DUPLEX ULTRASOUND ANATOMY

The venous anatomy of the leg is theoretically simple; however, its peculiarity is owing to its extreme variability

between individual normal subjects. Normal nonvaricose limbs show such different patterns that it is rare to see two identical anatomical arrangements in two different limbs. If we consider varicose limbs, these differences are greatly enhanced.

The most striking progress in the knowledge of venous anatomy for phlebologists is related to the easy visibility of the fascial sheets by duplex ultrasound (DUS) imaging. This DUS anatomical 'dissection' has offered the key for interpretation of these variations, providing a simple universal language for the easy identification of veins (Fig. 1.12).[28,29]

The result is that leg veins are not just 'deep' or 'superficial', but are arranged in three levels: deep (beneath the aponeurotic fascia), intermediate (between the aponeurotic fascia and the superficial fascia) and subcutaneous (between the superficial fascia and the skin) (Fig. 1.13).[8,28]

The subcutaneous space in which all superficial veins run is divided by a fascial sheet, called superficial or membranous fascia, into two layers: a superficial layer of loculated fatty tissue (Camper fascia) and a deep layer of collagen and elastic tissue that provides stronger support (Scarpa fascia). The superficial fascia is homologous with the Scarpa fascia of the anterior abdominal wall and may be considered as a single unit.

In the early nineteenth century two French anatomists, Cruveilhier[30] and Bayle[31] described for the first time that both saphenous veins lie in the deeper compartment of the subcutaneous space and are covered, for their entire length, by the superficial fascia. All other superficial veins (tributaries or collaterals of the saphenous) run into the superficial compartment, between the superficial fascia and the skin, in what is a true subcutaneous position. Despite evidence from anatomical dissection (Fig. 1.14),[32] the importance of

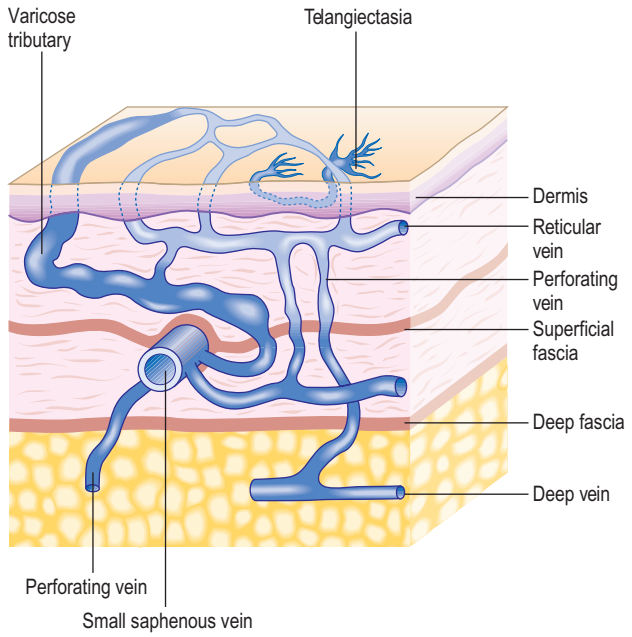

Figure 1.10 Schematic diagram of subcutaneous venous anatomy showing four types of flow from subcutaneous veins (SCV). SCV to GSV/SSV to SFJ/SPJ to deep system; SCV to GSV/SSV to perforator to deep system; SCV to perforators to deep system; SCV to deep system. *GSV,* Great saphenous vein; *SSV,* small saphenous vein; *SFJ,* saphenofemoral junction; *SPJ,* saphenopopliteal junction. (From Somjen GM, Ziegenbein R, Johnston AH, Royle JP. J Dermatol Surg Oncol 1993;19:940.)

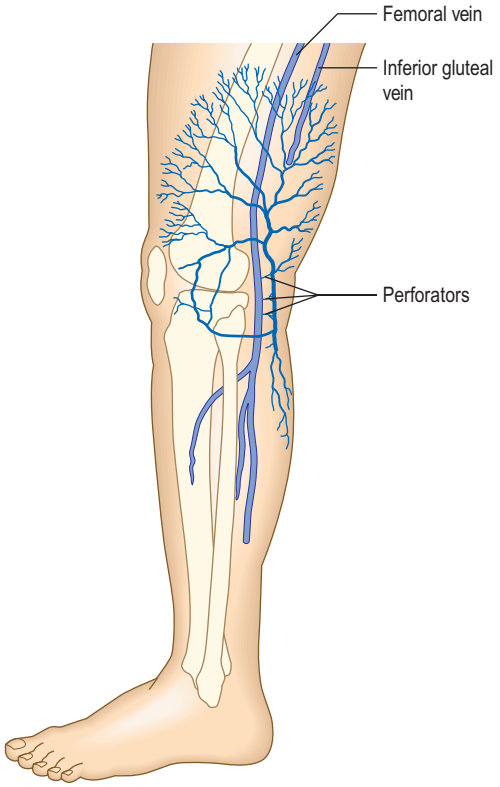

Figure 1.11 Lateral subdermal plexus commonly seen on the lateral thigh arising from perforator veins from the femoral vein.

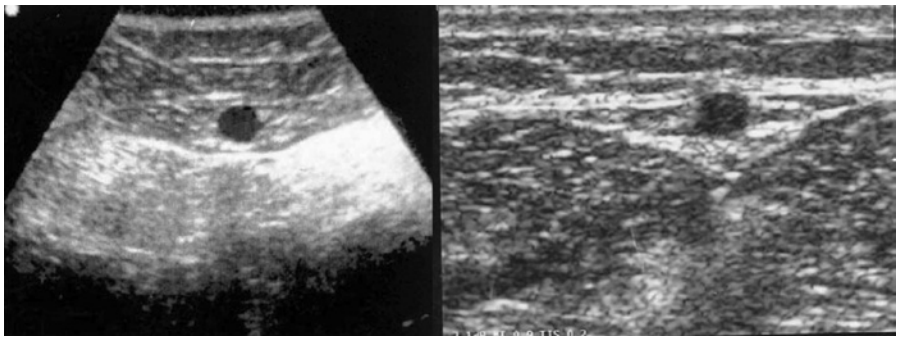

Figure 1.12 The easy visibility of the fascial sheets by ultrasound imaging offers the key for interpretation of the frequent variations of normal anatomy, providing a simple universal language for the easy identification of the veins. Here is the immediate recognition of the great saphenous vein on the *left* and the small saphenous vein on the *right*.

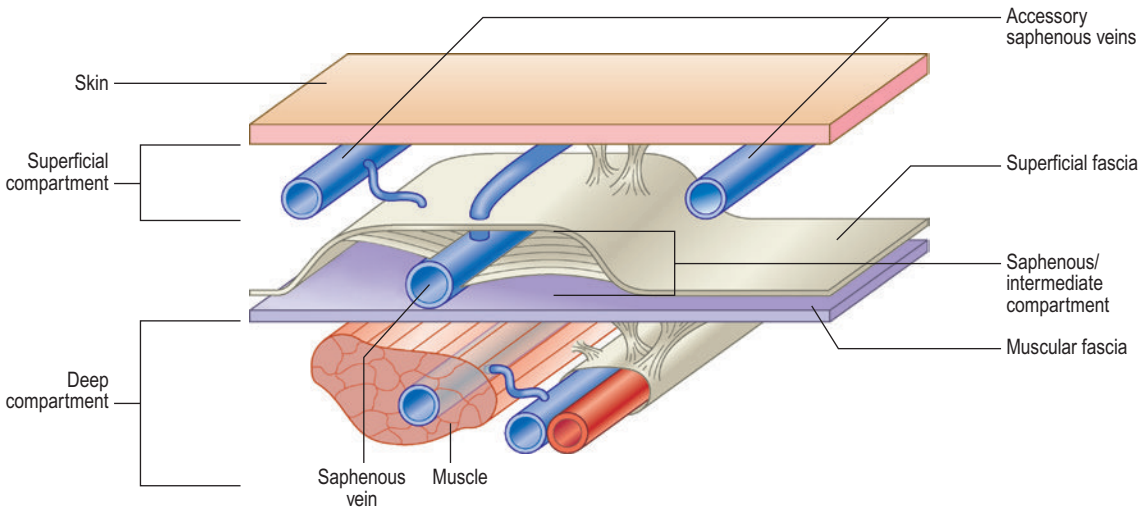

Figure 1.13 Diagrammatic representation of the compartments enclosing the saphenous and deeper veins. Ultrasound shows that lower limb veins are arranged in three levels: deep (beneath the aponeurotic fascia), intermediate (between the aponeurotic fascia and the superficial fascia) and subcutaneous (between the superficial fascia and the skin).

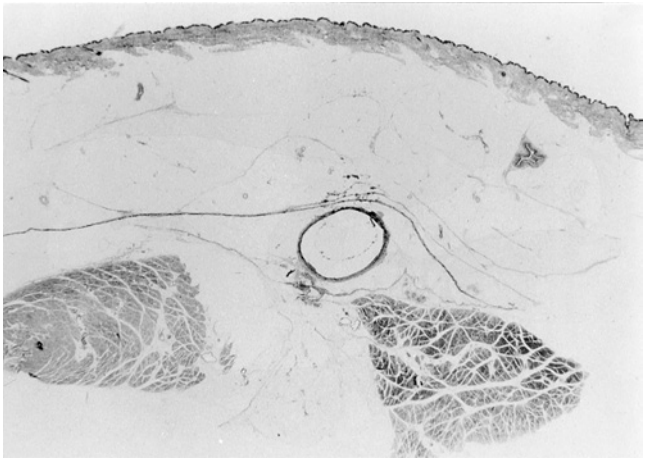

Figure 1.14 Transverse section from the medial aspect of the thigh showing the fibrous envelope that ensheathes the great saphenous vein and holds it against the deep fascia. (From Thompson H. Ann R Coll Surg Engl 1979;61:198. Copyright The Royal College of Surgeons of England. Reproduced with permission.)

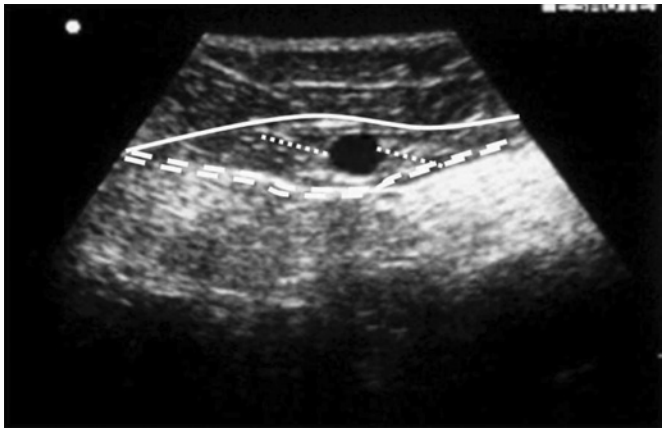

Figure 1.15 The interfascial compartment in which the great saphenous vein (GSV) runs has been called 'saphenous compartment', and the superficial fascia that covers it (*continuous line*), 'saphenous fascia'. The *interrupted line* follows the muscular fascia, the *dotted line* underlines a type of vein ligament that fixes the GSV inside the compartment.

the superficial fascia as an anatomical classification marker had been largely ignored until DUS became an established tool for venous investigation of leg vein anatomy.[29]

It was proposed to name the interfascial compartment in which the GSV runs the 'saphenous compartment', and the superficial fascia that covers it, 'saphenous fascia' (Fig. 1.15).[28] The superficial fascia is a marker for distinguishing the two levels of superficial veins. A few constant, and named, superficial veins run through specific intrafascial compartments (intermediated veins), covered by fascial sheet, and belong to the intermediate level. These intrafascial veins are (Fig. 1.16):[3,33]

- the GSV
- the proximal part of the AASV
- the SSV and its thigh extension (Giacomini or femoropopliteal vein)
- the medial and lateral marginal veins of the foot
- the dorsal foot arch.

These veins are longitudinal 'blood transfer' vessels of major importance in understanding varicose hemodynamics. Their position inside the close fibroelastic ensheathing and adventitial anchoring may explain the absence of varicosity in these veins (they enlarge but do not become varicose).[34] A pump mechanism during muscular contraction can also be another explanation, with caliber reduction owing to the fascial compression effect enhancing blood flow[8] (Fig. 1.17); similar, but less efficient to what happens in the deep compartment.

Every vein running superficially to the fascial sheet should be considered a collateral or tributary vein (Fig. 1.18). Its identification is consequently of paramount importance when treatment must be provided in a varicose

condition. Varicose veins typically belong to this superficial layer.[3,8]

With a thorough understanding of this scheme, all possible venous anatomical variations may be correctly understood.[35]

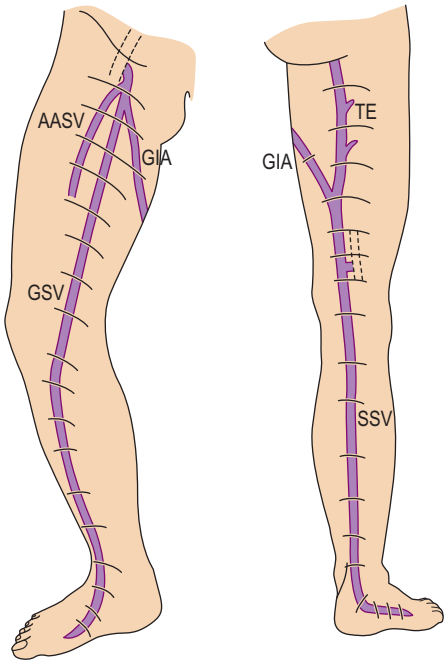

Figure 1.16 The interfascial veins are: the great saphenous vein (GSV), the proximal part of the anterior accessory saphenous vein (AASV), the small saphenous vein (SSV) and its thigh extension (TE) (Giacomini or femoropopliteal vein; GIA), the medial and lateral marginal veins of the foot and the dorsal foot arch. (Ricci S, Georgiev M, Goldman MP. Anatomical bases of ambulatory phlebectomy. In: Goldman MP, Georgiev M, Ricci S, editors. Ambulatory phlebectomy. Boca Raton: Taylor & Francis; 2005.)

DUPLEX ULTRASOUND MARKERS FOR VEIN IDENTIFICATION

The veins of the intermediate level have constant relationships with the surrounding anatomical structures—fascial sheets, muscles, bones, deep vessels—that are easily recognized by DUS and are therefore ultrasound 'markers' for vein identification.[3,33] It is from these markers that the following ultrasound identification signs derive.

THE 'EYE' SIGN

Bailly first described, in 1993, the 'eye' sign as the ultrasound marker for identification of the GSV in the thigh.[29] This sign is due to the superficial fascia being echolucent and easily observed by USI. In transverse scan the compartment in which the GSV runs resembles an Egyptian eye, where the saphenous lumen is the iris, the superficial fasci is the superior eyelid and the aponeurotic fascia the inferior eyelid (see Fig. 1.15). The description of the 'saphenous eye' could well be considered the beginning of ultrasound vein anatomy. The eye sign is always present and allows immediate and certain identification of the saphenous vein and its separation from subcutaneous collaterals running in parallel.

THE 'ALIGNMENT' SIGN

This sign, also suggested by Bailly,[37] helps recognize and distinguish the AASV from the GSV.[36,38] In the upper third of the thigh on transverse scan into the 'eye' there are often two veins instead of one: the GSV and the AASV. The latter lies anterior (lateral) to the GSV[40–42] and is identified by its subfascial position and by the fact that in transverse scan, it lies over (is aligned with) the common femoral vessels (artery and vein) (Fig. 1.19A). In addition to the alignment sign, in some cases the AASV has, in transverse scan, its own 'eye'[8] (Fig. 1.19B). However, it is the alignment sign that

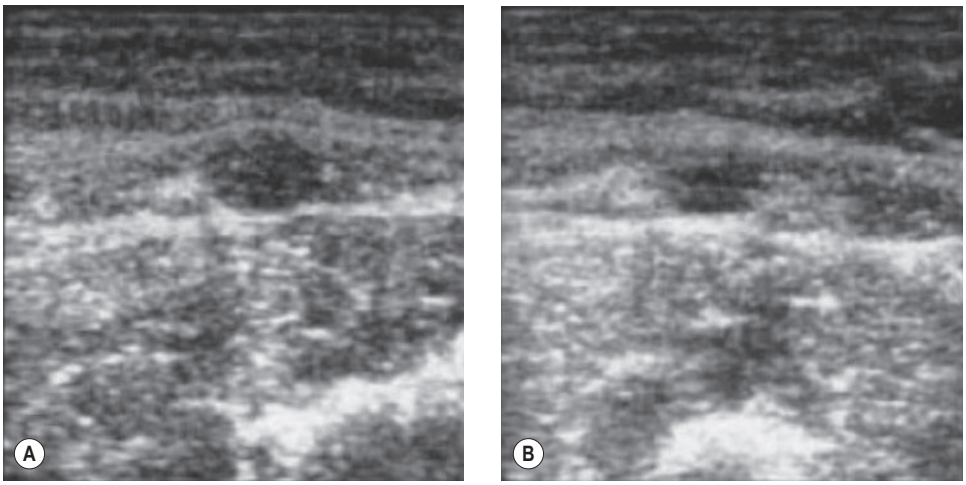

Figure 1.17 The great saphenous vein finds a shelter from its position below the superficial fascia, but also a pump mechanism during muscular contraction can be hypothesized, with caliber reduction owing to the effect of fascial compression enhancing blood flow. (From Franceschi C, Zamboni P. Principles of hemodynamics. New York: Nova Science; 2009. With permission from Nova Science Publishers, Inc.)

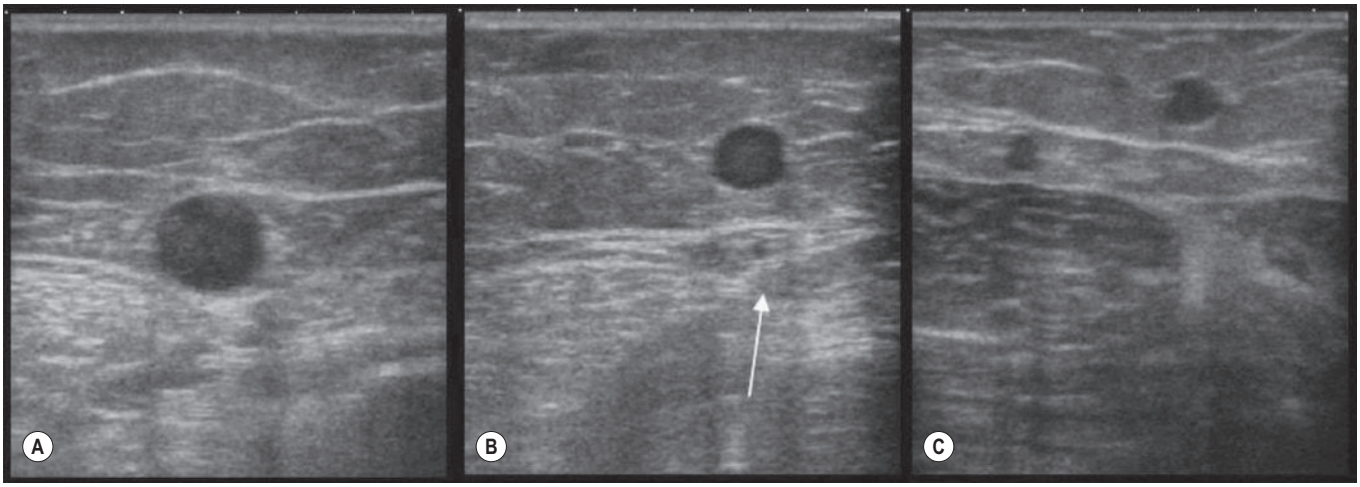

Figure 1.18 **A, C,** Under ultrasound, the apparent 'eye' that can be seen is the great saphenous vein (GSV). In **B** the prevailing vein is outside the compartment and must be classified as a tributary vein, whereas inside the compartment a hypoplastic GSV may be recognized (*arrow*). In **C** two veins are visible but only the one inside the compartment is the GSV.

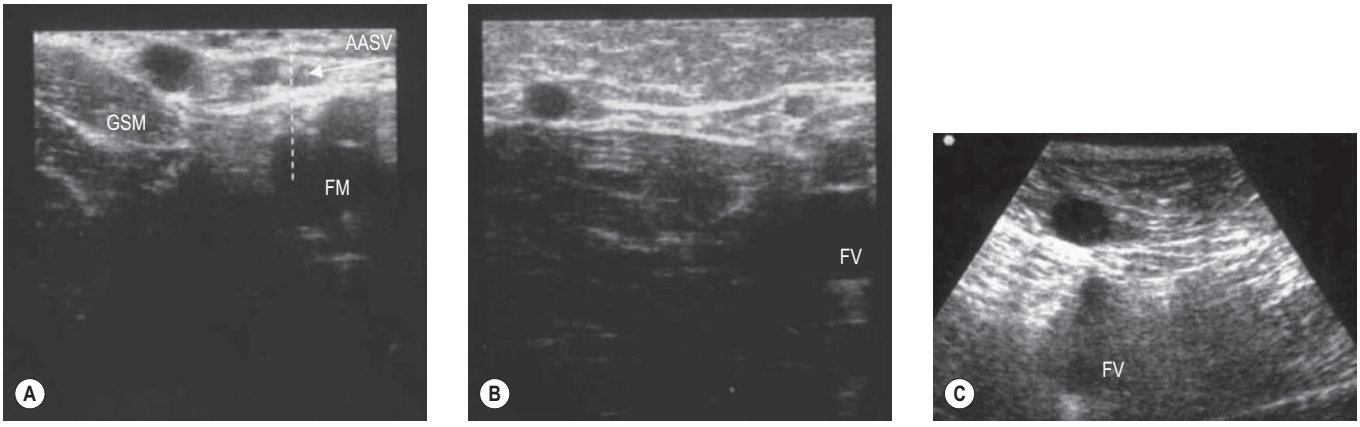

Figure 1.19 **A,** Two veins are present at the (left) groin. The GSV is medially sited, the anterior accessory saphenous vein (AASV) is lateral and aligned over the femoral vessels. **B,** Same as in **A** but more distal. The two veins may have their own separate 'eye'. **C,** Only one vein is present here, but its position over the deep vessels suggests that it is an AASV, while the GSV is not visible (hypoplastic).

shows that in some cases the only vein visible in the 'eye' is the ASV, whereas the GSV is not visible (absent or hypoplastic) (Fig. 1.19C).[38]

THE E POINT SIGN (Fig. 1.20)

The GSV tract crossing the abductor longus muscle, 3–5 cm below the SFJ, before entering the Scarpa triangle area, is relatively superficial, free from tributaries and perforators, covered by an echogenic thick layer of fascia superficialis and lying over a muscle fascia; however, it is very easy to identify. The site corresponding to the most superficial GSV tract has been named 'E (easy) point'. This aspect is very constant; as a consequence the absence of the E point sign (E–) corresponds to GSV aplasia, when the AASV has a prevalence. The E point, specific for the GSV, may be used in parallel to the alignment sign (although independent from AASV presence), with the advantage of being immediately identified simply following the saphenous stem. This particular saphenous vein anatomical reference has been used for office US-assisted GSV preterminal ligation/section.[39]

THE TIBIA-GASTROCNEMIUS ANGLE SIGN

This sign allows one to recognize the GSV below the knee, where fascial sheets are often so close to each other that the intrafascial compartment in which the GSV runs may be difficult to recognize.[36,43] In such cases the GSV is distinguished from other closely running veins by its position, on a transverse scan, in the angle formed by tibial and medial gastrocnemius muscle (Fig. 1.21A, B). This sign allows one to demonstrate, when the angle is empty, that in this area the GSV is absent or hypoplastic (Fig. 1.21C).

THE SMALL SAPHENOUS COMPARTMENT SIGN

The proximal portion of the SSV lies between the medial and lateral heads of gastrocnemius muscle, whereas its frequent thigh extension (TE) lies between the

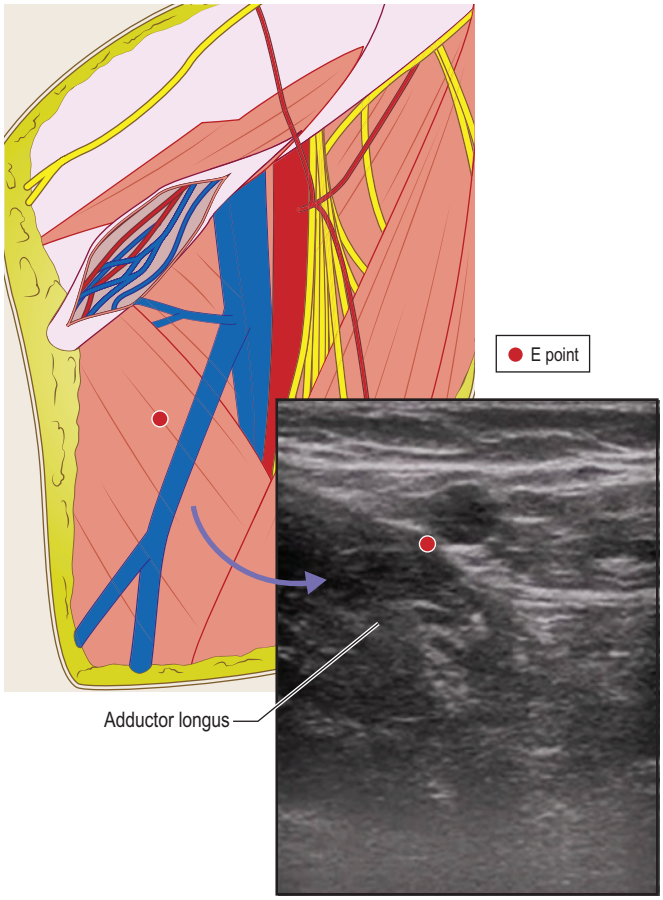

Figure 1.20 **A,** About 3 cm far from the ostium, the great saphenous vein (GSV) lies over the adductor longus muscle, in a point (E point*) free from collateral branches, lymph nodes, nerves, deep veins and arteries. (Modified from: Bardeleben KH, Haeckel E. Atlas of applied (topographical) human anatomy for students and practitioners. New York: Rebman Company; 1906.) **B,** At the E point (*) the GSV lies over the muscle plane and is covered by a clearly visible superficial fascial plane.

semitendinosus muscle (medially) and long head of the biceps muscle (laterally). The intermuscular grooves, along which these two veins run, are covered by a thick fascial sheet and appear as a characteristic triangle-shaped compartment on a transverse scan (Fig. 1.22A, B).[44,45] This triangle-shaped compartment is always present and allows immediate and certain identification of the SSV/TE and distinguishes it from parallel subcutaneous and deep collaterals. Distal to the gastrocnemius muscle the fascial sheet is still present (Fig. 1.22C), albeit less evident as it is thinner as it approaches the ankle and the marginal vein over the foot, indicating that it is the SSV. As for the GSV, it courses inside a specific compartment for its entire length.[3]

RELATIONSHIP BETWEEN SAPHENOUS VEINS AND COLLATERALS

The GSV is often accompanied by parallel veins of different lengths. They can be so large that they can be wrongly confused with the GSV itself or 'double' or duplicate saphenous veins. In fact these parallel veins are collaterals that pierce the superficial fascia to get out of the saphenous compartment and run subcutaneously at a more superficial level than the GSV (Fig. 1.23).[3,28,35] The relationship between the saphenous trunk and these subcutaneous collaterals could be schematized into three anatomical patterns with specific ultrasound appearance[46] (Fig. 1.24):

- Type I: The saphenous trunk is present, in full size and for its complete length in the saphenous compartment, and there are no large parallel collaterals.
- Type h: The saphenous trunk is present for its complete length, and there is also a large (even larger) collateral.
- Type S: The saphenous trunk pierces the superficial fascia and continues as superficial collateral, while distal to this point the saphenous trunk is either not at all or only barely visible on DUS (absent or hypoplastic).

GREAT SAPHENOUS VEIN

The GSV begins anterior to the medial malleolus as the continuation of the medial marginal foot vein and then ascends along the medial aspect of the tibia and thigh to empty into the common femoral vein in the groin. The GSV lies for its entire length (Fig. 1.25) in a compartment delimited by the aponeurotic and the superficial (saphenous) fascia. On transverse scan this compartment appears as an 'eye' (see Fig. 1.15).[3,28,29,33,35,36] This 'eye' is readily visible in the thigh, but may be difficult to recognize in very thin subjects, and in some areas such as the knee and ankle.[43]

SAPHENOFEMORAL JUNCTION

Situated at the level of the groin crease, the SFJ is covered by the superficial fascia that ends proximal to the inguinal ligament.

The GSV has a constant (terminal or ostial) valve, which is usually clearly visible at its junction (although separated by 1–2 mm from the ostium) with the femoral vein. Another valve (preterminal valve) can be found about 2 cm distal to it, at the distal border of the SFJ area. Between the two valves the GSV is joined by constant tributaries, divided into proximal and distal (Fig. 1.26).[3,47]

The proximal collaterals are, from lateral to medial: the superficial iliac vein, superficial epigastric vein and superficial pudendal vein. They may have different individual anatomical arrangements. They drain venous blood from the abdominal wall and pudendal areas. Their clinical importance is relevant when they feed a retrograde flow of the GSV in the presence of a competent terminal valve. This situation has been reported in 28% to 52% of cases of GSV reflux[48] (Fig. 1.27) and may preclude the need for direct GSV treatment in many cases.

The superficial external pudendal artery (immediately identified by color duplex) is intimately associated with the GSV at the SFJ, where it may bifurcate to enclose the GSV (Fig. 1.28).

The distal collaterals, lateral and medial, may be relatively large. The lateral collateral—the AASV—is present in 40% of subjects as a clearly distinguished vein (see Fig. 1.19B). In most cases the AASV joins the GSV within 1 cm of the SFJ, and there is typically a lymph node in the angle

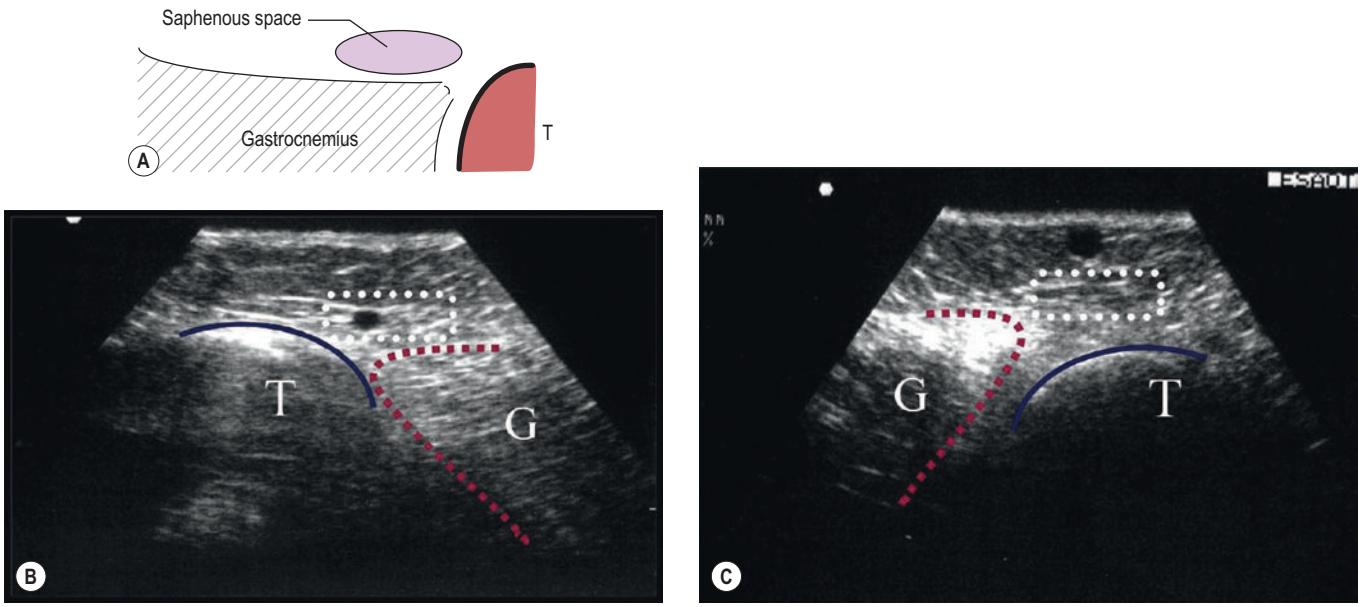

Figure 1.21 **A,** At the knee level the saphenous space is very narrow and can be identified in the angle between the tibia and the gastrocnemius (T-G angle). **B,** The vein inside the T-G angle is the great saphenous vein (GSV). **C,** If the T-G angle is empty, we can say that the GSV is hypoplastic and that a tributary has prevailed. (From Ricci S, Georgiev M. Ultrasound anatomy of the superficial veins of the lower limb. J Vasc Technol 2002;26:183.)

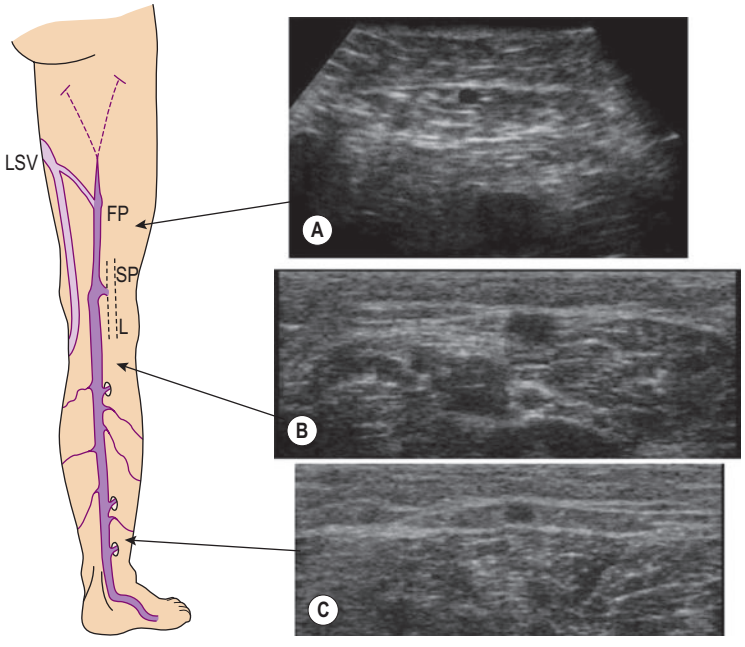

Figure 1.22 The intermuscular grooves along which the small saphenous vein **(B)** and its thigh extension **(A)** run are covered by a thick fascial sheet and appear as a characteristic triangle-shaped compartment on a transverse scan. Distal to the gastrocnemius muscle the fascial sheet is still present **(C)**, although less evident. (Adapted from Cavezzi A, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the superficial veins and perforators in chronic venous disease of the lower limbs, part II: Anatomy. Eur J Vasc Endovasc Surg 2006;31:288.)

between the GSV and the AASV before they merge (see Fig. 1.19A).

The medial collateral joins the GSV at a variable distance from the SFJ, often distal to the preterminal valve. The medial collateral may be the continuation of a large vein coming through the posterior thigh from the SSV as the Giacomini vein. The lymph node that is consistently found between the GSV and the AASV merger may have a large and incompetent central vein, sometimes becoming a source of reflux into the thigh and leg varicose veins.[48]

ARRANGEMENT OF THE GSV AND ITS SUBCUTANEOUS COLLATERALS IN THE THIGH

Based on the 'eye' sign, the following anatomical patterns were observed in 610 consecutive limbs with and without varicose veins[3] (Fig. 1.29):

- Single GSV vein running into the saphenous compartment, with no large parallel tributaries = 52% (317/610). Thigh portion of the GSV incompetent in 31% (Fig. 1.29A).

- The GSV divided in two parallel vessels, both running into the saphenous compartment for a length of 3 to 25 cm = 1% (6/610). GSV incompetent in one (17%) (Fig. 1.29B).
- GSV running into the saphenous compartment plus a large subcutaneous collateral that joined the GSV (piercing the fascia) at a variable level in the thigh = 26% (159/610). Proximal portion of the GSV incompetent in 44% with reflux along the collateral (Fig. 1.29C).
- Two veins, the GSV and the AASV, in two separate 'eyes' = 10% (61/610) in the proximal part of the saphenous compartment. An ASV incompetent in 30% with reflux to anterolateral thigh varicose veins (Fig. 1.29D).
- No GSV visible into the distal part of the saphenous compartment. A GSV 'substitute' outside the compartment as a subcutaneous collateral piercing the superficial fascia at a variable level in the thigh and becoming the 'true' GSV = 16% (67/610). Reflux in the GSV and its distal subcutaneous continuation in 45% (see Fig. 1.29E).

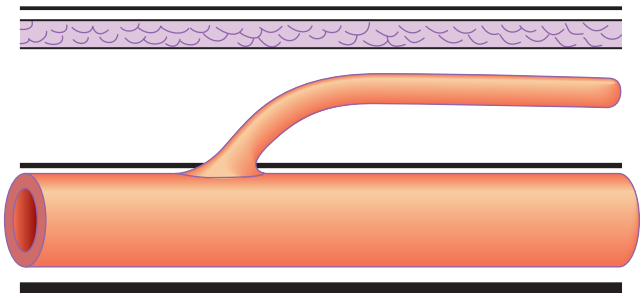

Figure 1.23 The great saphenous vein (GSV) is often accompanied by parallel veins of different length that may be confused with the GSV itself or mistaken for duplicate veins. They are collaterals that pierce the superficial fascia and run subcutaneously at a more superficial level than the GSV.

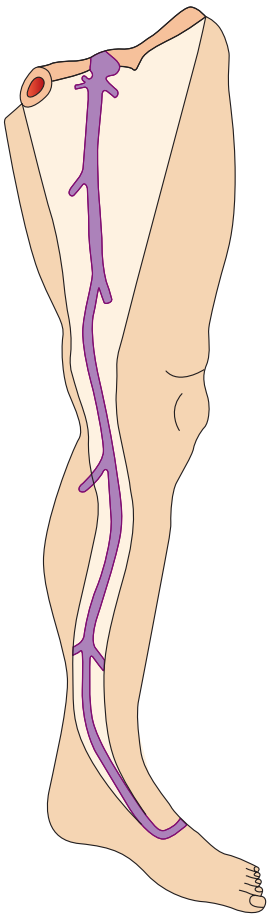

Figure 1.25 The whole length of the great saphenous vein lies within a compartment that is delimited by the aponeurotic and the superficial (saphenous) fascia.

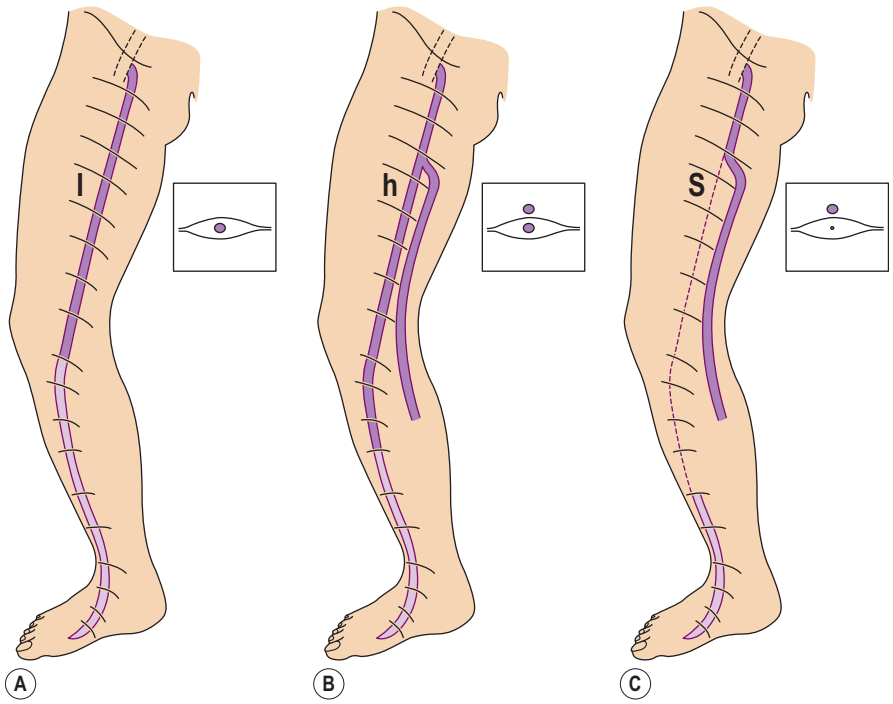

Figure 1.24 The three anatomical types (with specific ultrasound appearance) of relationship between the saphenous trunk and the subcutaneous collaterals. (Ricci S, Georgiev M, Goldman MP. Anatomical bases of ambulatory phlebectomy. In: Goldman MP, Georgiev M, Ricci S, editors. Ambulatory phlebectomy. Boca Raton: Taylor & Francis; 2005.)

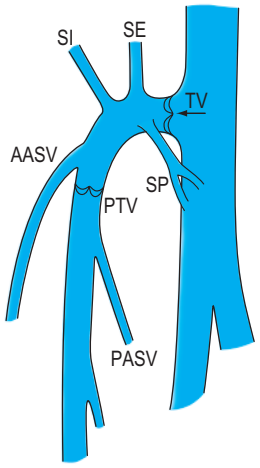

Figure 1.26 The great saphenous vein (GSV) has a constant valve (terminal valve; TV) at its junction (although separated by 1–2 mm from the ostium) with the femoral vein. Another valve (preterminal valve; PTV) can be found at about 2 cm distal to it. Between the two valves, constant tributaries merge—proximal and distal. The proximal collaterals are the superficial iliac (SI) vein, superficial epigastric (SE) vein and superficial pudendal (SP) vein. The distal collaterals are the anterior (AASV) and posterior accessory (PASV) saphenous veins, which may be relatively large. (Original sketch courtesy A Pieri.)

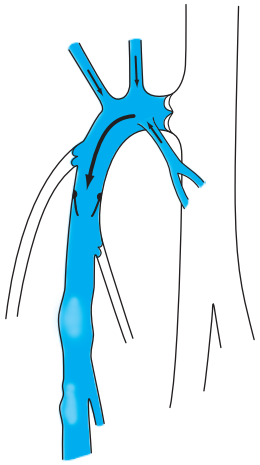

Figure 1.27 Proximal junction collaterals may feed a retrograde flow of the great saphenous vein (GSV) in the presence of a competent terminal valve. (Original sketch courtesy A Pieri.)

ARRANGEMENT OF THE GSV AND ITS SUBCUTANEOUS COLLATERALS AT THE KNEE

At the knee the vein anatomy is sometimes difficult to assess because of the presence of multiple collaterals and perforators clustered into a limited space.[43] In addition, the superficial fascia creating the saphenic eye may be difficult to recognize. However, the GSV can still be identified by its position in the angle formed by the tibia bone and gastrocnemius muscle (T-G angle)[29] (see Fig. 1.21A, B, C).

On transverse scan, and based on this sign, in a series of 500 consecutive limbs with and without varicose veins, the arrangement of the GSV and the collateral veins (CVs) along its middle portion (between the distal third of the thigh and the proximal third of the leg) presented the following patterns (Fig. 1.30):

- Type A: The GSV is present and no large CVs are observed (23% = 112/500). In 15% of these the GSV was incompetent down to the distal third of leg where reflux re-entered into the deep veins via a Cockett or foot perforator(s) (Fig. 1.30A).

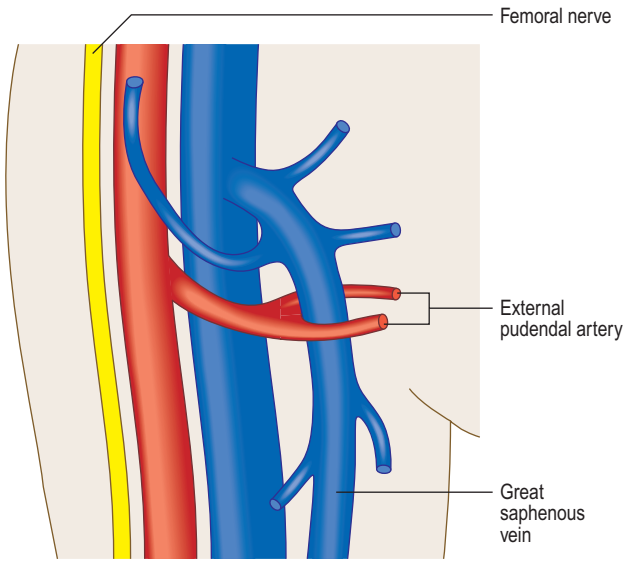

Figure 1.28 Illustration of a possible association of a bifurcated external pudendal artery at the saphenofemoral junction.

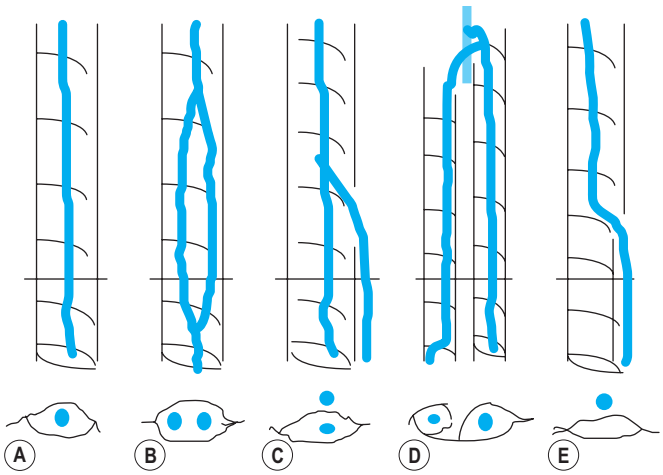

Figure 1.29 **A,** A single great saphenous vein (GSV) running through the saphenous compartment, with no large parallel tributaries. **B,** The GSV divided into two parallel vessels, both running through the saphenous compartment. **C,** The GSV running through the saphenous compartment, plus a large subcutaneous collateral piercing the fascia. **D,** Two veins, the GSV and the anterior accessory saphenous vein, in two separate 'eyes' in the proximal part of the saphenous compartment. **E,** No GSV visible in the distal part of the saphenous compartment, but in the outside compartment in a subcutaneous collateral acting as a GSV substitute pierces the superficial fascia, becoming the 'true' GSV. (From Ricci S, Georgiev M. Ultrasound anatomy of the superficial veins of the lower limb. J Vasc Technol 2002;26:183.)

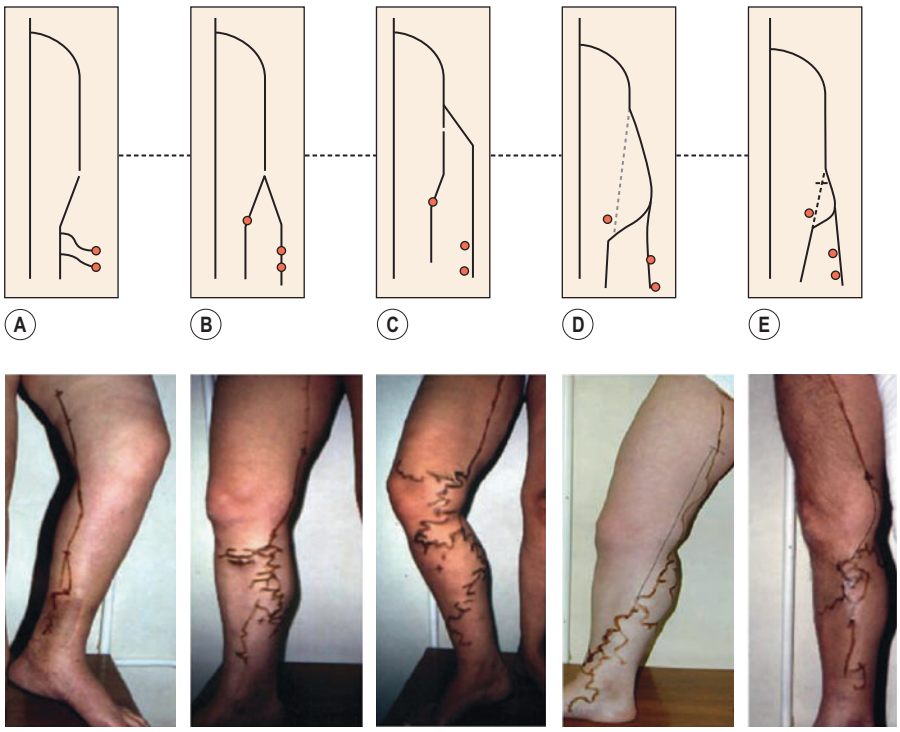

Figure 1.30 The arrangement of the great saphenous vein (GSV) and its collateral veins (CVs). The percentage of incidence in 500 subjects is given in parentheses, below each of the possible varicose vein patterns. **A,** The GSV is present, and no large CVs are observed. There is GSV incompetence down to the distal third of the leg to a Cockett or foot perforator(s). **B,** The GSV is present, with one or more CVs below the knee (posterior arch or Leonardo vein). GSV incompetence shows reflux following the varicose CVs, whereas the portion of the GSV distal to the CV confluence is competent. **C,** The GSV is present with a large CV that begins above the knee. In GSV incompetence the reflux may follow this way, as in **B**. **D,** The GSV is not visible for a certain distance from the distal thigh down below the knee, becoming a subcutaneous CV that distally, at the mid-leg enters again into the saphenous compartment. **E,** Same as **D** but the absent portion of the GSV is very short. (From Ricci S, Georgiev M. Ultrasound anatomy of the superficial veins of the lower limb. J Vasc Technol 2002;26:183.)

- Type B: The GSV is present, but there are also one or more CVs below the knee (27% = 133/500). The most typical example of such CVs is the 'posterior arch' or 'Leonardo' vein. In 53% of these the GSV was incompetent, with reflux following the varicose CV, in most cases, while the portion of the GSV distal to the CV confluence was competent (Fig. 1.30B).
- Type C: The GSV is present but there is also a large CV that begins above the knee (18% = 89/500). In 31% of these the GSV was incompetent. This CV corresponds to Type h in Figure 1.24 (Fig. 1.30C).

In the three patterns described above, the GSV is always present, although it is sometimes smaller than its normal or varicose collaterals. However, in about 30% of cases, the middle portion of the GSV was barely visible or not visible at all (absent or hypoplastic) for a variable length, with the 'missing' portion bypassed by a subcutaneous collateral. This arrangement presents two separate anatomical patterns:

- Type D: The GSV is not visible for a certain distance from the distal thigh down below the knee, but pierces the superficial fascia to become a subcutaneous CV that distally, usually at the mid-leg, enters again into the saphenous compartment. This arrangement corresponds to the 'S' type in Figure 1.24 and was found in 14% = 72/500 of cases. In 58% of these the GSV and the CV were incompetent and the latter visible (Fig. 1.30D).
- Type E: Same as the previous but the absent portion of the GSV was very short and from just below the knee down along the leg; 14% = 72/500. In 53% of these the GSV was incompetent and with varicose collaterals just distal to the knee (Fig. 1.30E).

In 3% of cases (15/500) the classification according to the criteria described before was not possible.

These data show that in one third of subjects, the middle portion of the GSV is absent (or hypoplastic) for a variable length (types D and E). In subjects with this pattern, varicose veins were present in 56% of cases, whereas in subjects where the GSV is present in its entire length (types A, B and C), varicose veins were present in 34% of cases. This may indicate that the subcutaneous vein that assumes the role of a saphenous vein becomes more readily varicose, probably because it is not protected by the superficial fascia. In such cases the anatomical pattern classified as types D and E might be a predisposing factor for varicose veins.[43]

T VEIN

A very constant tributary vein (known as the T vein), has been described.[49] It runs horizontally from the lateral aspect of the leg just distal to the knee and joins the GSV at the same level at a right angle (see Fig. 1.7), running inside the fascial compartment for a long distance (Fig. 1.31). It is consistently fed by reflux varicose veins, which are clinically visible in the paratibial region and/or in the lateral aspect of the leg.

THE ANTERIOR ACCESSORY SAPHENOUS VEIN

When two veins are present in the proximal third of the great saphenous compartment, the medially situated vein is the GSV whereas the laterally placed vein is the AASV.[33,38–42] The AASV is recognized and distinguished from the GSV by the 'alignment' sign[37] (see Fig. 1.19A), and may also have its own 'eye' (see Fig. 1.19B).[3]

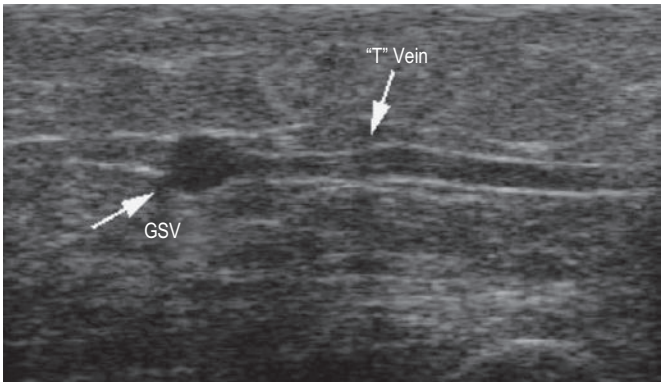

Figure 1.31 A vein can be seen running horizontally from the lateral aspect of the leg just distal to the knee and joining the great saphenous vein (GSV) at the same level at a right angle. What is peculiar is that it runs inside the fascial compartment for a long tract. (From Zamboni P, et al: The 'T' vein of the leg. EJVES 2003;25:313.)

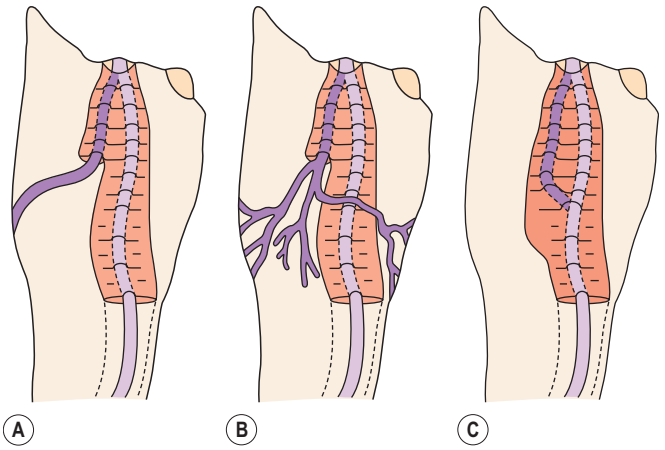

Figure 1.32 Anterior accessory saphenous vein (AASV) patterns: Following the vein backwards, the AASV pierces the superficial fascia of the saphenous compartment at a distance of 7–30 cm. It continues distally as subcutaneous collateral in an anterolateral direction in 72% of cases **(A)**; in a medial or anterior direction in 11%, and as more branches and in more directions in 11% **(B)**. In 6% of cases the AASV joins the great saphenous vein (GSV) without leaving the saphenous compartment **(C)**. (From Ricci S, Georgiev M, Cappelli M. Définition de la veine saphène accessoire antérieure et de son role dans la maladie variqueuse. Phlébologie 2004;57:135.)

The anatomy of the AASV was studied by transverse DUS of the saphenous compartment of the thigh in 172 consecutive limbs. In 48% of cases only the GSV was present, whereas in 41% both GSV and AASV were present. In these cases the AASV was invariably thinner than the GSV (average 2.4 vs 4.0 mm). Proximally, the ASV joined the GSV close to the SFJ and only rarely (in 3% of cases) terminated directly into the femoral vein. Following the vein backwards, the AASV pierced the superficial fascia and exited the saphenous compartment at a distance of 7–30 cm (average 16 cm), continuing distally as a subcutaneous collateral in an anterolateral direction in 72% of cases, in a medial or anterior direction in 11%, and as more branches and in more directions in 11%. In 6% of cases the AASV joined the GSV without leaving the saphenous compartment (Fig. 1.32).[38]

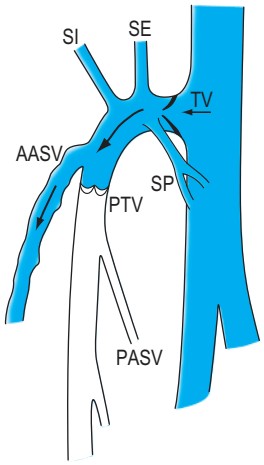

Figure 1.33 The anterior accessory saphenous vein (AASV) may be the only proximal reflux source while the great saphenous vein is competent: in these cases the terminal valve (TV) is incompetent whereas the preterminal valve (PTV) is normally competent. *PASV,* Posterior accessory saphenous vein; *SE,* superficial epigastric vein; *SI,* superficial iliac vein; *SP,* superficial pudendal vein. (Original sketch courtesy A Pieri.)

In the remaining 11% of the 172 observed limbs, only one vein was observed in the proximal part of the saphenous compartment, but according to the 'alignment' sign, this vein was the AASV, while there was no GSV in the expected position (saphenous aplasia—E point sign) (Figs 1.19C, 1.20). In these cases, 18–20 cm distally from the SFJ the AASV curved medially and continued downwards along the typical course of the GSV.[38]

The AASV is of clinical importance because in patients with varicose veins, it may be the only proximal reflux source while the GSV remains competent[3,47] (Fig. 1.33), or alternatively, both GSV and ASV may be incompetent. In a retrospective study of 1450 varicose limbs, the AASV was involved in 14% (203/1450) of cases (M. Cappelli, personal communication, 2000). The possible patterns of GSV and/or AASV incompetence at the SFJ are described elsewhere.[33]

SMALL SAPHENOUS VEIN

The SSV begins behind the lateral malleolus as a continuation of the lateral marginal foot vein. It ascends up the posterior aspect of the calf to empty into the popliteal vein. The SSV lies for its entire length in an intrafascial compartment delimited deeply by the aponeurotic (muscular) fascia and superficially by the superficial fascia. The distal part of this compartment appears on transverse scan, especially in obese legs, as an 'eye' similar to that of the GSV in the thigh. The proximal part of the compartment is typically of a triangular shape and is delimited by the medial and lateral heads of the gastrocnemius muscle and the superficial fascia that stretches over the intermuscular groove (Figs 1.12B, 1.22).[3,36] The SSV may occasionally be duplicated, with two (or even three) veins of various lengths running into the saphenous compartment.

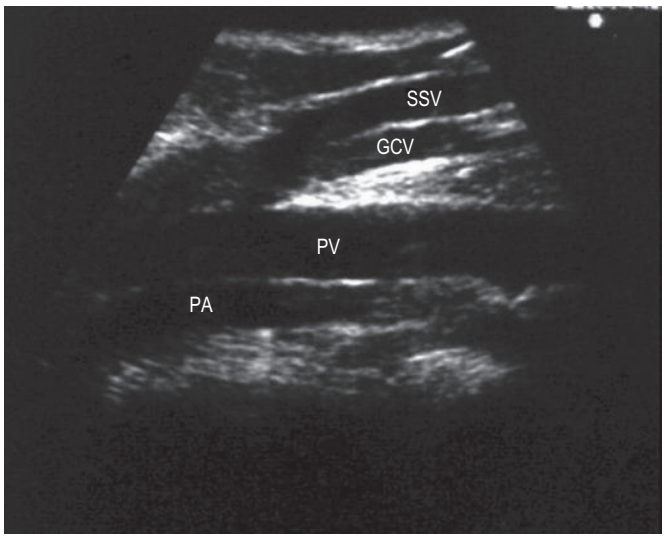

Figure 1.34 In 26% of cases the small saphenous vein merges with the gastrocnemius vein before joining the popliteal vein.

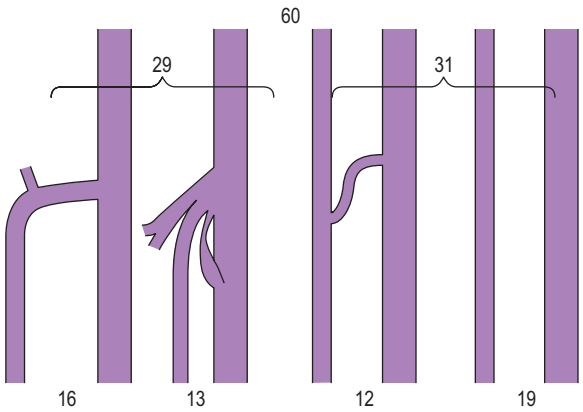

Figure 1.35 In about 50% of normal subjects the small saphenous vein has no popliteal junction at all or is just a tiny communicating vessel (*right*), the classical junction (the first on the *left*) being not the most frequent. (From Van der Stricht J. La petite veine saphène existe-t-elle, Phlébologie 2001;3:309.)

SAPHENOPOPLITEAL JUNCTION

The saphenopopliteal junction (SPJ) is situated, typically, within 5 cm proximal to the popliteal crease. In some cases the SSV merges with the gastrocnemius vein before joining the popliteal vein (Fig. 1.34). This has been found in 26% of cases in a series of 83 consecutive limbs with incompetent and dilated SSV.[50] Another point of surgical interest is that the SSV may join the popliteal vein at different sites on its circumference. In the series mentioned before, the SPJ was lateral in 42%, posteromedial in 30%, posterior in 15%, posterolateral in 12% and even anterolateral in 1% of cases.[50] Astonishingly, in normal subjects it has been observed that in about 50% of cases the SSV has no popliteal junction at all (see next paragraph), or is just a tiny vessel (Fig. 1.35).[51] In some cases, the SSV may be hypoplasic or absent.

THIGH EXTENSION OF THE SSV

In 1873 Giacomini described in detail the thigh extension (TE) of the SSV (Fig. 1.36).[52,53] Further anatomical dissections confirmed that the SSV extends into the thigh in about 50% of cases; in a third of these the SSV joins the popliteal vein (Fig. 1.37A) and then continues up into the thigh, whereas in the remaining two thirds of cases the SSV continues into the thigh without any connection with the popliteal vein[54] (see Figs 1.35, 1.37B). The anatomy of the TE of the SSV (also known as vein of Giacomini or femoropopliteal vein) has been confirmed by USI. The distal portion of the TE is recognized on DUS by its intrafascial position into a triangle-shaped compartment that resembles the GSV compartment and is delimited by the semitendinous muscle (medially), the long head of the biceps muscle (laterally) and the superficial fascia that stretches over the intermuscular groove (see Figs 1.9, 1.16, 1.22A). Proximally, the TE may join the GSV at various distances from the SFJ as intersaphenous thigh anastomosis (the 'true' Giacomini vein); continue straight up into the gluteal area as a single vein or be divided into many deep and superficial branches; join the deep femoral veins as a posterior or posterolateral thigh perforator; or divide into many muscular or subcutaneous branches of the posterior thigh. In many cases the proximal ending of the TE is a combination of the terminations mentioned before. The possible variants of proximal termination of the TE are presented in Figure 1.36. The

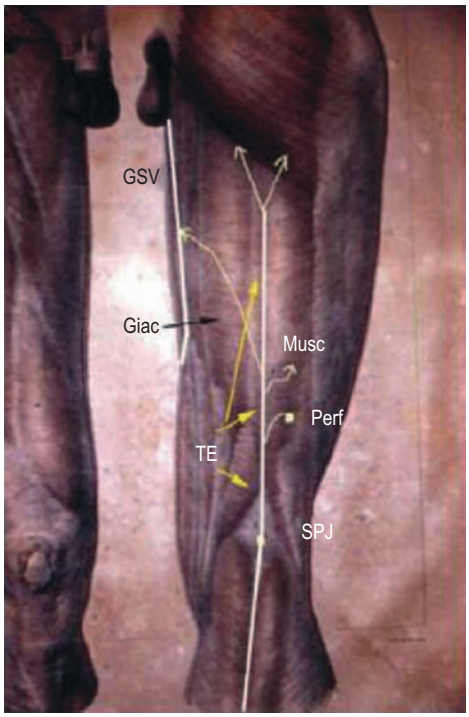

Figure 1.36 Proximally the thigh extension may join the great saphenous vein as intersaphenous thigh anastomosis (the 'true' Giacomini vein); continue straight up into the gluteal area as a single vein or be divided into many deep and superficial branches; join the deep femoral veins as a posterior or posterolateral thigh perforator; or divide into many muscular or subcutaneous branches of the posterior thigh. (From a design taken from Bourgery, Anatomie descriptive. In Delaunay CA, editor, [no title available] Paris, 1835. Courtesy M. Georgiev, MD.)

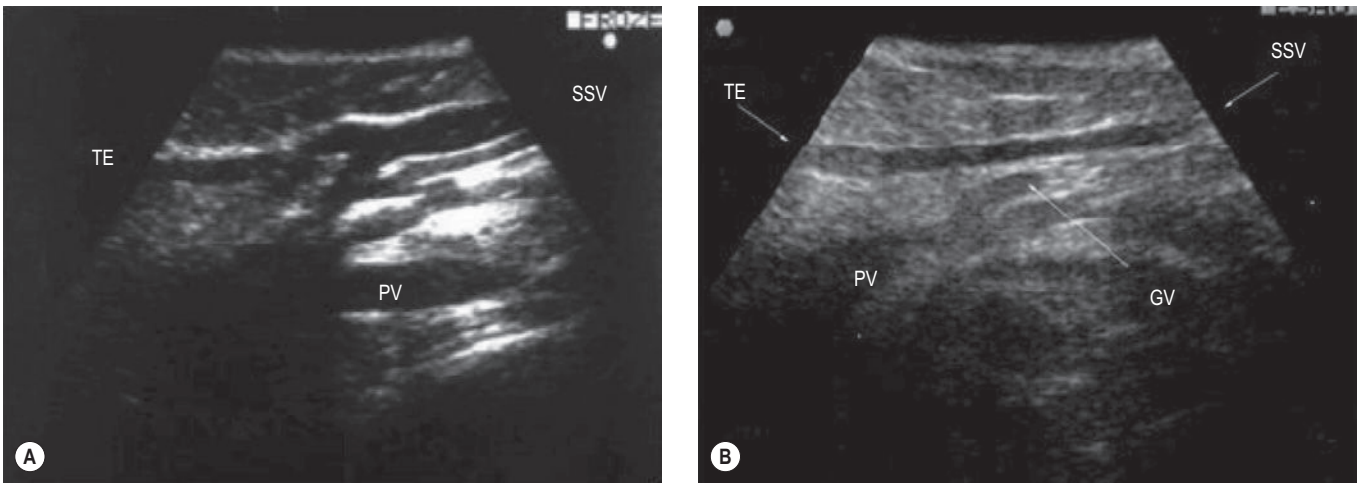

Figure 1.37 Ultrasound imaging aspects of small saphenous vein (SSV)–popliteal arrangement. **A,** The SSV extends into the thigh in about 50% of cases; in one third of these the SSV joins the popliteal vein and then continues up into the thigh **(B)**, whereas in the remaining two thirds of cases the SSV continues into the thigh without any connection with the popliteal vein (PV). *TE,* Thigh extension.

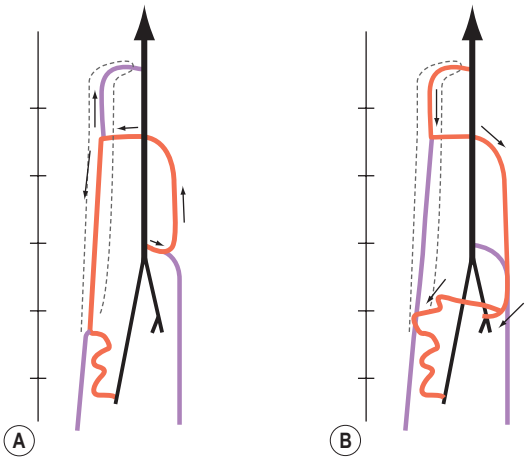

Figure 1.38 The thigh extension may transmit reflux from the incompetent saphenopopliteal junction up to the great saphenous vein and/or varicose veins of the thigh **(A)**, or vice versa, from the incompetent saphenofemoral junction and/or groin, to the small saphenous vein (SSV) **(B)**.

TE may transmit reflux from the incompetent SFJ and/or groin, gluteal and thigh perforators and/or collaterals to the SSV, or, vice versa, from the incompetent SPJ up to the GSV and/or varicose veins of the posterior thigh (Fig. 1.38A, B).[3,33]

ARRANGEMENT OF THE SSV AND ITS COLLATERALS

As with the GSV the subcutaneous collaterals of the SSV/TE are recognized because they pierce the superficial fascia to enter the saphenous compartment. One particular superficial collateral of the SSV deserves separate description. It is the so-called 'popliteal area vein' and was described by Dodd.[55] This vein runs subcutaneously along the posterior aspect of popliteal area, calf and leg, sometimes parallel to the SSV, and typically has a separate junction with the popliteal vein, usually lateral to the SPJ (Fig. 1.39).[3,56]

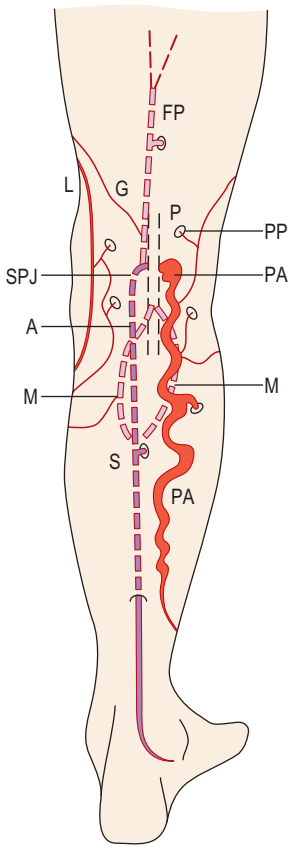

Figure 1.39 The so-called 'popliteal area vein' runs subcutaneously along the posterior aspect of popliteal area, calf and leg, sometimes parallel to the small saphenous vein, and typically has a separate junction with the popliteal vein, usually lateral to the saphenopopliteal junction (SPJ). (Adapted from Ricci S, Georgiev M, Goldman MP. Anatomical bases of ambulatory phlebectomy. In: Goldman MP, Georgiev M, Ricci S, editors. Ambulatory phlebectomy. Boca Raton: Taylor & Francis; 2005.)

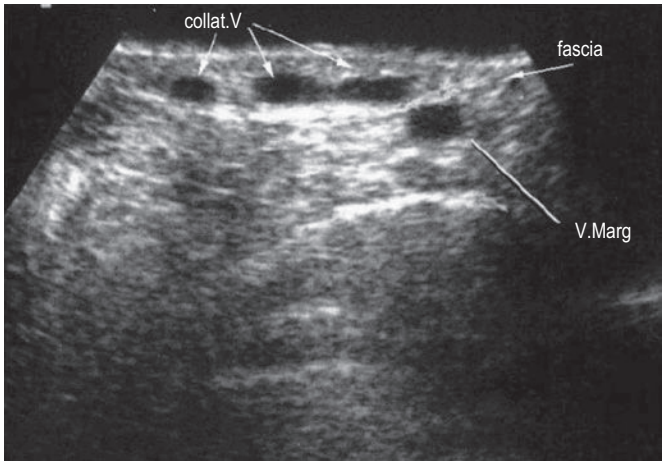

Figure 1.40 The dorsal venous arch and the medial and lateral marginal veins (V. Marg) (anatomic origin of the great and small saphenous veins) are similarly placed under the superficial fascia whereas the tributaries run more superficially (collat. V).

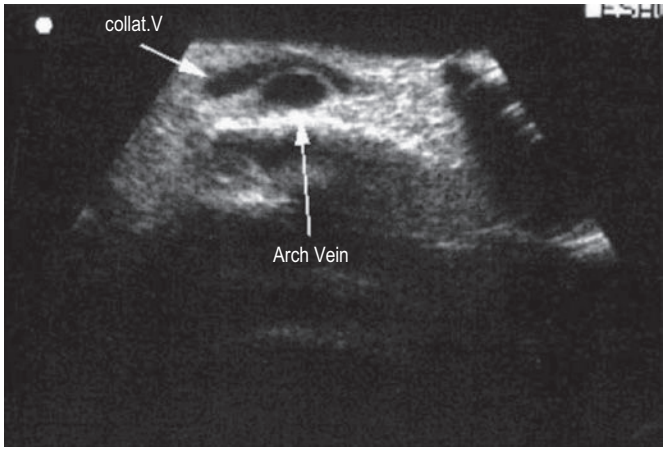

Figure 1.41 The collateral veins on dorsum of foot are the continuation of the subcutaneous collaterals of the leg and are also subcutaneous, overcoming the deeper arch vein.

FOOT VEINS

The arrangement of the superficial veins in two layers separated by the superficial fascia is also present in the foot and can be demonstrated by DUS. The dorsal venous arch and the medial and lateral marginal veins are the anatomical origin of the great and small saphenous veins, respectively, and are similarly placed under the superficial fascia (Fig. 1.40). The collateral veins on the dorsum of the foot are the continuation of the subcutaneous collaterals of the leg and are also subcutaneous (Fig. 1.41).[57]

PERFORATING VEINS

Perforating veins were first described in 1803 by von Loder.[58,59] They occur from the ankle to the groin, connecting the superficial veins to the deep veins; they 'perforate' the aponeurotic fascia, giving them their name. The fascial point of perforation is always visible with USI (Fig. 1.42).

The average number of perforating veins per leg has been found to be as great as 155[60] or as few as 64.[61] They are not distributed regularly along the limb's surface but increase in density from proximal to distal in a 1:2:8 proportion between the thigh, the leg, and the foot.[62]

Sixty percent of perforating veins, always the ones that are more important and named, are accompanied by an artery[60] (Fig. 1.43); and usually contain one to three one-way valves, depending on their length (see Fig. 1.42). These one-way valves can be thought of as check valves, which serve to prevent high venous pressure (from muscle contraction) from being transmitted to the superficial veins. Normally, perforating veins are thin walled, varying in diameter from less than 1 mm to 2 mm.[63] They may also be valveless, especially when less than 1 mm in diameter.[64] In such cases, their competence is maintained by their oblique orientation through muscle, or by the 'S' shape that they display (Fig. 1.44).

With muscular contraction, the deep fascia is tightened and the S curves are compressed. This puts the perforator

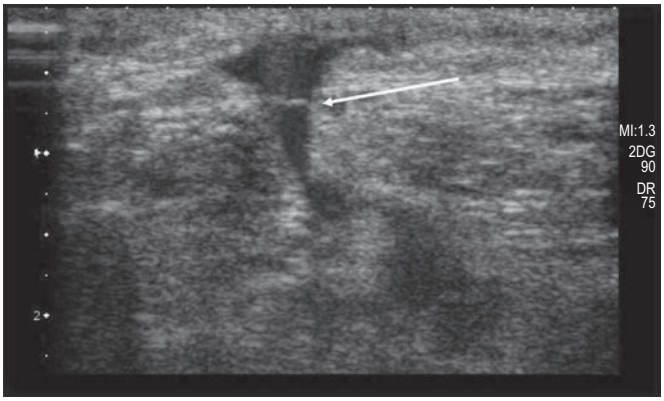

Figure 1.42 Perforating veins connect the superficial veins to the deep veins; they 'perforate' the aponeurotic fascia, giving them their name. The fascial point of perforation is always visible with ultrasound. Also, valves are visible, usually at the level of the fascial hole (*arrow*).

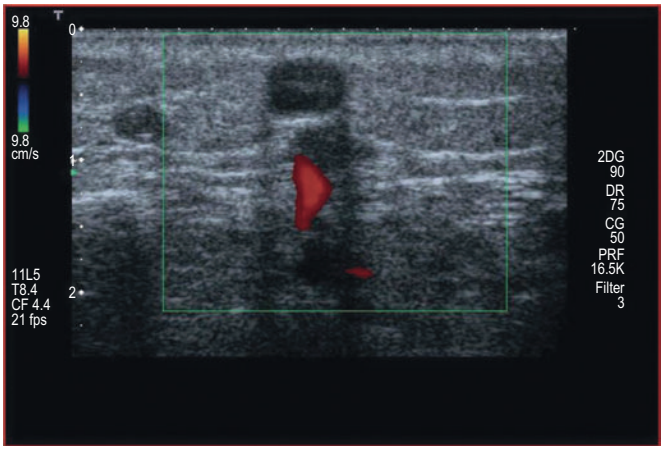

Figure 1.43 Perforators are usually accompanied by an artery easily visible by duplex and color ultrasound.

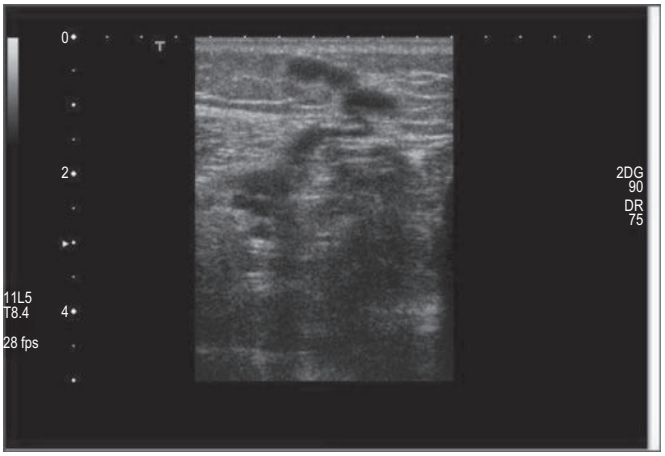

Figure 1.44 The 'S' shape of normal perforators is a mechanism helping to achieve competence.

veins under tension, closes the vein and prevents blood from escaping from the deep veins of the calf muscle pump into the superficial veins. Although variable in location, a number of perforating veins occur with marked regularity (Table 1.2).

Paratibial perforators connect the main trunk or tributaries of the GSV with the posterior tibial veins and course close to the medial surface of the tibia. These correspond to the so-called Sherman perforator vein (at the lower and mid leg) and Boyd perforating vein (at the upper leg). Posterior tibial perforators connect the posterior accessory GSV with the posterior tibial veins. These correspond to the so-called Cockett perforating vein, named first, second and third. As described by Frank Cockett, they can be indicated topographically as upper, middle and lower.

The most important perforators in the thigh are known as the Hunterian and the Dodd perforator(s), which are located in the medial thigh. These connect the GSV to the femoral vein in the middle third of the medial thigh (Hunterian) and the lower third of the thigh (Dodd).[65] Incompetence of the mid-thigh (Hunterian) perforator is a common cause for medial thigh varicose veins in patients with a competent SFJ.

Perforating veins have also been described in the foot. Raivio[66] has documented more than 40. One is situated about 2.5 cm below the inferior tip of the medial malleolus. A second occurs approximately 3.5 cm below and anterior to the medial malleolus. The other two are on an arc approximately 3 cm anterior to and below the medial malleolus. Perforating veins in the foot are valveless or have one-way valves that are reversed to allow blood to flow from the deep to the superficial veins.[67] The great number of perforating veins and venous anastomoses of the foot allows for their safe removal.

Table 1.2 Distribution of Incompetent Perforator Veins on 901 Lower Limbs

	Percentage of Limbs with Incompetent Veins	
Perforator Veins	**Right Limbs**	**Left Limbs**
Saphenofemoral junction	100.00	100.00
Saphenopopliteal junction	15.0	15.5
Mid-Hunterian perforator	7.0	6.7
Genicular perforator	2.9	1.6
Lateral thigh perforators	1.8	1.3
13.5-cm mid-calf Cockett	15.9	17.3
18.5-cm mid-calf Cockett	34.3	35.2
24-cm mid-calf Cockett	20.0	19.6
30-cm mid-calf Cockett	13.0	12.7
35-cm mid-calf Cockett	6.6	7.0
40-cm mid-calf Cockett	4.2	3.1
Calf perforators (other)	12.0	11.2
Gastrocnemius/peroneal muscle perforator	25.0	24.0
Anterior tibialis/peroneal perforator	3.1	2.9
Lateral tibial perforators	0.02	0.04
Lateral foot perforators	2.0	2.4
Medial foot perforators	3.5	2.9

Modified from Sherman RS. Ann Surg 1949;130:218.

VENOUS VALVULAR SYSTEM

Fabricius of Aquapendente (1533–1620) is credited with being the first to detail the anatomy of veins and their valves, in Padua in 1579. He suggested that valves '… insure a fair distribution of the blood … prevent distention … and stop blood from flooding into the limb …'.[68] However, a more recent historical review credits the Parisian Charles Estienne with mentioning venous valves in 1545 and Lusitanus and Cannano publicly demonstrating valves in Ferrera, Italy in 1555.[69]

The valves appear as translucent, thin structures that vibrate with blood flow. Numerous bicuspid valves appear down to vein diameters less than 100 micrometers (μm).[70] Recent studies demonstrate valves in venules as small as 40 μm in diameter.[71,72]

Studies of the embryologic development of veins show that the number of venous valves decreases in utero with fetal maturity. It has been suggested that this disappearance continues, albeit at a reduced but variable rate, during childhood, adolescence and adult life.[73,74]

A morphologic study of normal saphenous veins removed from cadavers has revealed an average of 8.7 valves, with 6.3 of these appearing above the knee and 2.4 below the knee.[75] Aging in itself does not appear to decrease the number of venous valves of the leg, nor does the number of venous valves appear to differ between men and women.[76]

The number of venous valves has been found to be fewer in varicose veins than in normal veins. Valvular insufficiency occurs in undamaged valves as well as damaged valves. Competent venous valves withstand pressures of up to 3 atmospheres.[77] Therefore, for incompetence to occur, the valve annulus dilates to render the valves incompetent. This observation is supported by investigations that reveal no difference in viscoelastic behavior in perivalvular vein wall tissue.[78] Chronic venous dilation may lead to sclerosis. It is postulated that this is caused by turbulent blood flow.[79] However, sinus wall and valvular defects have been found in autopsy studies in up to 90% of adults without apparent

varicosities.[80] Therefore, valve and valvular sinus abnormalities, at best, comprise only one factor in the development of varicose veins. A full explanation of the pathophysiologic significance of valvular deficiency and dysfunction is addressed in Chapter 3.

NERVES OF THE LEG OF PHLEBOLOGIC INTEREST

The sural nerve (SuN) and the saphenous nerve (SaN) are interesting in varicose vein treatment because of their proximity to the SSV and the GSV at the leg, respectively.

The SuN, running along the SSV, is formed by two different branches merging at different leg levels to form the definitive nerve. The tibial branch (nervus cutaneus medialis surae; NCMS) branches from the tibial nerve at the popliteal fossa and runs parallel to the SSV in the groove of the gastrocnemius muscles, ventrally and outside the SSV compartment. Generally at the middle third of the calf (but with large variations), it meets the peroneal branch of the SuN and enters the saphenous compartment, coming in straight contact with the SSV, extending down to the foot.

The peroneal branch of the SuN (nervus cutaneus lateralis surae; NCLS) originates from the common peroneal nerve. This nerve comes down laterally to the popliteal fossa along the biceps femoris muscle to the head of peroneus. During this course, it sends a 'communicating branch', the NCLS, directed distally and medially, to join the NCMS to complete the SuN (Fig. 1.45).

This typical anatomical arrangement (Fig. 1.46) has great variations. The two branches can run independently.[81] The point of contact with the SSV may be found by DUS at different levels of the calf. This point has been called the 'risk point' because possible nerve injury during varicose vein treatments[82] is more probable from this point distally.[83] The SaN takes origin from the femoral nerve 2 cm below the inguinal ligament, comes down along the adductor canal following the femoral artery, continues behind the sartorius muscle, becoming superficial at the knee where it runs between the sartorius and gracilis muscle tendons. At this point the nerve is visible by DUS behind the GSV and in deeper position. Progressively the SaN becomes superficial and runs anterior to the GSV, coming in close contact with the vein (Fig. 1.47) at about 2–3 cm below and medial to the tibial tuberosity. From this point down, the nerve follows the GSV extending to the foot. It is also possible to identify the 'risk point' for the SaN (Fig. 1.48).[84–87]

HISTOLOGY

VEIN WALLS

The first part of the venous system consists of the venule, which serves as a collecting tube for capillaries. The cutaneous microcirculation is organized as two horizontal plexuses. One is situated 1–1.5 mm below the skin surface. The

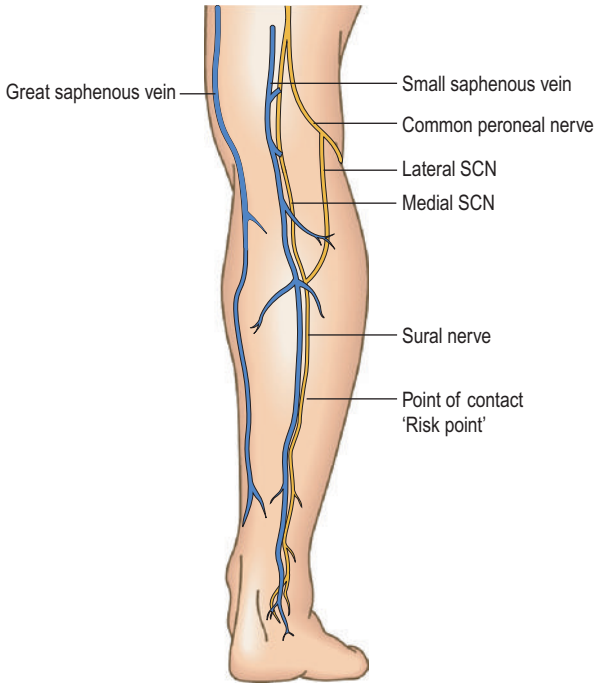

Figure 1.45 The sural nerve is formed by two branches, one coming from the tibial nerve (TN), the medial sural cutaneous nerve (Medial SCN), the other coming from the common peroneal nerve, the lateral sural cutaneous nerve (Lateral SCN). Both form the sural nerve that runs in close contact with the distal small saphenous vein.

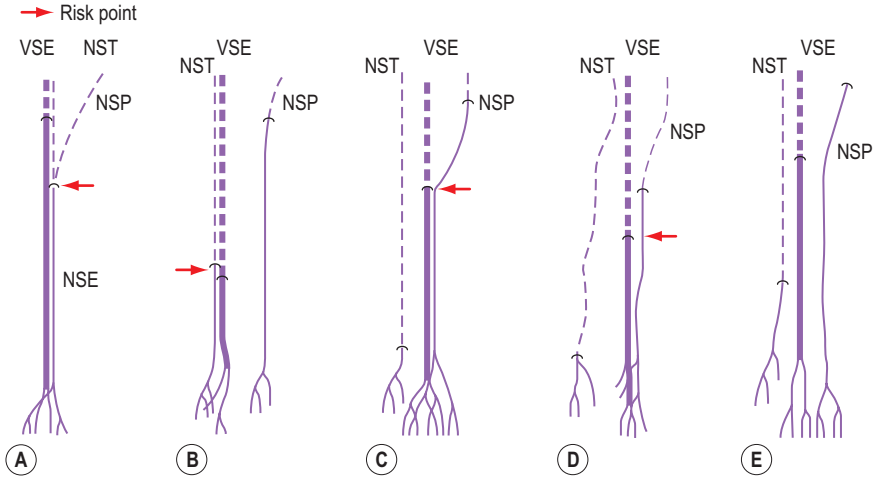

Figure 1.46 Different anatomical combinations of the two branches of the sural nerve and different levels of nerve-to-vein contact ('risk point'). *NSE,* Sural nerve; *NSP,* lateral sural cutaneous nerve; *NST,* medial sural cutaneous nerve; VSE = SSV). (Adapted from Payen B. Rappel anatomique de la veine saphène externe. Phlébologie 1985;38:453.)

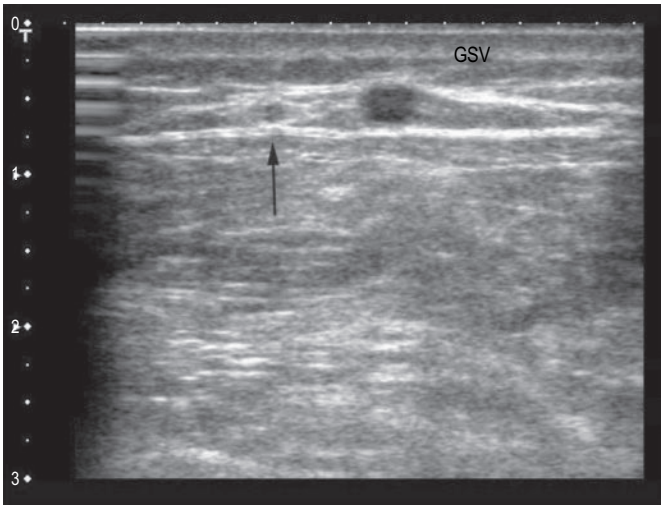

Figure 1.47 The saphenous nerve, initially in a deeper position, becomes superficial and anterior to the GSV, coming in close contact with the vein ('risk point') at about 2–3 cm below and medial to the tibial tuberosity. The nerve is visible using ultrasound with a high frequency probe (12–18 MHz).

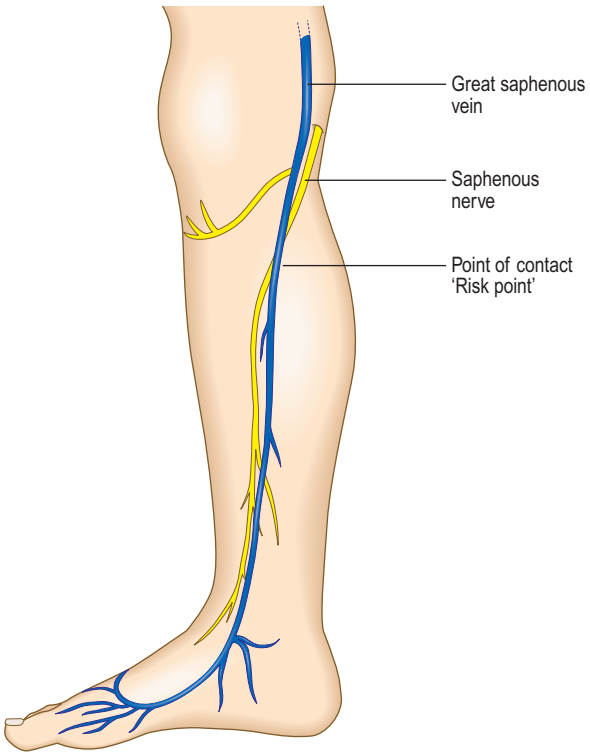

Figure 1.48 Intimate association of the saphenous nerve with the great saphenous vein below the knee joint. The saphenous nerve originates from the femoral nerve, follows the femoral artery in the adductor canal, becomes superficial at the knee passing between the sartorius and gracilis muscle tendons, getting in close contact with the great saphenous vein (GSV). From this point down, the nerve follows the GSV until it reaches the foot. It is also possible to identify the 'risk point' for the saphenous nerve.

other is at the dermal subcutaneous junction. Arterioles ascending into these layers and venules descending are paired while they connect the two plexuses. The arterial capillaries form dermal papillary loops and at the dermal subcutaneous junction collecting veins contain bicuspid valves oriented to prevent retrograde flow of blood.[88] The venule is approximately 20 µm in diameter and consists of an endothelium surrounded by a fibrous tissue composed of a thin layer of collagenous fibers. The venule increases in diameter, with smooth muscle cells appearing within the fibrous sheath when the diameter is approximately 45 µm. At a diameter of 200 µm, the muscular layer becomes better defined. At a clinically recognizable diameter consistent with small phlebectasia (venectasia), the vessels are composed of a thick media with myocytes. Collagenous fibers are clearly organized into bundles, and elastic fibers can be observed.[89] Larger diameters contain elastic fibers and a more organized structure.

Telangiectasias commonly seen in the skin of lower extremities can be explained by abnormalities in the organization and ultrastructure of the cutaneous microvasculature rather than by neovascularization. The telangiectasias seen in essential telangiectasia and in scleroderma are clearly a dilation of the postcapillary venules of the upper horizontal plexus.[90]

Microscopically, the normal young internal saphenous vein is a musculofibrous conduit with both passive and active functions. The normal vein is slightly oval, with the short axis perpendicular to the skin. In response to an increase in intraluminal pressure, the diameter increases and the vein loses its oval appearance. Veins tend to assume an elliptical shape, particularly at low transmural pressures. These qualities of shape deformability allow veins to change volume with very little force, thus aiding their role as a high-capacitance system.[91,92] With continued increases in venous pressure or progression of varicose disease, the vein increases in both length and diameter and becomes tortuous. Whether normal or varicose, the saphenous vein is composed of three tunics: intima, media and adventitia.

The *intima* is a thin structure consisting of a layer of endothelial cells and a deep fenestrated basement membrane bounded by a thin, fragmented elastic lamina.[93] The central portion of the cell containing the nucleus bulges into the lumen and, on its free surface, exhibits multiple small microvilli. Although endothelial cells are easily destroyed by chemical and physical insults, they demonstrate a marked capacity for regeneration.[94]

The *media* is composed of three layers of muscle bundles. The inner layer consists of small bundles of longitudinally arranged muscle fibers. Loose connective tissue and small elastic fibrils separate the muscle bundles.[93] The middle layer is composed of wide bundles of smooth muscle in a circular orientation. The muscle bundles may be separated by thin or thick layers of elastic fibrils.[93] In addition, the outer layer is quite variable, being composed of longitudinal muscle bundles spread out through thick fibrous tissue. The outermost cells of the circular layer interdigitate with the innermost cells of the longitudinal layer to improve contractile efficiency.[95]

The amount of muscle within the vein wall is not uniform throughout the venous system. There is an increasing smooth muscle content from the proximal to the distal and

the deep to the superficial veins.[96] The obvious functional importance is to counteract hydrostatic pressure. In addition, the greatest extent of circular muscle occurs at the level of insertion of the valve leaflets. This composition helps to prevent valvular dilation and incompetence and is the last region to dilate in a varicose vein.[97] This area is known to be dilated in primary valvular insufficiency.

The *adventitia* is the thickest portion of the vein wall. It is primarily composed of collagen, with interlacing fibers oriented in longitudinal, spiral and circular fashions.[94] In larger vessels of the thigh, a considerable network of elastic fibers occurs and stretches from valve to valve.[98] The collagen layer merges with the perivenous connective tissue and contains the vasa vasorum and adrenergic nerve fibers.[99,100] The vasa vasorum provides the arteriovenous circulation in the wall of the blood vessel. These vessels arise as branches from arterioles present in perivenous connective tissue that are fed by neighboring arteries.[101] Venous capillaries of the vasa vasorum form venules that empty into veins running in the loose perivenous connective tissue. As discussed in Chapter 3, alterations of the vasa vasorum may lead to the development of arteriovenous fistulas.

VENOUS VALVES

Venous valves are composed of a thin layer of collagen and a variable amount of smooth muscle covered on both surfaces by endothelium.[102] An increase in muscle fibers is found at the base of the valve cusp running circumferentially and longitudinally for a variable distance along the length of the valve cusp.[97,103] Elastic fibers extend along the whole length of the cusp and lie close to the endothelium. Collagen fibers are concentrated at the base, thinning out toward the free edge of the cusp. The valve is avascular and thus dependent on humeral blood for its oxygen supply.[104,105]

Fegan[98] proposes that the muscle fibers play an active role in regulating blood flow. Through an evaluation of anatomical dissection of multiple valves, he believes that contraction of the circular muscles at the base of the valve reduces the vein diameter, and contraction of the longitudinal fibers shortens and thickens the cusp. This type of coordinated muscle action maintains tone in the vein wall in the face of increased pressure from retrograde blood flow.

The valve cusp changes with age.[106] In the parietal layer, collagen becomes thicker and denser with an increase in the elastic lamellae. The luminalis develops deep, narrow depressions. The vein wall at the valve sinus thickens with an increase in adipose tissue, muscle cells and connective tissue. These changes produce less flexibility of the valve cusp, which may produce abnormal blood flow currents and eddies that could lead to valvular incompetence.

VEIN WALL VARIATION

The composition of vein walls varies with the type and location of the veins. Depending on their location, veins assume many different functions, and the muscular content of the vein wall varies accordingly. They are used as pumps and reservoirs and must withstand variations in gravitational and intravascular pressure demands. The percentage of smooth muscle increases with distal locations. Veins in the lower extremities are the only veins that are composed of more than 40% smooth muscle, with veins in the foot having 60–80% smooth muscle compared with 5% in axillary veins.[96] However, the hydrostatic pressure within the vein also correlates with smooth muscle content and superficial veins have more smooth muscle than deep veins.[107] The differences in vein wall content may affect sclerotherapy treatment, as described in Chapter 7.

The function of the vein wall collagen is to prevent overdistention, whereas elastin produces elastic recoil. With advancing age, multiple changes may occur in the vessel wall. The intima thickens, increasing and disorienting elastic fibers.[93] The media develops a more disorganized arrangement of muscle bundles and hypertrophy of the outer muscular layer. Elastic fibers become more irregular and dystrophic, and the elastic lamina becomes more fragmented, atrophic, thin and irregular.[93] The adventitia becomes increasingly fibrous. Thus the lack of an organized elastic support and smooth muscle degeneration in an aged vein render it more susceptible to pressure-induced distention.

Some histologic studies demonstrate that fibrotic wall changes are a common finding in the GSV in all age groups without venous disorders.[107] The incidence of fibrotic change increases from 25% to 50% in the population under 40 years of age to 100% in those over 70 years of age.

Other studies have confirmed the fact that varicose saphenous veins have significantly larger wall areas and larger amounts of collagen. This is true more so in the proximal GSV compared with the distal GSV. Also there is excess smooth muscle and elastin in varicose veins proximally compared with distally. This has suggested to some that varicose veins are a dynamic response to venous hypertension. Others believe that the vein wall in varicose disease is thinned rather than dynamically responsive.[108]

In saphenous veins subjected to biopsy during arterial bypass surgery, intimal thickening has been found to be common. Smooth muscle hyperplasia, elastosis and fibrosis contribute to this intimal thickening. In addition, medial longitudinal muscle hypertrophy is seen.[109]

VENULES

Venules in the upper and mid dermis usually run in a horizontal orientation. The diameter of the postcapillary venule ranges from 12 mm to 35 mm. Collecting venules range from 40 mm to 60 mm in the upper and mid dermis and enlarge to become 100 to 400 mm in diameter in the deeper tissues.[110] One-way valves are found at the subcutis (dermis)–adipose junction on the venous side of the circulation.[71] Valves are usually found in the area of anastomosis of small to large venules and also within larger venules unassociated with branching points. The free edges of the valves are always directed away from the smaller vessel and toward the larger and serve to direct blood flow toward the deeper venous system. The structure of these valves is identical to that of the valves found in deep and larger veins.

Postcapillary venules are composed of endothelial cells covered by a basement membrane, some collagen fibers, and, rarely, smooth muscle cells. Collecting veins in the deep dermis gradually receive more muscle cells until they become veins with a continuous muscle coat (see Fig. 1.49).[111,112]

TELANGIECTASIAS

Histologic examination of simple telangiectasias demonstrates dilated blood channels in a normal dermal stroma with a single endothelial cell lining, limited muscularis, and adventitia.[113] Therefore, such vessels probably evolve from capillaries or early venules.

Blue-to-red arborizing telangiectasias of the lower extremities are probably dilated venules, possibly with intimate and direct connections to underlying larger veins of which they are direct tributaries.[114–116] Electron microscopic examination of 'sunburst' varicosities of the leg has demonstrated that these vessels are widened cutaneous veins.[87] They are found 175–382 μm below the stratum granulosum. The thickened vessel walls are composed of endothelial cells covered with collagen and muscle fibers. Elastic fibers are also present. Electron microscopy reveals an intercellular collagenous dysplasia, lattice collagen and some matrix vesicles. These findings suggest that telangiectatic leg veins, like varicose veins, have an alteration of collagen metabolism of their walls. Therefore, like varicose veins, these veins are dysplastic.

Alternatively, arteriovenous anastomoses may result in the pathogenesis of telangiectasias. These were demonstrated by de Faria and Moraes[116] in 1 of 26 biopsy specimens of leg telangiectasias.

Skin biopsy of more unusual forms of telangiectasia, such as unilateral nevoid telangiectasia, may show an accumulation of mast cells.[117] In these cases permanent vasodilation may be induced by the chronic release of one or more products of mast cells, particularly heparin.[118,119]

INNERVATION

Innervation of the vein plays an important part in the regulation of venous tone. Different stimuli are known to produce venous constriction: pain, emotion, hyperventilation, deep breathing, Valsalva maneuver, standing and muscular exercise.[120] Although muscular veins have little or no sympathetic innervation, cutaneous veins are under hypothalamic thermoregulatory control and have both α- and β-adrenergic receptors.[121] Because the outermost media and adventitia contain the nerve endings, myogenic conduction contributes to the neurogenic activation by coordinating venous contraction.[103,122] Even in the outer layers of the media, the separation of muscle cells from nerve endings is rarely less than 1000 Å (0.1 nm).[123] Therefore, an intact smooth muscle layer is important in vein physiology.

Venous constriction and dilation occur through both central and local nervous stimuli.[124] This may be problematic when veins are used as arterial conduits. One report describes spasms of a vein graft 14 months after operation, causing anginal symptoms.[125] Localized cooling provides both a potentiation of adrenergic stimulation and a direct stimulus for venous smooth muscle contraction;[126,127] venoconstriction is reduced by warming.[127] Venoconstriction also occurs with infusions of norepinephrine (noradrenaline),[128] epinephrine (adrenaline), phenylephrine, serotonin and histamine.[129] Veins dilate in response to phenoxybenzamine, phentolamine, reserpine, guanethidine, barbiturates and many anesthetic agents.[130] Therefore, circulating adrenergic and pharmacologic substances influence vein diameter, and this may explain why central mechanisms may also be responsible for venous tone. Evidence for a central sympathetic control of venoconstriction has been demonstrated by the failure of such venoconstriction to occur with the tilting of sympathectomized patients.[131] Even the stress of mental arithmetic or unpleasant thoughts has been shown to activate adrenergic nerves connected to cutaneous veins.[120] Veins may become more distensible during sleep because of a change in either respiration or nerve stimulation.[132] This is one reason for recommending continuous compression of sclerotherapy-treated veins during the endosclerotic stages after treatment (see Chapter 8).

Local chemical changes produced through exercise also provide for the distribution of blood flow in accordance with local metabolic needs. Venous smooth muscle is also sensitive to endothelium-derived vasoconstrictor substances and peptides such as endothelin.[125] Finally, the increasing smooth muscle content from proximal to distal veins, and a thicker muscular media in superficial veins compared with muscular deep veins, supports the physiologic concept of increasing venous contractility in the distal venous system.

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2

Adverse Sequelae and Complications of Venous Hypertension

Mitchel P. Goldman, with contributions by Joanna Bolton

PATHOGENESIS

Chronic venous insufficiency, which must be semantically distinguished from venous disease or disorder, may be defined as relative impedance of venous flow back to the heart and may be responsible for clinical consequences. When this occurs in the lower extremities, the normal reabsorption of perivascular fluids by osmotic and pressure gradients is impaired, resulting in accumulation of perivascular and lymphatic fluid. This leads to edema and impaired oxygenation of surrounding tissue (Figs 2.1 and 2.2). This disruption of the normal vascular and lymphatic flow of the lower extremities may result in pain, cramping (especially at night), restlessness, pigmentary changes, dermatitis and ulceration (Fig. 2.3).[1–3] The association of abnormal venous flow with various signs and symptoms has been noted for centuries: first by Hippocrates in the fourth century BC and by Wiseman in England in 1676.[4] It has been estimated that chronic venous insufficiency will develop in almost 50% of patients with major varicose veins.[5,6]

Several alterations of normal venous flow cause venous hypertension. Such hypertension in the lower extremities is usually caused by a loss or disruption of the normal one-way valvular system. This may occur because of deep vein thrombosis (DVT), thrombophlebitis or a dilation of veins from other causes.[7,8] When perforating vein valvular function becomes incompetent, there may be shunting of blood flow from the deep to the superficial venous system through the incompetent perforating veins, with resultant adverse sequelae.[9–11] The superficial veins respond by dilating to accommodate the increased blood flow, which produces superficial valvular incompetence leading to the development of varicosities.[12] In addition, with muscular movement in the lower limbs, the high venous pressure normally occurring within the calf is transmitted straight to the superficial veins and subcutaneous tissues.[13,14] Venous pressure in the cuticular venules may greatly exceed the normal value of 100 mmHg in the erect position.[15] This causes venular dilation over the whole area, resulting in capillary dilation, increased permeability[16–19] and increase in the subcutaneous capillary bed.[17,20] This is manifested as telangiectasia and venectasia (Fig. 2.4). Venous hypertension has also been demonstrated to destroy the venous valves that are present in the subcuticular vascular system.[21] This destruction promotes persistent and progressive changes in the venous drainage system of the skin and subcutaneous tissues. The greater the degree of venous hypertension, the greater the risk of venous ulcer development.[22,23] Fortunately, both sclerotherapy and surgical treatment are capable of normalizing abnormal venous hypertension.

Venous hypertension and subsequent insufficiency may also derive from venous obstruction, either at lower limb level or at iliocaval level, usually associated with reflux.[24]

MOLECULAR MECHANISMS

The molecular mechanisms involved in leukocyte adhesion and activation in chronic venous disease (CVD) are beginning to be elucidated. Circulating leukocytes and vascular endothelial cells express membrane adhesion molecules. For example, binding of L-selectin on the leukocyte surface to E-selectin on endothelial cells may be involved in leukocyte 'rolling' along the endothelial surface (Fig. 2.5A). Then, when leukocytes are activated, they shed L-selectin into the plasma and express molecules of the integrin family, including CD11b, which binds firmly to intercellular adhesion molecule-1 (ICAM-1). Integrin binding can promote firm adhesion of leukocytes, the starting point for their degranulation[8] and migration through the endothelium.

Several studies have looked at markers of leukocyte and endothelial adhesion and activation in CVD. After venous hypertension was induced by standing for 30 minutes, levels of L-selectin and integrin CD11b on circulating neutrophils and monocytes in patients with CVD were found to decrease, reflecting the trapping of these cells in the microcirculation. At the same time, plasma levels of soluble L-selectin increased, reflecting the shedding of these molecules from leukocyte surfaces during leukocyte–endothelial adhesion.[24] Similarly, basal plasma levels of the adhesion molecules ICAM-1, endothelial leukocyte adhesion molecule-1 (ELAM-1), and vascular cell adhesion molecule-1 (VCAM-1) were higher in patients with CVD than controls and increased significantly in response to venous hypertension provoked by standing.[25] Baseline levels of plasma von Willebrand factor, a marker for endothelial cell damage, were also higher in patients with lipodermatosclerosis than in those without skin changes.[26] Lactoferrin and neutrophil elastase are enzymes released from neutrophil granules. Plasma levels of these molecules are therefore markers of neutrophil activation, and both were found to be higher in patients with CVD than in age- and sex-matched controls.[27]

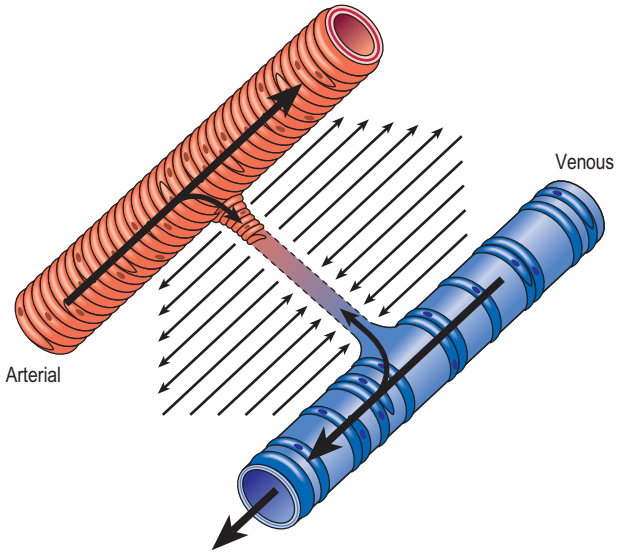


Figure 2.1 Schematic diagram showing the normal resorption of pericapillary fluid in response to precapillary and postcapillary pressure and interstitial pressure.

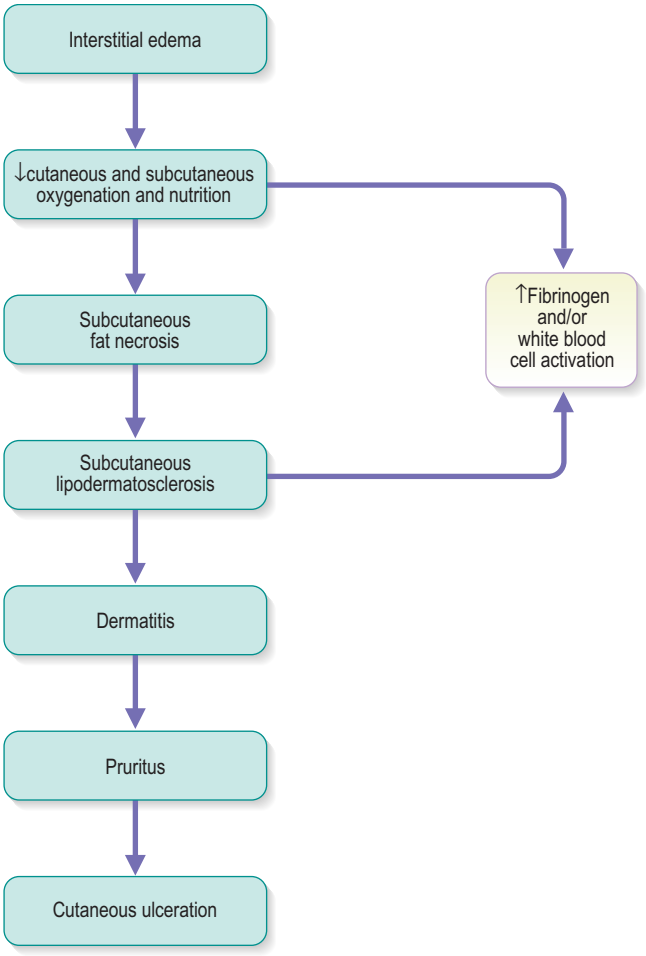


Figure 2.3 Flowchart showing etiology of cutaneous manifestations of venous hypertension.

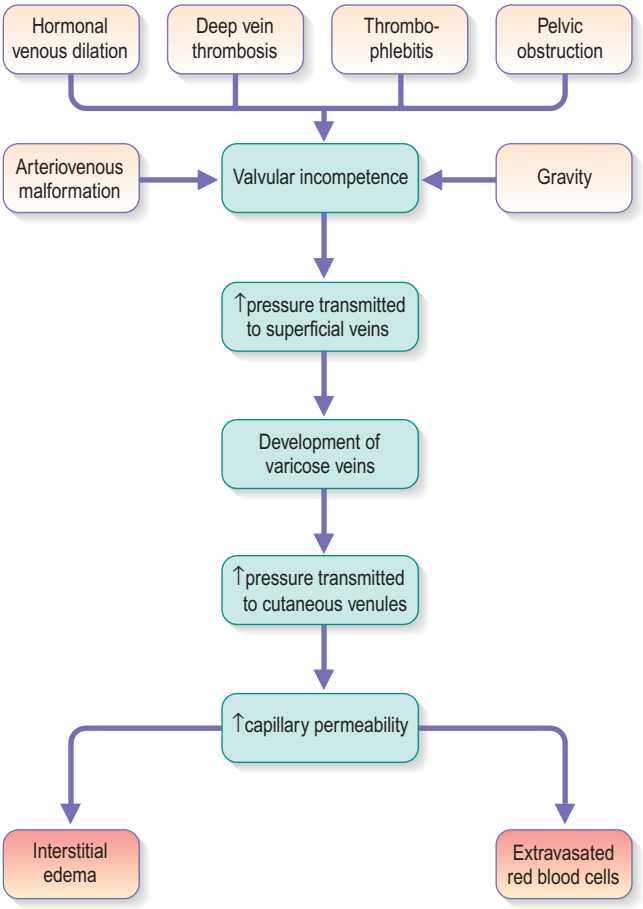


Figure 2.2 Flowchart showing etiology of cutaneous venous hypertension.

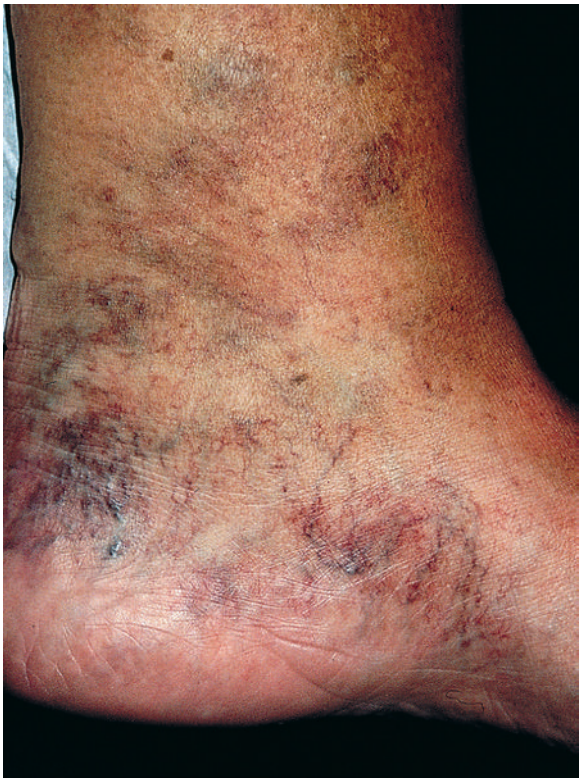


Figure 2.4 Telangiectasia in the medial ankle/pedal area in a patient with chronic venous insufficiency, referred to as corona phlebectatica.

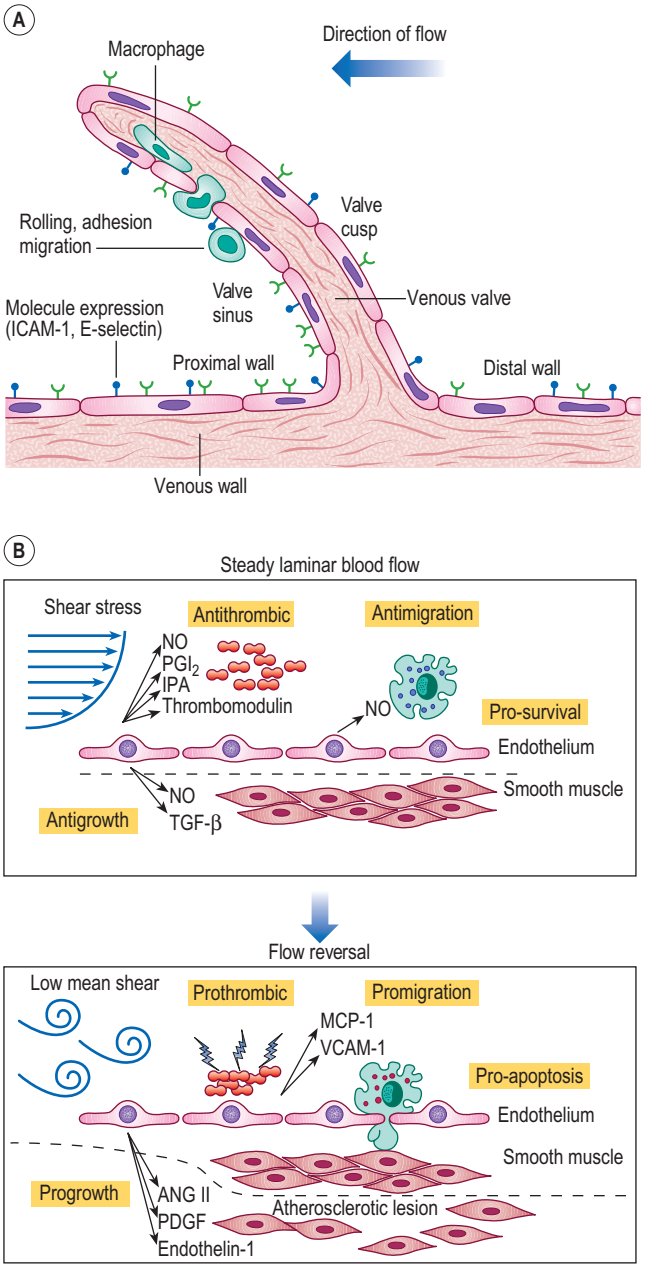


Figure 2.5 **A,** Leukocyte-endothelial interactions on a venous valve. *ICAM-1*, intercellular adhesion molecule-1. **B,** Summary of contrasting effects of steady, laminar shear stress (*upper panel*) and turbulent or reversing shear stress (*lower panel*) on vessel walls. *ANG II*, angiotensin II; *MCP-1*, monocyte chemotactic protein-1; *NO*, nitric oxide; *PDGF*, platelet-derived growth factor; *PGI_2*, prostacyclin; *TGF-β*, transforming growth factor beta; *t-PA*, tissue plasminogen activator; *VCAM-1*, vascular cell adhesion molecule-1. (**A,** Modified from Takase S, Bergan JJ, Schmid-Schönbein GW. Ann Vasc Surg 2000;14:427 and from Coleridge Smith PD, Bergan JJ. Inflammation in venous disease: In: Schmid-Schönbein GW, Granger N, editors. Molecular basis, or microcirculatory disorders. Paris: Springer-Verlag; 2003. pp 489–500, with permission. **B,** Modified from Traub O, Berk BC. Arterioscler Thromb Vasc Biol 1998;18:677, with permission.)

In most of these studies, prolonged standing induced venous hypertension. However, in patients with chronic venous insufficiency, increases in plasma levels of ICAM-1 and VCAM-1 can be induced by walking,[28] presumably in response to hydrodynamic pressure increases generated by the musculovenous pump being transmitted to subcutaneous and cutaneous small vessels through incompetent perforating veins.

In addition to local factors operating in relation to venous hypertension, patients with CVD have a tendency for systemically elevated leukocyte adhesion. Venous hypertension in the upper limb (where the local vessels and tissues are presumably normal) produced by means of a pressure cuff causes greater leukocyte accumulation in patients with venous leg ulcers than in normal subjects.[29] Evidence has been found for an activation factor in the plasma of patients with CVD.[15] Plasma obtained from patients with CVD induced greater degrees of activation as shown by production of oxygen free radical production and pseudopod formation in healthy granulocytes than did plasma taken from normal subjects. Also, there was a trend toward more activation in more severe cases of chronic venous insufficiency. The nature of the plasma factor responsible for leukocyte adhesion and activation is presently unknown.

INFLAMMATION AND SKIN CHANGES

There has also been progress in linking the chronic inflammatory state seen in patients with CVD with the specific skin changes typical of the condition. In lipodermatosclerosis, the skin capillaries become elongated and tortuous, giving the appearance in histologic sections of elevated capillary density.[30] In advanced skin disease, especially in the ulcerative stages, the capillaries may take on a glomerular appearance,[31] and it seems clear that substantial proliferation of the capillary endothelium occurs. Several factors could contribute to endothelial proliferation, but vascular endothelial growth factor (VEGF) is an obvious candidate. VEGF is known to be involved in inflammatory and healing processes in the skin and has been shown to increase microvascular permeability both acutely and chronically.[32] Plasma levels of VEGF have been shown to increase during the venous hypertension induced by 30 minutes of standing both in normal subjects and in patients with CVD. Both supine and standing VEGF levels are higher in patients than in normal controls.[33] Furthermore, plasma VEGF levels are higher in patients with CVD with skin changes than in patients with CVD with normal skin.[34]

Another feature of the skin changes associated with CVD is dermal tissue fibrosis. Transforming growth factor-β_1 (TGF-β_1) is a known fibrogenic cytokine. Detailed analysis of punch biopsy specimens has shown that skin from the lower calf of patients with CVD had significantly elevated active TGF-β_1 levels compared with normal skin. In addition, this was true relative to skin taken from the lower thigh region of the same patients.[35] Immunohistochemistry and immunogold labeling showed the TGF-β_1 to be located in leukocytes, fibroblasts and on collagen fibrils. Pappas el al[36] proposed that activated leukocytes migrate out of the vasculature and release TGF-β_1, which stimulates increased collagen production by dermal fibroblasts. Over an extended period, such a process could contribute to the typical dermal fibrosis seen in CVD.

Altered collagen synthesis has also been reported for dermal fibroblasts taken from apparently healthy areas of skin in patients with varicose veins.[37] It has been possible to correlate altered levels and distributions of growth factors, including basic fibroblast growth factor (bFGF),

transforming growth factor-3 (TGF-3) and the receptor for epidermal growth factor (EGF), with different types of skin change, including venous eczema, pigmentation, lipodermatosclerosis and ulceration.[38]

Advanced cutaneous changes of lipodermatosclerosis appear as an erythematous, telangiectatic, edematous plaque with mottled hyperpigmentation, distinguished by the so-called 'inverted champagne bottle' sign. The most well-recognized association is with vascular damage, most notably, venous incompetence/hypertension and to a lesser extent arterial ischemia.[39] Histologic examination shows advanced stasis changes, including zones of ischemic necrosis in the central part of fat lobules. Septal fibrosis, fat macro- and micropseudocysts, membranous fat necrosis, calcification of adipocytes and sclerosis occur later. In a clinicopathologic study of 25 cases, there was minimal, if any, chronic inflammation within the fat lobules, consisting mainly of lymphocyte, plasma cells and few eosinophils, and vasculitis was not seen.[39] This advanced clinical–histologic change is termed *sclerosing panniculitis*.[40] With superficial venous insufficiency alone, changes in the histologic appearance of capillaries are moderate. The combination of deep venous insufficiency, with or without superficial venous insufficiency, produces more profound changes.[41,42]

Venous hypertension is not a benign condition. The cutaneous chain of events following the onset of venous stasis is thought to occur in the following temporal order: localized edema, induration, pigmentation, dermatitis, atrophie blanche and, in untreated cases, eventual ulceration, infection, scarring, lymphatic obstruction and sensitization to applied medications.

Labropoulos et al[43] studied 255 limbs in 217 patients. These had superficial venous insufficiency alone, with normal perforating veins and deep veins. Color-flow duplex imaging techniques were used. The researchers concluded that aching, ankle edema and skin changes in limbs with reflux confined to the superficial venous system were associated predominantly with reflux in veins below the knee. An important finding was that ulceration occurred only when the entire great saphenous vein (GSV) was involved or when reflux was extensive in both the great and small saphenous systems.

CLASSIFICATION OF VENOUS DISEASE

An international ad hoc committee of the American Venous Forum developed the CEAP classification for CVD in 1994. The goal was to stratify clinical levels of venous insufficiency. The four categories selected for classification were: clinical class (C), etiology (E), anatomy (A) and pathophysiology (P). The CEAP classification has been endorsed worldwide despite its acknowledged deficiencies, and remains the gold standard of classification of chronic venous disorders today.[44] It has been adopted in Europe, Asia and South America and is considered the only modern method for reporting data in the United States.[45–47]

Venous disease is complex, but can be described. The first step in evaluating a patient with CVD is to establish his or her clinical class. The patient's clinical class will dictate the need for further evaluation. The CEAP classification is shown in Box 2.1. Each clinical class (C) is further characterized

Box 2.1 CEAP Classification

C: Clinical Findings

C0: No visible or palpable signs of venous disease.
C1: Telangiectatic or reticular veins.
C2: Varicose veins—separated from reticular veins by a diameter of 3 mm as the upper limit of size of a reticular vein.
C3: Edema.
C4: Changes in the skin and subcutaneous tissue secondary to chronic venous disease are divided into two subclasses to better define the differing severity of venous disease:
C4a: Pigmentation or eczema (commonly occur and do not necessarily predict the appearance of ulcers);
C4b: Lipodermatosclerosis or atrophie blanche (commonly predict the development of ulcers).
C5: Healed venous ulcer is usually associated with skin changes.
C6: Active venous ulcer.
S: Symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
A: Asymptomatic

E: Etiology

Ec: Congenital (present at birth)
Ep: Primary
Es: Secondary

A: Anatomic Findings

As: Superficial veins
1. Telangiectatic/reticular veins
2. Greater saphenous vein, above knee
3. Greater saphenous vein, below knee
4. Small/lower saphenous vein
5. Nonsaphenous veins

Ad: Deep veins
6. Inferior vena cava
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament veins, other
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
16. Muscular: gatrocnemial, soleal veins, other

Ap: Perforator veins
17. Thigh
18. Calf

P: Pathophysiologic Component

Pr: Reflux
Po: Obstruction
Pr,o: Reflux and obstruction
Pn: No venous pathophysiology identifiable

Adapted from Fronek HS, Bergan JJ. The Fundamentals of phlebology: venous disease for clinicians. 2008. pp 85–87.

by a subscript for the presence of symptoms (S, symptomatic) or their absence (A, asymptomatic). Symptoms include aching, pain, tightness, skin irritation, heaviness and muscle cramps, as well as other complaints attributable to venous dysfunction. A basic CEAP, using at least the C class and the higher descriptor (e.g., C3s instead of C2–3sE…A…P…), is suggested. For the practicing physician, CEAP is an instrument for correct diagnosis, to guide the treatment and assess the prognosis. In modern phlebologic practice, the vast majority of patients will undergo a duplex scan of the venous system of the leg, which will provide data on E, A and P. In basic CEAP where a duplex scan is performed, E, A and P should be utilized. Multiple descriptors should be permitted for all four components in basic CEAP; for example a patient could be classified as C234s Ep As-$_{1,2,3}$ d-$_{14,15}$ Pr. Use of all components of CEAP is encouraged. Current diagnostic definitions that apply to the CEAP classification are shown in Box 2.2.With a reported incidence as high as 1 in 10 patients, Cafasso et al propose that any future modifications of the CEAP classification should include a consideration of heterotopic subcutaneous ossification (phleboliths) to better recognize this serious complication of longstanding chronic venous insufficiency.[48]

However, the basic CEAP is a description of the disease, not an assessment of its severity. It serves for classification, not evaluation. For this reason, several scores have been added to the CEAP, such as the VCSS (venous clinical severity score).[49] However, a physician-reported outcome such as the VCSS is influenced by the 'experimenter-expectancy effect', and so the need for the application of patient-reported outcomes (PROs) to clinical trials is now recognized.[50] Revicki summarizes: '… the patient's perspective and patient-reported HRQL (health related quality of life) is the ultimate outcome for health care interventions.'[51] Basically, a PRO will increase the validity of randomized controlled trials (RCTs) especially when they cannot be double or even single blinded. The influence of the experimenter's opinion about the efficacy of a treatment significantly changes the RCT results in many different fields of medicine.[52] An additional precaution for outcome evaluation could be the use of an external evaluation, but this would not take into account the patient's point of view and self-appraisal.

The patient's opinion is a factor that, albeit obvious, has been too long neglected. Several Quality of Life questionnaires, generic (e.g. SF12[53]) and specific (e.g. CIVIQ,[54] AVVQ) already exist and have been successfully used.[55] However, they have not taken into account the only sure thing we could ever state*: if the patient is not happy with the result of the treatment, it means it (you) failed.* Therefore, the need to assess the patient's own appraisal in detail, with satisfactory sensitivity and specificity, appears of utmost importance. Guex et al addressed this point and observed that patients with CVD had one main concern belonging to one of the following five groups: discomfort/pain, appearance/attractiveness, risk/threat to health, restriction of movements/activities, emotional distress.[56] They have therefore constructed a novel PRO (the SQOR-V), specially dedicated to CVD and based on these five patient concerns.[57] Its values range from 20 to 100, 20 to 30 being normal, 30 to 50 moderate consequences of CVD and >50 being severe CVD. This questionnaire is free to use and is available in several languages, including French, English and Spanish.

Pittaluga et al have established a classification of venous refluxes based on the extent of saphenous vein reflux.[58] They noted a positive correlation between age and progression of superficial venous insufficiency.

To denote the severity of a symptom, Fronek and Bergan suggest an additional number may follow the 's' (symptomatic), when assessing the clinical findings ('C') using the CEAP classification. These recommended clinical disability scores for chronic venous insufficiency are: 0 (asymptomatic,

Box 2.2 CEAP Definitions

Telangiectasia: a confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs and thread veins.

Reticular veins: dilated bluish intradermal veins, usually from 1 mm in diameter to less than 3 mm in diameter. They are usually tortuous. This excludes normal visible veins in people with transparent skin. Synonyms include blue veins, intradermal varices and venulectasias.

Varicose veins: subcutaneous dilated veins equal to or more than 3 mm in diameter in the upright position. Varicose veins are usually tortuous, but refluxing tubular veins may be classified as varicose veins. These may involve saphenous veins, saphenous tributaries or nonsaphenous veins. Synonyms include varix, varices and varicosities.

Corona phlebectatica: fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. Its significance is unclear, but commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare.

Edema: perceptible increase in volume of fluid in the skin and subcutaneous tissue characterized by indentation with pressure. Venous edema usually occurs in the ankle region, but it may extend to the leg and foot. It can be difficult to differentiate from lymphedema which usually involves the toes.

Pigmentation: brownish darkening of the skin initiated by extravasated blood which usually occurs in the ankle region but may extend to the leg and foot.

Eczema: erythematous dermatitis, which may progress to a blistering, weeping or scaling eruption of the skin of the leg. It is often located near varicose veins but may be located anywhere in the leg. Eczema is usually caused by chronic venous disease (CVD) or by sensitization to local therapy. Synonyms include venous dermatitis and stasis dermatitis.

Lipodermatosclerosis: localized chronic inflammation and fibrosis of the skin and subcutaneous tissues, sometimes associated with scarring or contracture of the Achilles tendon. It is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which is often referred to as hypodermitis. The absence of lymphangitis, lymphadenitis and fever differentiates this condition from erysipelas or cellulitis. Lipodermatosclerosis is a sign of severe CVD.

Atrophie blanche or white atrophy: circumscribed, often circular, whitish and atrophic skin areas surrounded by dilated capillary spots and, sometimes, hyperpigmentation. This is a sign of severe CVD. Scars of healed ulceration are excluded in this definition.

Venous ulcer: chronic defect of the skin most frequently around the ankle that fails to heal spontaneously because of CVD.

no disability), 1 (symptomatic, but can function without a support device), 2 (symptomatic, can work an 8-hour day only with a support device), 3 (symptomatic, unable to work even with a support device).[59]

INCIDENCE

Lower extremity venous disease is a worldwide health problem costing billions of dollars.[60] Varicose veins have been noted to increase in incidence with age and have been estimated to occur in 7% to 60% of the adult population in the United States.[5,15,61–65] Epidemiological studies in France and Hungary have shown prevalence of lower-extremity varicose veins between 30% and 57%.[66,67] Varicose veins occur in 8% of women aged of 20 to 29 years, increasing to 41% in the fifth decade and 72% in the seventh decade of life.[62,68,69] A similar rate of increase in the incidence of varicose veins occurs in men: 1% in the third decade, increasing to 24% in the fourth decade and 43% in the seventh decade.[62,68] The Basle study III found that the greatest correlation between age and incidence of varicose veins occurred in those with varicose veins only, rather than in those with the presence of telangiectasias (hyphenwebs) or reticular veins (Fig. 2.6).[5] The Framingham study,[70] curiously, showed no difference in the incidence of varicose veins with age. Telangiectasia afflicts between 30% and 60% of both men and women, between 16 and 64 years of age, with most studies reporting a higher incidence among women than men.[60] Interestingly, a study out of Budapest verified risk factors of advancing age, pregnancy, jobs requiring a lot of standing, blue-collar work and excess body weight; however, neither female gender nor the use of oral contraceptives or hormone replacement therapy were identified as a contributing factor.[67]

Varicosities in childhood are rare, occurring almost exclusively in association with congenital vascular malformations (see Chapter 3). When varicosities occur, they usually appear as a subtle physical finding, such as a slight bulge over the popliteal fossa (Fig. 2.7). One estimation on the incidence of telangiectasias in children was performed by Oster and Nielsen[71] in Denmark. Of 2171 Danish schoolchildren examined, 46.2% of the girls and 35.1% of the boys had telangiectasias on the nape of the neck; 1% of these children had pronounced telangiectasias elsewhere; that is, on the shoulders, thorax, cheeks and ears. No mention was made of the occurrence of telangiectasias on the legs. An examination of 403 children in the former East Germany, aged 8 to 18 years, disclosed a 50% incidence of 'very discrete' venous abnormalities of leg veins. Of the children examined, 15% had clear symptoms (without visible varices) that could be assigned to a prospective varicose disease. Only between the ages of 17 and 18 years could reticular varicose veins be identified. In the 403 children studied by venous Doppler, 2.3% had incompetent communicating veins and 3.2% had an incompetent saphenofemoral junction.[72] An epidemiologic study of 419 Czechoslovakian children aged 8 to 13 years, with clinical examination plus digital photoplethysmography, showed clinically apparent varices in 8.7% and an impairment of venous function in 14.3% of the examined extremities.[73]

The most recent and complete studies of 518 children aged 10 to 20 years, using photoplethysmography in addition to venous Doppler, are the Bochum I, II and III studies. This continuing investigation initially demonstrated a 10.2% incidence of reticular varicose veins without other venous abnormalities in children who were 10 to 12 years of age.[74] When these children were examined 4 years later, the incidence of reticular veins was 30.3%; 2% of the children had developed varicose veins and 4% had developed incompetent communicating veins. When they were examined

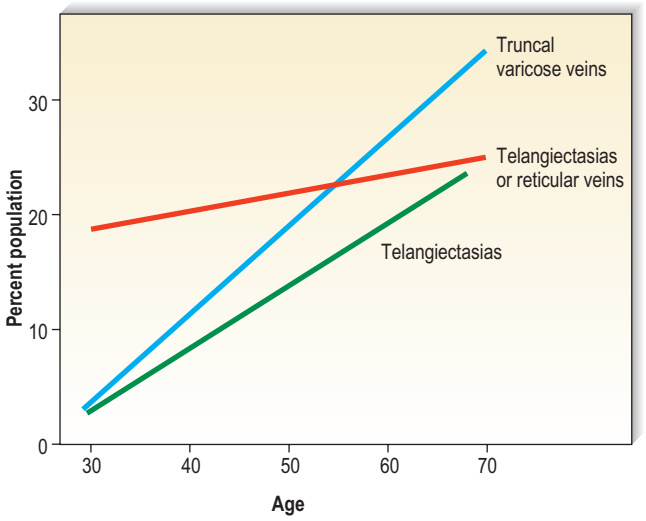


Figure 2.6 Risk of varicosity by age. Increasing age best correlated with the development of varicose or reticular veins. (From Widmer L. Peripheral venous disorders: prevalence and socio-medical importance: observations in 4529 apparently healthy persons, Basle Study III. Bern, Switzerland: Hans Huber; 1978.)

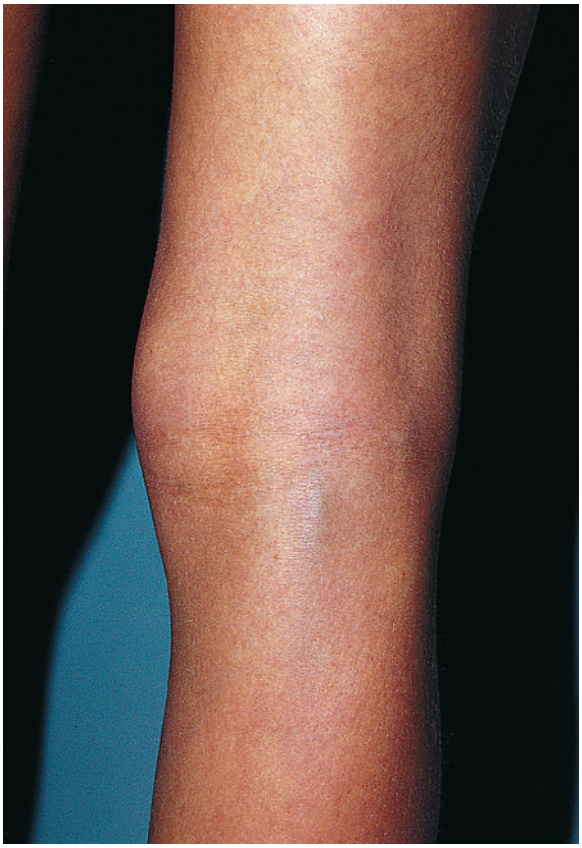


Figure 2.7 Subtle, asymptomatic varicosity of the great saphenous vein at the junction in the popliteal fossa of an 11-year-old girl. There is no significant family history of varicose veins.

another 4 years later, the frequency of saphenous refluxes and large varices was still increasing (19.8% saphenous refluxes, 3.3% truncal varices, 5% tributary varices and 5.2% incompetent perforators). The incidence of reticular veins increased to 35.5%, and the incidence of telangiectasia increased to 12.9%.[75] Therefore, venous disease can be demonstrated in a small number of children, its progression can be documented and saphenous reflux is a risk factor for the development of truncal varices.

SYMPTOMS AND SIGNS

Varicose veins may be symptomatic in addition to being large and unsightly (Box 2.3). They can result in aching, swelling, itching, cramping and if left untreated, commonly lead to more advanced signs of chronic venous insufficiency (CVI) including the development of venous leg ulcers (VLUs).

A study of 4280 town and country inhabitants of Tübingen, Germany, found symptoms in 98% of patients with clinically relevant venous alterations.[76] One American health survey found that nearly 50% of those with varicose veins were bothered by their symptoms once in a while, and 18% noted frequent to continuous symptoms.[77] Galen[78] described the symptoms of varicose veins as 'a heavy and depressing pain'. Pain is related most likely to pressure on the dense network of somatic nerve fibers present in the subcutaneous tissues adjacent to the affected nerve. Alternatively (or in addition), pain may occur from the dilated vein compressing adjacent nerves or from lactic acid accumulation that results from retrograde, circular or slower venous blood flow clearance. Symptoms may precede the clinical appearance of the varicosity and are proportional to the presence of intermittent edema. At this point, discomfort usually occurs during warm temperatures when the patient is standing for prolonged periods.[79] These patients may respond to systemic hydroxyrutosides, which decrease inflammation of the vein wall.[80–82] Paroven—a mixture that mainly consists of mono-, di-, tri- and tetra-*O*-β-hydroxyethyl rutosides containing at least 45% troxerutin (Zyma, UK)—250 mg three or four times a day has been reported to help.[83] Reduction in venous hypertension or excision of the involved segment usually causes prompt relief of pain.[4]

Almost all patients with postthrombotic obstruction complain of 'bursting' calf pain that is exacerbated by exercise.[84] Venous claudication is an appropriate term to use in this situation to emphasize the relationship of exercise to pain. Pain during exercise may be caused by nociceptor stimulation of the distended vein wall.[85] Alternatively, exercise pain may be caused by an accumulation of tissue metabolites or an increase in interstitial pressure. Patients with acute DVT have an increased intramuscular pressure that is proportional to the degree of thrombosis.[86,87]

Kistner[88] has found that perforator incompetence leads to indurated skin with ulceration, whereas incompetence of the tibial, popliteal or femoral system produces aching and swelling in the leg. There are patients who have a significant amount of valvular incompetence without symptoms. Clinical symptoms vary based on the effectiveness of the calf muscle pump to compensate for venous hypertension. Young, thin and more athletic patients have fewer symptoms than older and obese patients.

Varicose vein pain is described usually as a dull aching of the legs, particularly after prolonged standing or during certain times of the menstrual cycle (especially during menses).[89] A small number of women also experience painful varicose veins after sexual intercourse.[90] It is proposed that the increase in venous pressure with distension of the varicose vein contributes to heaviness and tightness of the lower legs.[4,91] The Basel study III found a similar range of complaints in both men and women (Fig. 2.8) and an increased incidence of complaints among women and older patients.[5] Many patients in the Basel study III had complaints without evidence of peripheral vascular disease. Strandness and Thiele[4] suggest that symptoms specifically caused by varicose veins improve with aging as the level of activity declines.

Symptoms in varicose veins are often disproportionate to the amount of actual pathologic change. Patients with small, early-stage varices may complain more than those with large, longstanding varicosities.[92–96] A survey of 350 patients who presented for sclerotherapy treatment of veins that were less than 1 mm in diameter noted that 53% of these patients complained of swelling, burning, throbbing and cramping

Box 2.3 Symptoms of Varicose Vein/Venous Stasis Disease (Chronic Venous Insufficiency)

- Aches and pains
- Night cramps
- Swelling
- Cutaneous pigmentation
- Dermatitis
- Ulceration
- Hemorrhage
- Superficial thrombophlebitis

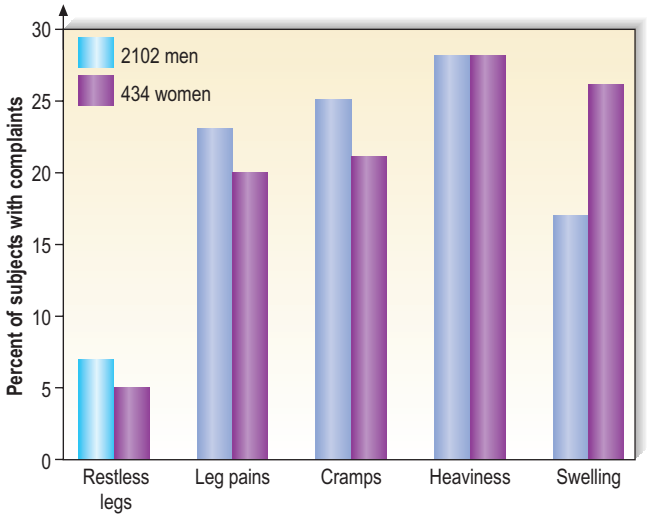


Figure 2.8 Type of complaint according to sex. Except for an increase in the complaint of ankle swelling, men with varices have complaints similar to those of women. (From Widmer L: Peripheral venous disorders: prevalence and socio-medical importance: observations in 4529 apparently healthy persons, Basle Study III. Bern, Switzerland: Hans Huber; 1978.)

of the legs in addition to a 'tired feeling'.[97] A retrospective analysis of 401 patients who sought treatment solely for telangiectasia showed 69% with various symptoms, including pain, cramping, burning, throbbing and heaviness.[98] These symptoms are so insidious that most patients fail to realize how good their legs can feel until after treatment of these blood vessels by either compression sclerotherapy or by wearing lightweight (20 mmHg) graduated compression stockings.[64] Patients with nonsaphenous reflux had twice the incidence of painful legs (43%) than did patients with saphenous reflux (22%).[99]

The increased incidence of symptomatic varicose veins in women may have a hormonal etiology. It has been estimated that 27.7% of women with varicose veins have premenstrual pain in their varices.[100] Varicose veins during pregnancy appear to be more symptomatic than those unassociated with pregnancy. In a study of 150 pregnant women with varicose veins, 125 noted pain and 26 were unable to stand for more than 1 to 2 hours because of the pain.[101]

Warm weather tends to increase the severity of pain, as does continual standing. Cooling the legs with water immersion or compresses, or raising the legs, relieves the symptoms.

The differential diagnosis of leg pain is extensive and not necessarily attributable to a patient's varicosities (Box 2.4). Symptoms derived from varicose veins can usually be distinguished from arterial symptoms. Pain associated with arterial diseases often disappears at rest and is exacerbated with walking. Pain associated with varicosities is dull, vague and localized on the medial side of the legs. It is usually relieved with walking. In addition to the dull aching, varicose veins associated with venous hypertension may produce cramping or painful spasms of the legs and an increase in leg fatigue and restless legs, especially at night. Unfortunately, a patient's perception and reporting of pain are subjective in nature and difficult to document. Browse et al[102] advocate the use of compression hosiery as a diagnostic test to determine if the pain is of venous origin. The authors have found that if a patient's symptoms are alleviated with 20-mmHg graduated compression stockings, sclerotherapy treatment also alleviates the symptoms.

Box 2.4 Differential Diagnosis of Leg Pain

- Varicose veins
- Thrombophlebitis
- Osteoarthritis
- Rheumatoid arthritis
- Malignancy
- Osteomyelitis
- Meniscal tear
- Achilles tendonitis or tear
- Intermittent (arterial) claudication
- Venous claudication
- Spinal claudication
- Myalgia
- Peripheral neuropathy
- Lymphedema

From Browse NL, Burnand KG, Thomas ML. Diseases of the veins: pathology, diagnosis, and treatment. London: Edward Arnold; 1988.

In a study that compared groups matched by age as well as gender, it was found that subjects with venous disease were markedly symptomatic compared with control individuals. Symptoms specific to venous disease were found to correlate with the presence of both small vein and large vein disease. Vein size did not predict the presence or severity of symptoms.[103] A study of 1366 people in Edinburgh, UK, found that women were more likely than men to report a wide range of lower limb symptoms.[104] In men, only itching was significantly related to the presence of varicose veins. In women, there was a significant relation between varicose veins and heaviness or tension, aching and itching.

Using the Aberdeen varicose vein questionnaire, a prospective cohort of 137 patients was studied and the results compared with the well-accepted short form (SF-536). The two questionnaires correlated highly. Both showed the patients having worse health preoperatively than postoperatively. After surgery, all domains of health were improved and reached significance, chiefly in mental health. The conclusion of the authors of this study was that persons with varicose veins have a reduced quality of life (QOL) compared with the general population and that this discrepancy is significantly improved at 6 weeks after surgery.[105]

Two QOL studies were conducted on people with varicose veins. An analysis of 5688 consecutive outpatients in Belgium, Canada, France and Italy found that the QOL in patients with varicose veins is associated with concomitant venous disease, rather than the presence of varicose veins per se.[106] Sixty-five percent of patients with varicose veins also have concomitant venous diseases such as edema, skin changes or ulcers. A study of 2404 employees of the University of California, San Diego Medical Center, also found an adverse effect on QOL in patients with CVD.[107] The effect of venous disease is more on the functional scale (what a person can do) and does not seem to affect the well-being aspects (how a person feels). Thus, venous disease is more than simply a cosmetic problem to most patients.

The lack of an adequate patient-centric way to assess symptom relief from treatment of varicose veins led to the development of the recently reported VVSymQ instrument.[108] This electronic patient-reported outcome (EPRO) instrument is a five-item tool that assesses symptoms most important to patients with varicose veins (HASTI = heaviness, achiness, swelling, throbbing and itching). The tool was used in preintervention and postintervention follow up in a 40-patient validation study and subsequently as a daily electronic diary in two randomized, controlled, phase 3 clinical trials of polidocanol foam for GSV ablation. Patients were highly compliant (≥97% in the validation study) in completing the daily diaries, and the instrument demonstrated ability to detect overall change and the ability to detect change that is meaningful to patients compared with other widely used questionnaires by clinicians (i.e., VEINES-Qol/Sym [VQS], VCSS).

In addition to the direct symptoms of varicose and telangiectatic veins, varicose veins may be a cutaneous marker for venous insufficiency, where they occur in more than 50% of patients (Box 2.5).[109–112] Certainly, deep venous insufficiency as a result of valvular incompetence is the major etiologic factor for the cutaneous manifestations of CVI. In fact, when descending venography was used to examine patients with CVI, reflux occurred in the superficial system alone in only

Box 2.5 Venous Stasis Disease Signs

- Ankle edema
- Dilated veins and venules
- Telangiectasias
- Corona phlebectasia
- Pigmentation
- Venous dermatitis
- Atrophie blanche
- Ulceration

2% of the 644 examined limbs. Eighteen percent of the limbs had combined deep and superficial reflux.[113] Studies using ascending venography have shown that more than 20% of patients with chronic venous insufficiency have isolated perforator incompetence as the only demonstrable abnormality.[114] However, a significant group of patients has superficial venous insufficiency alone (13–38%) or in combination with deep venous insufficiency (28–78%).[112,115–120] In addition, Walsh et al[121] found that treating the incompetent superficial venous system with ligation and stripping the GSV to the knee with stab avulsion of distal varices restored competency to the femoral vein. Therefore, identification of patients with superficial venous insufficiency is important because they may respond to sclerotherapy or surgical treatment of the superficial venous system alone.

It has been estimated that between 17% and 50% of the population with varicose veins have cutaneous findings.[2,122] Approximately 70% of limbs with CVI have clinical findings.[116] There is a strong association between the severity of clinical signs (described later in this chapter) and superficial venous incompetence.[116] Almost all patients with cutaneous abnormalities have incompetence of perforator veins and all patients with either active or healed venous ulcerations have evidence of perforator incompetence.[122] The cutaneous manifestation appears as edema, hyperpigmentation, dermatitis or ulceration. In 2011, of the estimated 226 million inhabitants of the United States who were at least 20 years of age, 23% were estimated to suffer from varicose veins and CVD, with 6% (nearly one fourth of the total) having more severe CVI (C4-6 of the CEAP classes).[123] In other words, there are currently more than 50 million American adults who have symptomatic varicose veins that often affect activities of daily living and lifestyle and at least 13 million who have evidence of CVI (skin changes, healed venous ulcers or active venous ulcers).Thus, varicose and telangiectatic leg veins are not merely of cosmetic concern but represent a widespread, serious medical problem with significant psycho-socioeconomic burden.

EDEMA AND LIPODERMATOSCLEROSIS

Ankle edema is usually the first manifestation of CVI and is characterized by swelling that can lead to skin changes, exaggerated skin folds, ulceration, exudate and recurrent cellulitis not only of the ankle, but eventually larger portions of the lower leg.[124] It is a distressing chronic symptom that is the result of several conditions including but not limited to CVD, immobility, obesity, diabetes and arthritis. In the UK, it has recently been estimated that 3.99:1000 of the population is affected by chronic edema.[125] This

Box 2.6 Differential Diagnosis of Ankle Edema

- Cardiac failure
- Renal failure
- Deep vein thrombosis
- Venous obstruction from other causes
- Hypoalbuminemia
- Fluid retention syndromes
- Lymphedema
- Lipodystrophy
- Hemihypertrophy (Klippel–Trénaunay syndrome)
- Venous valvular agenesis
- Calcium channel blockers

prevalence increases to 10.31:1000 in those over 65 years and 28.57:1000 for those aged >85, and is higher among women across all ages. The increased size and weight of limb(s) can cause pain, affect mobility and the ability to wear certain clothing and footwear, resulting in reduced self-esteem, body-image alteration and reduced employment opportunities.[126]

Ankle edema tends to be worse in warm weather[2] and toward the end of the day.[64] It is especially common in persons who stand a great deal.[64] True 'pitting' edema is rare,[92] perhaps resulting from increased dermal fibrosis present in lipodermatosclerosis. The edema usually found is restricted to a limited area drained by capillaries that empty directly into the varicose or incompetent perforating veins.[127] This area has been termed the gaiter area and refers to the ankle and lower calf. (In the 1800s it was commonly covered by a cloth or leather material (gaiter) to protect the ankle and instep from the environmental elements. Such protection is still used today by cross-country skiers.) Ankle edema caused by venous hypertension and varicose veins must be differentiated from that caused by other conditions (Box 2.6). However, as previously described, lymphatic edema may also be present in patients with chronic venous leg ulcers.[128]

The incidence of leg edema may not be related to the extent of varicose vein disease. A statistical study of 9100 civil servants in the German cities of Düsseldorf and Essen disclosed a statistically significant increase only in leg swelling in those with leg veins less than 1 mm in diameter compared with those without such veins.[129] There was no difference in muscle cramps, restless legs and itching. Pain was not evaluated.

The protein-rich edema fluid stimulates fibroblastic activity, which entangles blood vessels and lymphatics into a fibrous mass.[130] Histologically, a microedema around capillaries is seen.[131] The edema, which contains fibrin (forming pericapillary fibrin cuffs), proteins and neutral polysaccharides, is probably the main reason for the lack of nutrition of the skin.[132,133] The resulting lymphedema and the hypertrophy of the skin and subcutaneous tissues disrupt the flow of cutaneous nutrition. In women with venous stasis and fat, hairless, erythrocyanoid-type ankles, the resulting decrease in nutrition for the sizable fatty subcutaneous tissue and the decrease in local tissue oxygenation may cause sudden and massive fat necrosis of the subcutaneous tissue.[2,15] The affected area may then appear erythematous, indurated and

Box 2.7 Contraindications to Compression Therapy

- Acute cellulitis
- Acute deep venous thrombosis
- Unstable congestive heart failure
- Severe peripheral arterial disease
- Severe peripheral neuropathy
- Untreated truncal or genital edema

Adapted from Todd M. Venous disease and chronic oedema: treatment and patient concordance. Br J Nurs 2014;23:466.

tender to the touch, having progressed to the more severe stage of lipodermatosclerosis. The advanced histopathologic changes associated with lipodermatosclerosis were described earlier in this chapter.

Guex et al have correlated ankle circumference, symptoms and QOL scores in 1036 patients with venous symptoms.[134] They demonstrated the relevance of moderate ankle swelling to be secondary to CVI.

Treatment of ankle edema caused by increased venous pressure, with or without lipodermatosclerosis, is directed primarily toward the prevention of trauma and alleviation of superficial venous hypertension.[19] Temporizing treatments include leg elevation, systemic diuretics and localized compression bandaging.[19] Graduated compression bandaging can normalize lymphatic flow over time. In fact, compression therapy remains the mainstay in the management of CVD, edema and VLU, with a few contraindications to consider (Box 2.7).[125] Thus this 'conservative' form of treatment is actually therapeutic as well (see Chapter 6).

Lipodermatosclerosis can be associated with severe pain, leaving sufferers unable to tolerate compression therapy. Fibrinolytic enhancement with stanozolol, an anabolic steroid with known fibrinolytic properties, has been studied and found to be successful in reducing the symptoms of pain, induration and cutaneous thickening in patients with lipodermatosclerosis, particularly in the acute phase, since an early report in the 1970s.[135] The authors of that report used stanozolol (5 mg by mouth, twice daily) in 14 patients with longstanding lipodermatosclerosis resulting from venous disease. Of these 14 patients, 11 noted improvement within 3 months. The exact mechanism of action of stanozolol remains unknown, but this steroid decreases the level of tissue plasminogen activator inhibitor.[136] Over the last 40 years, additional trials have been conducted to study and fine-tune treatment with stanozolol[136–139] Doses ranging from 2 to 10 mg, twice daily, with durations varying from 8 weeks up to 6 months are generally reported. The duration of therapy in patients with acute lipodermatosclerosis rarely exceeds 6 months because, within weeks, pain is remarkably reduced, and by 2 to 3 months the skin becomes less indurated. Low-dose stanozolol, 2 mg, twice daily, appears to be most favored if there is beneficial response by 3 to 4 weeks, because even at this dose asymptomatic and temporary elevation of liver transaminases and depression of the high density lipoprotein (HDL) level are seen in a significant portion of patients.[139] As a result of the nature of stanozolol (a steroid), a number of screening tests should be performed before treatment.[136] Blood pressure should be measured throughout therapy (weekly for 2–3 weeks, then monthly), and liver function monitored every 3 to 4 weeks. Following successful treatment, many patients are able to tolerate compression therapy. Relapse of acute lipodermatosclerosis is noted to be uncommon if compression stockings are used regularly.

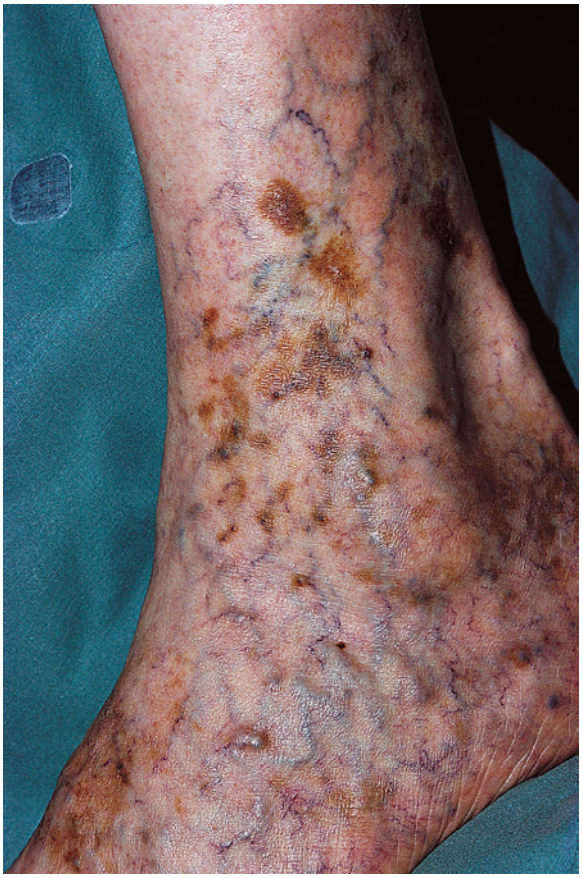


Figure 2.9 Hyperpigmentation around dilated telangiectasias and venules in a 70-year-old man. There had been no history of cutaneous trauma.

PIGMENTATION

Pigmentation (Fig. 2.9) is a sign of venous stasis disease. Legs afflicted with CVD may undergo skin changes ranging from small spot-like pigmentation to large ulcers.[45] Hemosiderin is considered to be the cause of the brownish skin pigmentation typical of CVD. An increasing interest in the role of hemosiderin in the pathogenesis of venous disease followed the demonstration of pro-inflammatory properties of ferric ions, and the link between venous ulcer and genetic inborn errors of iron metabolism.[140–143] In fact, more recent data supports that no severe skin changes occur in legs with CVD until iron overload occurs.[144] Iron overload is not present in the less severe skin changes resulting from CVD but lipodermatosclerosis and VLUs are always accompanied by hemosiderin deposition.

The elongated, distended vascular system underlying areas of stasis is more susceptible to trauma than are normal vessels. Even minor blunt injuries may cause rupture of the vascular wall with extravasation of erythrocytes into the cutis.[12,18,130] Histologically, cutaneous hyperpigmentation

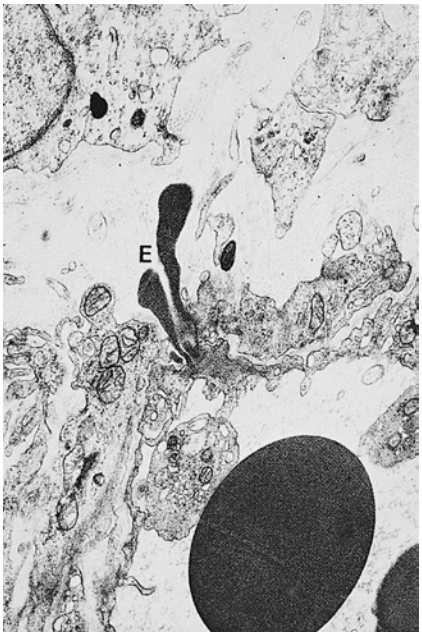


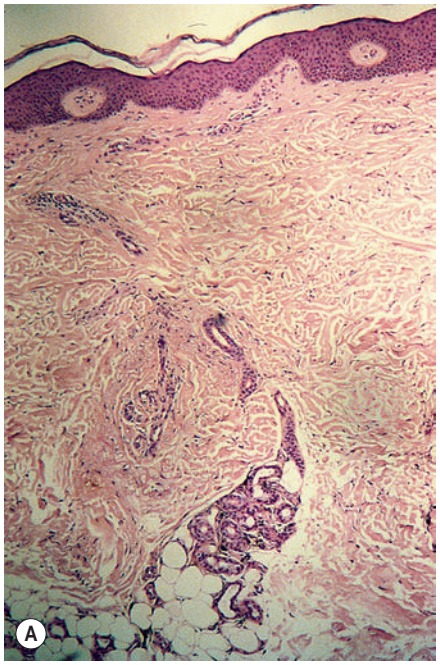
Figure 2.10 Two deformed erythrocytes wind through an intercellular space *(E)* into the pericapillary tissue. (Osmium–cacodylate ×18,100.) (From Wenner A, Leu HJ, Spycher M, Brunner U. Exp Cell Biol 1980;48:1.)

represents increased melanin early on and extravasated erythrocytes and hemosiderin-laden macrophages interspersed between dilated and tortuous capillaries in later stages and in inflammatory stages.[12,145,146] Erythrocytes appear either intact or to have become fragmented during their passage (Fig. 2.10). Extravasation appears to be caused by increased intravascular pressure and not chemotaxis, as occurs with white blood cells.[145]

Extravasated erythrocytes may be found in the deep dermis around adnexal structures (Fig. 2.11). When present clinically, they are a reliable guide to the existence of microangiopathy. A more acute 'eruptive' cutaneous pigmentation has also been noted as a 'blow-out' of erythrocytes into the dermis as a result of tremendous back pressure within the cutaneous microvasculature.[147] This phenomenon has been ascribed as the cause of lichen aureus (Fig. 2.12).[148] The only treatment for this condition is correction of the underlying venous hypertension (sclerotherapy and/or surgery), including graduated compression stockings and leg elevation. Fortunately, when venous hypertension is treated, dark pigmentation gradually fades. After correction of the etiology for the venous hypertension, a Q-switched nanosecond or picosecond laser specific for hemosiderin can then be used to remove or minimize the pigmentation (see Chapter 8). In addition, a noncoherent intense pulsed light source has also been demonstrated to lighten pigmentation.[149]

VENOUS (STASIS) DERMATITIS

The next dermatologic manifestation to occur in the chain of events following venous hypertension–stasis is 'stasis' dermatitis. This dermatitis has been given many names, including stasis eczema, varicose eczema, stasis syndrome, hypostatic eczema, congestive eczema and dermatitis



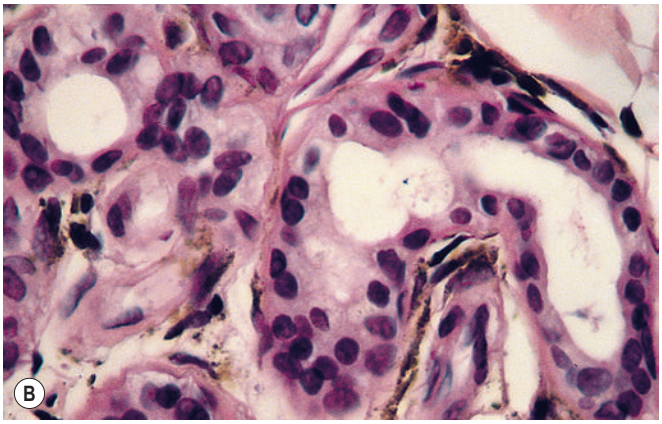


Figure 2.11 Skin biopsy specimen taken from the medial malleolar area of a 38-year-old man with ankle-pedal telangiectasias and venulectases with associated hyperpigmentation. Note hemosiderin-laden macrophages interspersed among eccrine glands in the deep dermis. (Hematoxylin–eosin; A, ×50; B, ×200.)

hypostatica. Because there may not be a true 'stasis' in the lower leg with venous insufficiency, but rather venous hypertension, this condition is best referred to as 'venous' dermatitis. Although a number of pro-inflammatory cellular and molecular mediators, biochemical mechanisms and structural changes leading to venular hypertension have been described in detail, the exact pathogenesis of venous dermatitis is still not completely understood.[150,151]

Venous dermatitis occurs more frequently in women, obese people, middle-aged men and women and those with a history of DVT and thrombophlebitis.[3] Edema, which causes the change from the normal cutaneous venous circulation to a high pressure system with increased vascular permeability, is the precursor of this dermatitis.[148,149,152–154]

A random sample of 476 people over the age of 65 years in Sheffield, UK, found an incidence of venous dermatitis of 21% in men and 25% in women.[155] In Denmark, the incidence in a random sample of people in homes for the

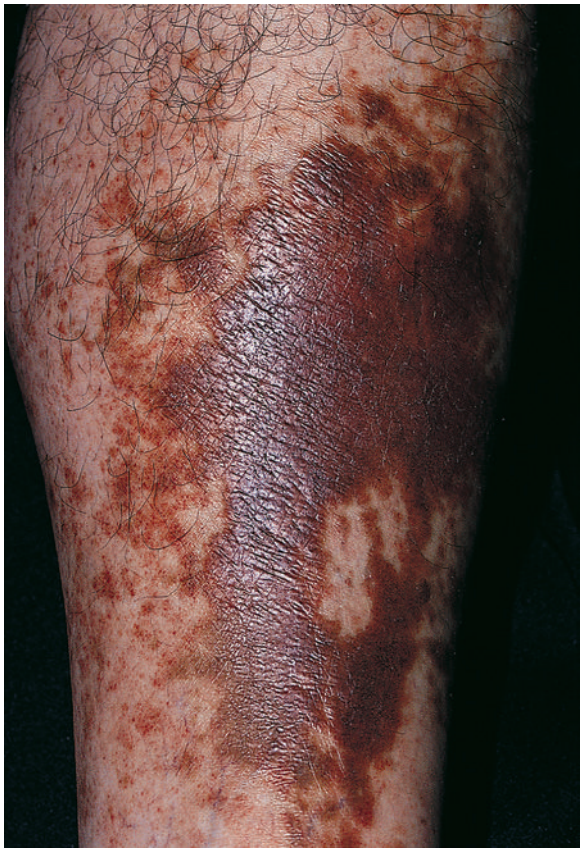


Figure 2.12 A 52-year-old woman with a 1 to 2 year onset of cutaneous hyperpigmentation of the anterior tibial and medial malleolar areas. Venous Doppler examination was diagnostic for an incompetent communicating vein.

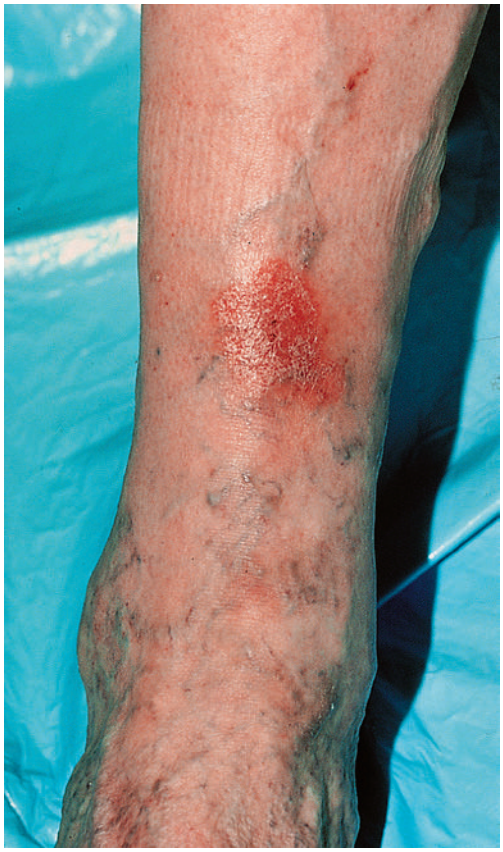


Figure 2.13 Early venous eczema appearing as a nummular eczema overlying prominent dilated venules and reticular veins in a 58-year-old woman.

aged (55–106 years old; mean age, 80 years) was 6.9%.[156] The authors speculated that the difference resulted from better nutrition in the Danish population. A similar incidence of venous dermatitis (5.9%) was found in a randomized examination of noninstitutionalized volunteers aged 50 to 91 years (average age, 74 years) in Boston, MA.[157] Interestingly, a survey of dermatologic patients in the Filipino population aged 60 years and over disclosed a 12% incidence of venous dermatitis, with 49% of all patients having varicosities.[69] This is contrary to the popular belief (see Chapter 3) that there is a lower incidence of venous disease in non-Western races.

The dermatitis usually begins in the medial paramalleolar region. This region is particularly vulnerable because the vascular supply, skin nutrition and subcutaneous tissue are less abundant here than in other areas of the lower extremity.[158] Venous dermatitis appears clinically as a sharply marginated, erythematous, crusted plaque (Fig. 2.13). With time and cutaneous trauma resulting from pruritus, overlying lichenification may occur,[3] as well as exudation, depending on the extent of the inflammation and associated edema. However, an indolent venous flow may make the skin assume a much paler color with less moisture.[159] The color of the lesion darkens as a result of an increase in melanocytic postinflammatory hyperpigmentation and dermal hemosiderin (Fig. 2.14).[2,160] The dermatitis may also be complicated by a generalized systemic hypersensitivity or 'ID' reaction.[2]

Venous dermatitis may manifest as a solitary lesion in 7% of patients and may mimic neoplasms, including squamous cell carcinoma and basal cell carcinoma.[161] Early recognition of the solitary venous dermatitis lesion should lead to appropriate treatment of venous hypertension, which may prevent further morbidity.

Recently, an association of venous dermatitis with amlodipine (a long-acting calcium channel blocker used in the treatment of hypertension, chronic stable angina and vasospastic angina) has been reported.[162] It is thought that amlodipine use may predispose those with venous insufficiency to leg edema and venous hypertension. Therefore, it is prudent to question patients with new onset stasis dermatitis about medication use.

Histologic examination (Fig. 2.15) of the dermis demonstrates a diffuse homogenization of collagen, fragmentation or absence of elastic fibers, thickening and partial occlusion of arterioles and atrophic changes of appendages.[12,163] There may also be an associated acanthosis and hyperkeratosis of the epidermis, which rarely results in pseudoepitheliomatous hyperplasia.[3] The lymphatic vessels are usually thickened and fibrotic, and there may be an associated dermal inflammatory infiltrate.[3] Because these changes are those of a nonspecific dermatitis, the histologic diagnosis of venous dermatitis can be certain only with clinical correlation.

Other conditions can give the appearance of venous dermatitis and should be ruled out; three cases of myelogenous

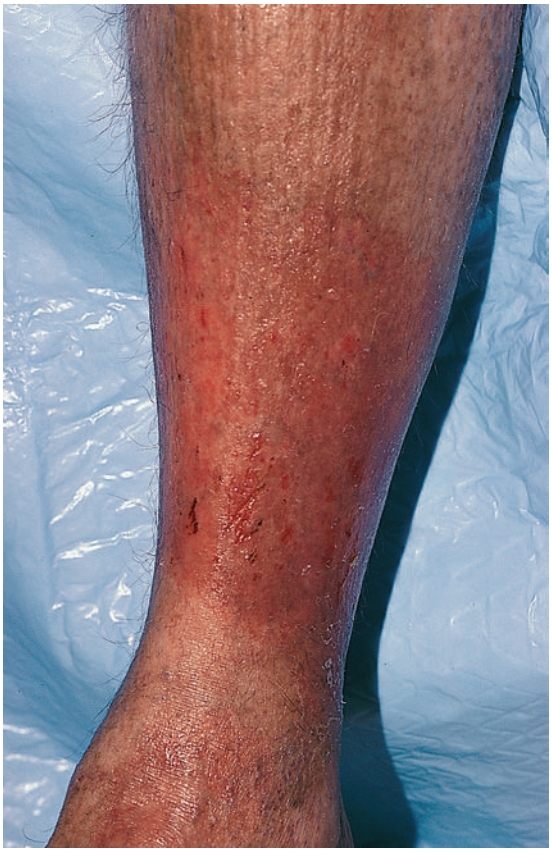
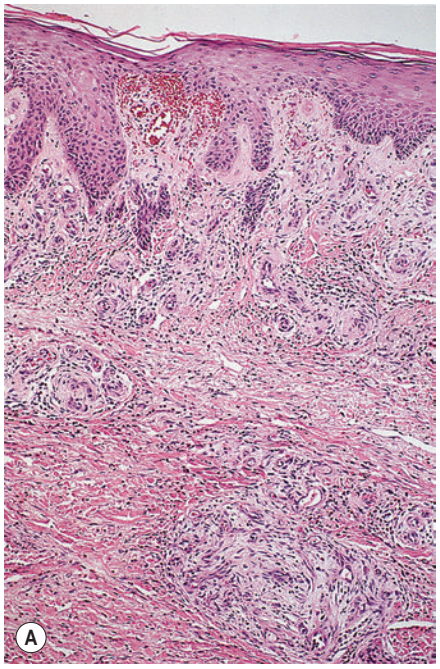


Figure 2.14 Typical appearance of venous dermatitis. The affected area is erythematous, sharply marginated and scaly with hyperpigmentation and excoriations.



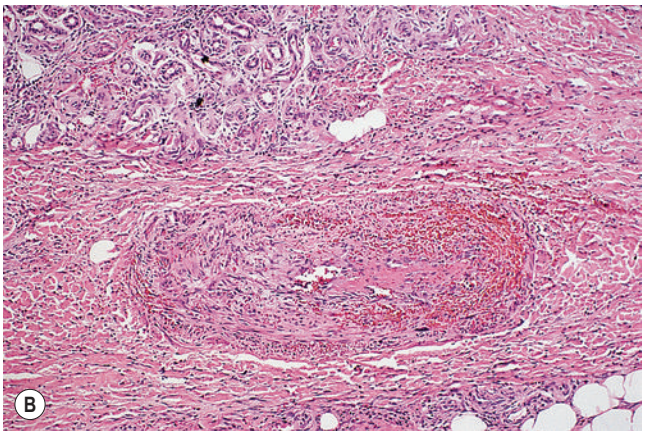


Figure 2.15 Histologic examination of a patient with longstanding venous hypertension and overlying venous dermatitis. (See text for description.) (Hematoxylin–eosin; A, ×50; B, ×200.)

leukemia cutis have been reported which appeared to be venous dermatitis.[164–166] Similarly, three reported cases of primary cutaneous diffuse large B-cell lymphoma, leg type, each of which presented atypically as large erythematous, infiltrated patches/thin plaques as opposed to ulcerated plaques or tumors, posed diagnostic challenges resulting from location and appearance.[167] Clinically all three had skin changes suggestive of possible venous stasis/dermatitis. Skin biopsy made the correct diagnosis in these cases, underscoring the importance of biopsy specimens of unusual patches/thin plaques or annular lesions on the legs of patients that do not respond to conventional treatment. A case of acroangiodermatitis, a benign uncommon vasoproliferative disorder that affects the lower extremities, secondary to CVI has been reported.[168] In this case, biopsy was instrumental to help rule out Kaposi sarcoma, which the clinical presentation mimics.

ATROPHIE BLANCHE

Atrophie blanche is the descriptive name given to the appearance of porcelain-white scars seen on the lower extremities as a result of infarctive lesions of the skin (Fig. 2.16). This condition was attributed originally to syphilis or tuberculosis in 1929.[169] The white plaques are bordered by hyperpigmentation and telangiectasias. Histologically, meandering capillaries are detected at the border of lesions, with their apex oriented toward the avascular center.[170]

The process usually occurs in middle-aged women with associated varicose veins and signs of venous insufficiency. However, this descriptive term represents the sequelae of many disease processes, including venous dermatitis, arteriosclerosis, dysproteinemia, diabetes mellitus, hypertension, systemic lupus erythematosus, scleroderma, juvenile rheumatoid arthritis and idiopathic segmental hyalinizing vasculitis. Therefore, this physical condition is best thought of as an intermediate stage between venous dermatitis and varicose ulceration; the term atrophie blanche is best reserved for the idiopathic vasculitic condition.

Patients with atrophie blanche have been compared with patients having severe venous insufficiency but without atrophie blanche. In turn, these have been compared with 10 healthy controls. Laser Doppler perfusion imaging was used, as were transcutaneous oxygen tension measurements. The overall results showed that resting blood perfusion was greater in atrophie blanche areas than in healthy

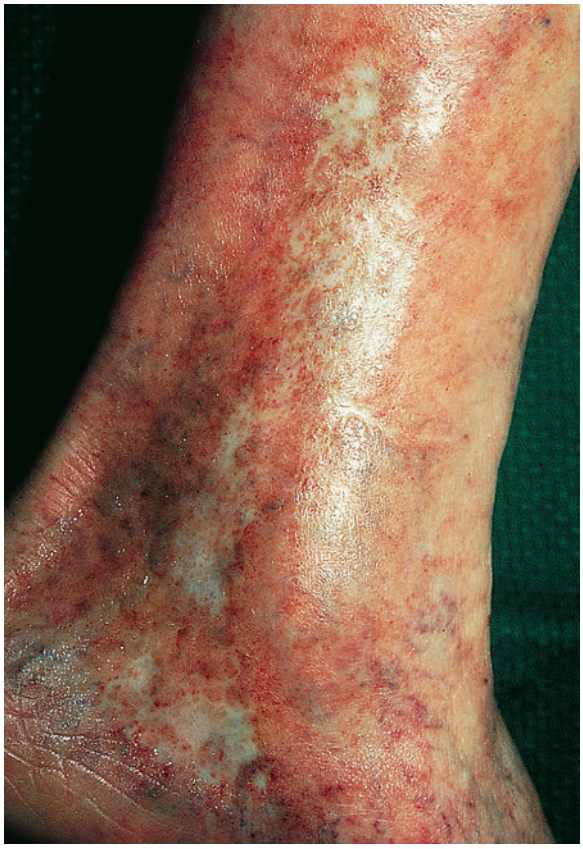


Figure 2.16 Middle-aged woman with venous insufficiency and atrophie blanche of the medial malleolar area. (Courtesy Kim Butterwick, MD.)

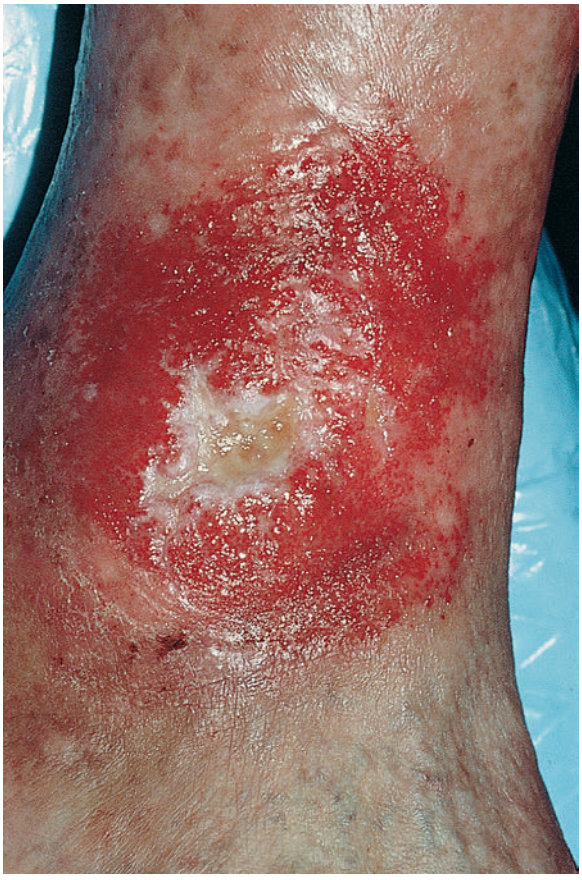


Figure 2.17 Chronic venous insufficiency with cutaneous ulceration in a 68-year-old man before treatment.

controls, and the venoarterial response was significantly increased in these atrophie blanche areas. In contrast, there was a decrease in transcutaneous oxygen pressure values in areas of atrophie blanche lesions and in the skin of patients with chronic venous insufficiency without atrophie blanche. The authors of this study concluded that basic resting flow in atrophie blanche is higher compared with that in normal skin and in patients with chronic venous incompetence, but there is also marked decrease in flow in response to venous occlusion in these affected areas.[171] In addition to treating venous hypertension, treatment with antifibrinolytics (i.e., aspirin, dipyridamole); anti-inflammatory agents (i.e., dapsone) and pentoxifylline have demonstrated to be helpful, especially in patients with idiopathic forms.[172]

ULCERATION

Cutaneous ulceration represents the end-stage manifestation of venous stasis disease. This relationship has been noted for millennia. Hippocrates was the first to record the association.[173] More than 300 years ago, Wiseman[174] noted that valvular incompetence caused by venous thrombosis could result in a circulatory defect leading to ulceration of the skin.

The prevalence of varicose or postthrombophlebotic ulcers has been estimated to be as high as 1% of the total United States population and 2% of the Swedish population (Fig. 2.17).[3,175–177] Although VLUs may have an onset in early adulthood, they increase in frequency with age and peak at approximately 70 years.[176–179] They have been estimated to afflict between 1% and 3% of the elderly population (ages 65–95) in the United States and Europe,[177] with actual numbers that may be higher because of misdiagnosis and underreporting. The ratio of females to males is approximately 3:1 after the age of 40, with an equal incidence before 40 years of age.[178]

Seventy-two different causes of leg ulcers have been recognized and grouped into three categories.[179] Between 75% and 90% are of venous etiology,[3,180,181] 40% to 60% of which are associated with varicose veins,[181–183] and 35% to 90% are associated with a history of DVT.[3,181–185] Nonvenous causes of leg ulceration include arterial disease (8%) and ulcers caused by trauma or those that have bacteriologic, mycotic, hematologic, neoplastic, neurologic or systemic origins (2%).[180] The most common chronic leg wound is the VLU, accounting for approximately 80% of all leg ulcers,[186] followed by diabetic foot ulcers, pressure ulcers and arterial ulcers, in order of frequency.

The cost of treating leg ulcers in the United States was estimated in 1991 to be between $775 million and $1 billion, based on the annual cost of ulcer care in Sweden.[187] Between 2007 and 2011, the annual payer burden in the United States to treat VLUs alone was estimated to be $14.9 billion.[188]

Recent data from the UK suggests the management of VLUs is thought to cost a staggering £400 million (~$627 million) per year and accounts for 13% of all nursing visists.[125] In addition to this cost, there is an estimated loss of 2 million working days annually in the United States because of leg ulcers.[189] Therefore, optimizing treatment, or better yet, prevention, is important. Curiously, despite its importance, very little government funding is allocated toward ulcer treatment. Patients diagnosed with leg ulcers in the United States spend, on average, 12.1 days in hospital.[190] Because leg ulcers frequently take much longer to heal with bed rest and ancillary care, this form of therapy is impractical and not properly reimbursable.

Color duplex investigation of limbs with reflux and ulceration has shown that distal venous reflux has an important influence over skin changes and ulceration, and reflux in the superficial veins appears to be more harmful than that confined to the deep veins even when such deep venous reflux extends through the length of the limb.[191] Reflux in the local area near the ulcer also influences ulceration. Local reflux may be influenced by perforating vein incompetence and outward flow. Isolated perforating vein outward flow without accompanying superficial reflux or deep reflux is seen in 4% to 6% of limbs with ulceration.[192] There is much controversy about the role of surgery in treating such reflux. However, most of the available data suggest that ablation of superficial venous reflux and ablation of outward flow through perforating veins is an appropriate method for the management of patients with primary venous leg ulceration.[193]

Between 20% and 25% of ulcerations have superficial venous insufficiency, either alone with perforating vein incompetence or as a significant component combined with deep venous insufficiency.[101,105,106,194,195] In one practice of more than 20,000 lifetime patients, it was estimated that nearly 15% of patients with major varicose veins developed ulcerations.[6] Although ulcerations are more common in patients with DVT, 13% of all venous ulcerations are observed in limbs with superficial venous insufficiency alone.

Cutaneous ulceration usually occurs 10 to 35 years (mean, 24 years) after the onset of varicose veins[196] and is commonly assumed to be specifically associated with incompetent calf perforating veins (see Chapter 9).[15,197–199] Dodd and Cockett[15] surgically explored 135 limbs with ankle ulceration and found that the most severe lesions were always associated with an incompetent perforating vein. Lawrence et al[198] studied patients with varicosities, both with and without associated ulceration, using Doppler ultrasound. They found sustained retrograde flow in incompetent veins in eight of nine ulcer patients but found it in only one of seven patients with varicose veins without ulceration. However, a recent study using duplex sonography showed no direct correlation between incompetent perforators and venous ulceration. Plethysmographic examination indicated that venous hypertension in superficial veins was the more important factor.[200] One study of 213 consecutive patients with venous ulceration demonstrated that 90% of patients had sustained ulcer healing (with a mean follow-up period of 3.4 years) when treated with saphenous ligation alone, without perforating vein treatment, even when incompetence of the perforating veins had been demonstrated.[201] Thus, any operative procedure on varicose ulcers must correct the underlying abnormal communicating superficial or perforating veins. Interestingly, no evidence or history of DVT was reported in up to 24% of patients with chronic venous leg ulcers;[183,202] therefore, the etiology may be multifactorial, with the majority of patients having a similar initiating event: superficial venous hypertension. This may arise from incompetent perforating veins alone, associated with an abnormal deep venous system, or with an incompetent superficial venous system.[203,204]

Stasis ulcerations, unlike most other causes of cutaneous ulcerations, appear in the gaiter area.[183,205] The ulcers appear cyanotic, edematous and friable. The base is usually covered with thick granulation tissue that rarely penetrates the deep fascia. The skin edges are painless, thickened and bleed easily. Adjacent skin is edematous and inflamed, with associated dilated venules, eczematous changes and pigmentation.[185,206] Calcification of the subcutaneous tissue, often not even adjacent to the ulceration, occurs in a significant number of patients;[152,207,208] up to 25% in one study (Fig. 2.18).[209] The calcium, acting as a foreign body, may perpetuate the ulceration or actually may be an essential cause of the lesion. Calcification is probably caused by venous insufficiency and represents the last stage of the inflammatory response. It almost always precedes the ulceration.[152]

In contrast to venous stasis ulceration, ischemic ulcers occur most commonly on the anterior and/or lateral leg and ankle. However, lateral ankle ulcerations may arise from incompetent small saphenous veins.[210] The base of an ischemic ulcer is often obscured by a pale yellow, purulent exudate. Often the borders are poorly epithelialized, with a 'punched-out' appearance, and are necrotic with islands of gangrenous skin. Deep fascia and tendon may be exposed at the base, with little or no spontaneous granulation tissue.

Individual leg ulcers can also have multiple causes, making classification more difficult. Two case reports of mixed skin ulcers misdiagnosed as pyoderma gangrenosum and rheumatoid ulcer successfully treated with ultrasound-guided injection of polidocanol microfoam, were reported in 2006.[211]

Several medical conditions occur commonly in patients (defined as >10% of patients) who develop VLUs.[212] These include anemia, asthma, angina, cellulitis of the lower extremity, depression, diabetes, limb edema, hypertension, osteoarthritis, pneumonia and urinary tract infections. Additional conditions associated with development of a VLU include congestive heart failure, history of deep vein thrombosis and subsequent postthrombotic syndrome, peripheral vascular arterial disease of the lower extremity, rheumatoid arthritis, history of hip surgery, history of venous surgery/ligation, being female and advancing age. Many of these medical conditions make biological and anatomical sense and are associated with reduced capacity for wound repair. The association between lower extremity venous surgery and the development of a VLU was not expected, because this is often discussed as a therapy for patients with a VLU,[213] suggesting a confounding factor. The important message is that physicians, nurses and other healthcare workers caring for patients with VLUs should be aware of the many concomitant medical conditions that can promote

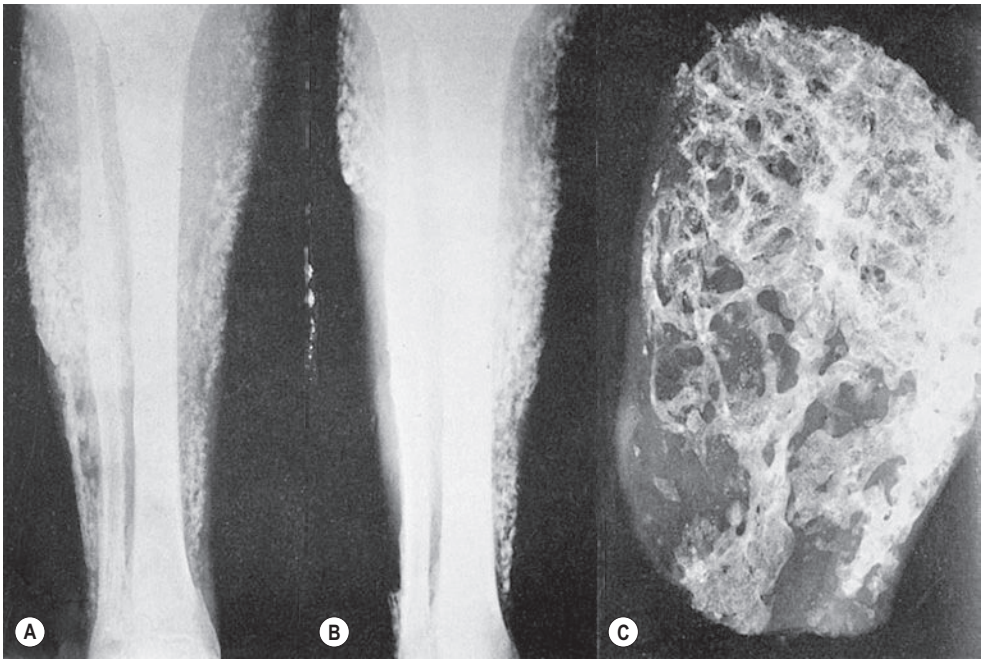


Figure 2.18 A 65-year-old woman with varicose veins, stasis dermatitis, and medial malleolar ulcerations bilaterally. **A,** Right leg; **B,** left leg; **C,** close-up view of left medial calf demonstrating extensive subcutaneous calcium deposits.

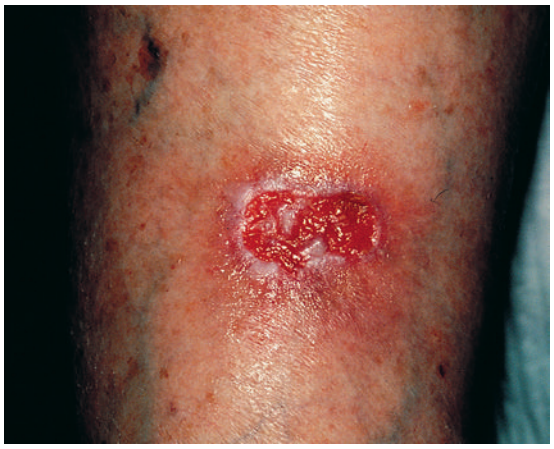


Figure 2.19 Basal cell carcinoma (keratinizing type) arising in an ulcer in the setting of chronic venous insufficiency in a 77-year-old woman. The ulceration had been present for at least 6 years. An incompetent perforating vein was found at the base of the ulceration.

development of ulcers, impede wound healing and make treatment and long-term control challenging.

MALIGNANT DEGENERATION

A potentially fatal, but fortunately rare, secondary change in venous ulcers is malignant degeneration (Fig. 2.19). There have been more than 100 case reports of malignant degeneration of a stasis ulcer in the world literature.[199,214–222] To determine the frequency of skin cancers associated with chronic leg ulcers (CLUs), presumably of vascular origin, and failing to heal despite 3 months or more of appropriate treatment, a prospective, multicenter, cross-sectional study was performed in France.[223] Biopsy revealed skin cancer in 16 of the 154 nonhealing CLUs (10.4%). The study concluded systematic biopsy of a wound refractory to 3 months or more of appropriate treatment is supported based on the findings.

The most common cancers reported are carcinomas (squamous and basal cell) and sarcomas (fibrosarcoma, osteosarcoma and angiosarcoma). Even malignant melanoma has been reported to occur in chronic venous ulceration.[224] In the French study, 9 squamous cell carcinomas (SCCs), 5 basal cell carcinomas (BCCs), 1 melanoma and 1 leiomyosarcoma were reported; 56.3% had persisted for at least 3 years.[223] The incidence of malignant degeneration of venous stasis ulcerations is 0.4% to 1%.[221,225–227] The average duration of the ulcer before tumor growth is 21 years, with a reported span of 10 to 40 years.[227] The onset of malignant change usually appears as a rapid growth of exuberant cauliflower-like masses, an increase in pain, or, in a smaller number of cases, a rapid extension of the ulcer crater.[227] An increase in induration of the ulcer borders and surrounding tissue and a failure of the ulcer to respond to prolonged conservative treatment are also suspect.[228] Transition into a malignant growth is thought to be stimulated by many factors, including chronic dermatitis, irritation and infection.[228,229] Implanted epithelial cells may produce a chronic foreign-body reaction with subsequent neoplasia.[230] Chronic scarring from the sequelae of ulceration mentioned earlier may obliterate lymphatic channels, leading to decreased immune surveillance of the scar by immunologically competent cells. This relatively localized immune deficiency provides less protection against cellular mutation, which allows cellular progression into neoplasia.[231] Therefore it seems prudent to perform a biopsy of the base and border areas of ulcers with these characteristics or of ulcers that persist for more than 4 months. This is particularly important when

surgically correcting the ulceration with a skin graft. One patient developed a squamous cell carcinoma following split skin grafting and, in spite of amputation and radiotherapy, died from multiple metastases.[199]

Although the appearance of malignant degeneration in a nonhealing leg ulcer is often characteristic, BCC in the ulcer may either appear as exuberant and translucent 'granulation tissue' or may have no clinical features to suggest malignancy.[216,219,232]

A study of SCCs complicating chronic venous leg ulcer has revealed some interesting facts. The mean age at cancer diagnosis was 78.5 years; the median survival was 1 year. Of these tumors, 11 were well differentiated, 10 moderately differentiated, and 4 were poorly differentiated. All patients with poorly differentiated tumors died within 1 year. Metastases were certain in 8 cases.[233] The disease was lethal in 10 cases, which included all of the poorly differentiated tumors. This suggests that when SCC in CLUs is found, a thorough investigation must include the degree of differentiation and a definition of extent of spread. Aggressive treatment is indicated because poorly differentiated tumors and some moderately differentiated tumors are fatal.

SECONDARY COMPLICATIONS OF VENOUS HYPERTENSION–STASIS

In addition to the varicose ulcers and dermatologic abnormalities already discussed, external hemorrhage, superficial thrombophlebitis and DVT are the three most severe and acute complications of varicose veins.

HEMORRHAGE

Hemorrhage from varicose veins may not be a rare event. Tretbar[234] reported treating 12 patients in 3 years for 18 episodes of hemorrhagic varicose veins. All but two of his patients had had varicose veins for more than 20 years. The bleeding area typically consisted of a mat of 'blue blebs', each of 1 to 2 mm in diameter, on the medial ankle. Doppler examination usually disclosed an underlying incompetent communicating vein. None of Tretbar's patients developed serious sequelae from the bleeding episodes and all were treated successfully with compression sclerotherapy of the affected veins. However, bleeding can be profuse and, if unnoticed or improperly treated, can be fatal.[15,235–237] A report on the mortality of varicose veins from Australia between 1997 and 2000 disclosed 51 deaths where varicose veins were indicated to be the primary cause of death.[238] In one third of these cases, hemorrhage was the cause.

Hemorrhage is usually spontaneous but may also occur when the skin overlying a varicose vein becomes traumatized or eroded. Most cases described in the literature occur in patients with ulcers overlying varices, but profuse bleeding may also occur from varicosities 1 to 2 mm in diameter (Fig. 2.20). Twenty-three fatal cases of hemorrhage were reported in England and Wales in 1971.[235] The patients most at risk are solitary elderly patients with longstanding varicose veins. These patients usually live alone and are unable to apply pressure to the bleeding varix or to get help because of physical disabilities. Rarely, patients may have no history of longstanding varices or overlying ulcers. Hemorrhage in this setting is usually attributable to the rapid development of venous hypertension that occurs from DVT.[239]

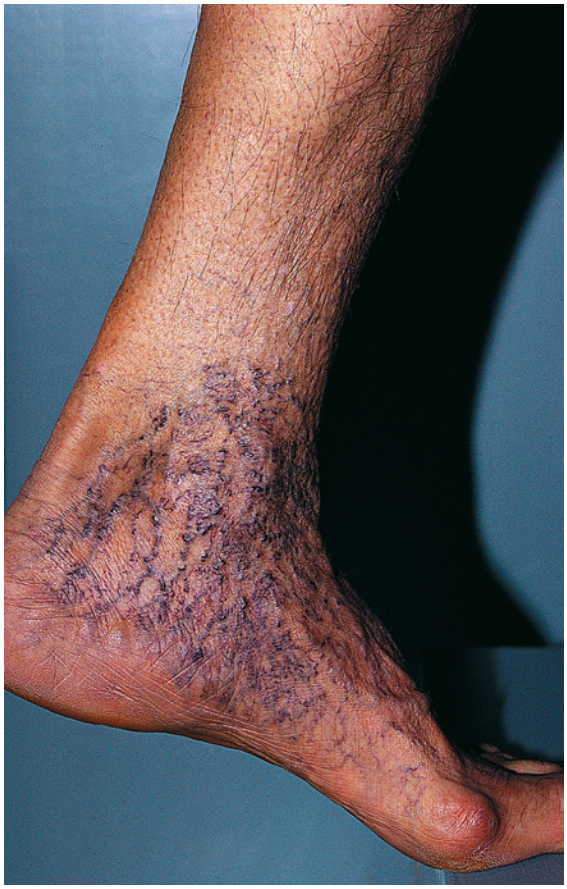


Figure 2.20 Venulectasia in a 90-year-old man that bled profusely while the patient was standing. Sclerotherapy caused rapid healing.

If the varicose vein is under high pressure from venous insufficiency, as it usually is, the acute hemorrhage may appear to be arterial in origin. This may result in the inappropriate application of a tourniquet, which only increases venous hypertension. If properly recognized, bleeding of venous origin is easily controlled by raising the affected area above the level of the heart and applying localized pressure to the bleeding vein. Leg elevation stops hemorrhage within seconds to minutes. Sclerotherapy or ligation of the affected vein is curative but may not prevent further episodes of hemorrhage from other varices.

Direct pressure over the area of hemorrhage stops the bleeding, and maintaining that pressure for 5 to 7 days allows complete healing of the epidermis over the area of the hemorrhage.[240] It has been found that a suture of the area of hemorrhage, usually done in a hospital emergency department, causes venous ulceration. Direct suture, therefore, should be avoided.

Injection of potentially hemorrhagic veins is mandatory (Fig. 2.21). In these cases, usual aesthetic concerns do not apply and it is logical to inject the fragile venules at the very beginning of the treatment, before the necessary reduction of venous hypertension. Sclerosing injections of bleeding veins provide an elegant solution to the problem; provided the sclerosing agent induces a spasm (polidocanol, sodium

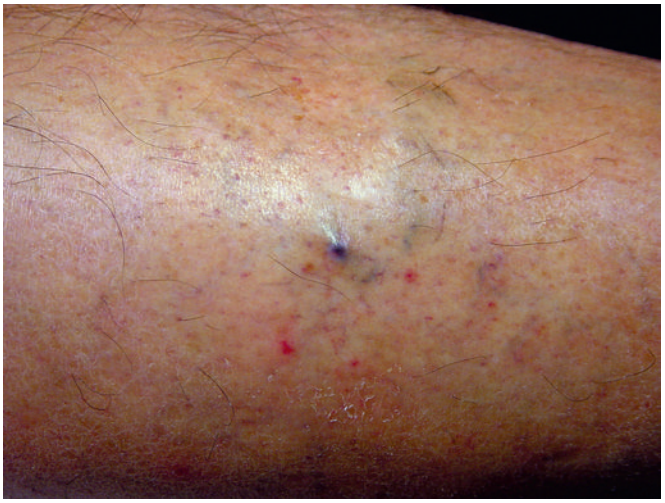


Figure 2.21 Injection of potentially hemorrhagic veins is mandatory.

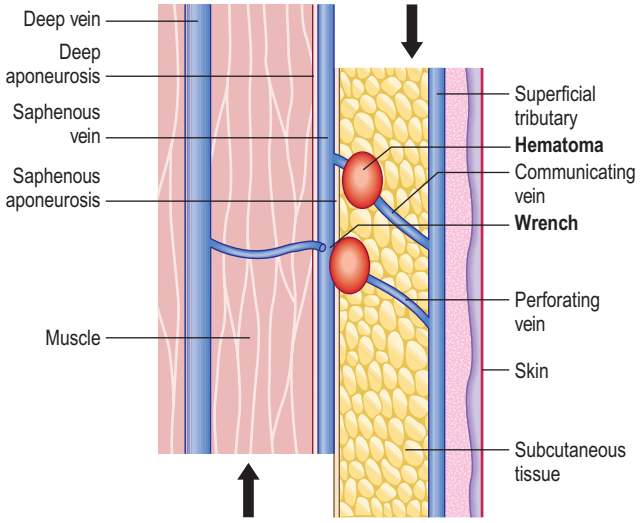


Figure 2.22 During a quick movement of the lower limb, inertia of muscle and fat tissues create a relative displacement of the different anatomic layers.

tetradecyl sulfate), it stops the hemorrhage and usually prevents a recurrence. The leg should be elevated during injection, and higher than usual concentrations of sclerosing solution are often required. Foamed sclerosant may also help stop the bleeding more quickly.

Because the responsibility for skin abrasion and subsequent hemorrhage lies mostly with patients themselves, advice should include careful nail trimming and filing, and nocturnal wearing of socks (and maybe even gloves as well). Avoiding scratching of the skin is also a prerequisite, as fewer complications are caused by corticosteroid creams than by ulcers and hemorrhages caused by scraping.

The 'shear off' phenomenon can explain 'spontaneous' acute pains of the calf, known in the French literature as 'whip pains of the calf'. During a quick movement of the lower limb, inertia of muscle and fat tissues creates a relative displacement of the different anatomical layers (Fig. 2.22) responsible for wrench of communicating or perforating veins, resulting in pain, hematoma and ecchymosis. This atraumatic lesion is more common on varicose veins because of the venous wall remodeling and dysplasia, and because of venous hypertension. Duplex ultrasound shows edema and a small hematoma, and usually no sign of superficial thrombophlebitis. Local compression and massage with nonsteroidal anti-inflammatory cream is the sole treatment.

SUPERFICIAL THROMBOPHLEBITIS

Superficial thrombophlebitis (ST) is a painful condition that fortunately seldom results in serious embolic complications. In the absence of malignancy, thrombophlebitis of the leg is almost invariably associated with varicose veins.[4,241–243] Patients with varicose vein ST are younger and have a decreased incidence of coexistent DVT (9.75% versus 43.75%).[242] The condition results from the development of a clot in a varicose vein caused by one or more of the following factors: trauma to the varicosity, stasis of blood flow or occlusion of blood flow. Fifty percent of cases may occur spontaneously.[241,244] An evaluation of 51 consecutive patients with venous thrombosis and varicose veins found 8% with an underlying malignancy, 7% with an antiphospholipid syndrome and a total of 26% with other systemic illnesses.[245] Therefore it is recommended that a search for an underlying cause be made.

The great saphenous system is the usual site of ascending ST. Clinically, one notes a painful, tender, hot erythematous swelling along the course of the vein, with a variable amount of perivascular edema. The pain associated with ST is often severe, probably resulting from inflammation of the dense network of somatic nerve fibers in the associated subcutaneous tissue.[4]

Incidence of ST, irrespective of the presence of varicose veins, increases with advancing age and inactivity, and with bed rest as the result of surgery, childbirth or cardiac disease.[246,247] In patients in whom the incidence of varicose veins is not stated, ST has been estimated to occur in 0.7% of women in their fourth decade of life, increasing to 2.6% of women in the seventh decade.[62] In men, the incidence of ST has been estimated to be 0.4% in the fourth decade, increasing to 1.7% in the seventh decade.[62] The actual number of patients with ST in the United States was estimated in 1973 to be 123,000 yearly. The incidence of ST is substantially higher when related to the presence of varicose veins.[4] A review of the lifetime work of one physician with more than 20,000 patients notes an incidence of ST in as many as 20% of patients with prominent major varicosities.[6] Older papers have estimated a 50% lifetime incidence of thrombophlebitis in patients with varicose veins.[248] Fegan[90] estimates that ST occurs in approximately 4% of those with varicose veins.

Although the condition is usually treated as a benign complication of varicose veins, the development of DVT, venous hypertension and pulmonary emboli may occur in a significant percentage of patients.[241,244,249–253] A review of 340 cases of ST in a university hospital disclosed a 10% incidence of pulmonary emboli with five deaths,[244] and this risk has been confirmed by others.[254] The development of pulmonary emboli may also be related in some cases to a coexistent DVT.[4,255,256] One study of 44 consecutive patients with ST found coexistent DVT in 23%. All of these cases

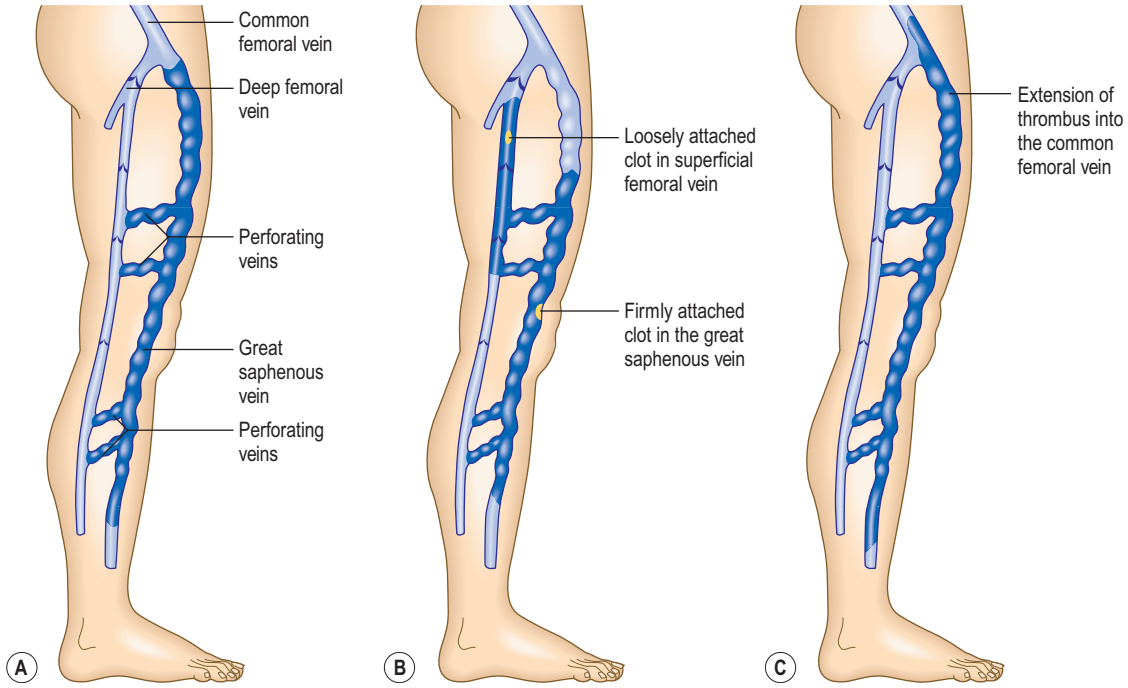


Figure 2.23 Diagrammatic representation of three methods of propagation of superficial thrombophlebitis. **A,** Thrombophlebitis limited to the superficial system with blockage by the perforating vein valves and at the saphenofemoral junction. **B,** Extension of the thrombus into the deep system through destruction and incompetence of perforating veins. **C,** Direct extension of the thrombus into the femoral vein at the saphenofemoral junction. (Redrawn from Totten HP. Angiology 1965;16:37.)

were occult clinically, with the site of the ST not predictive of DVT.[243] Thus, noninvasive deep venous studies are recommended for all patients with ST.

Pulmonary emboli and DVT, by definition, were supposed not to complicate ST unless the thrombus progressed into the deep venous system, but it has been observed that DVT can occur in other venous networks. This may happen because of either progression into a perforating vein or ascending involvement of the common femoral vein at the saphenofemoral junction (Fig. 2. 23) or simply because of the presence of a hypercoagulable state.[257] When either of these events occurs, superficial or deep venous hypertension develops as a result of valvular destruction.[247] Propagation of the thrombotic process into the deep system has been reported to occur in 6%[258] to 32%[249] of all cases of ST. In an 11-year retrospective series, 17% of 133 patients were noted to have extension of the clot into the deep system.[259] Surgical exploration of the saphenofemoral junction, followed by ligation, thrombectomy and limited vein stripping, has been advocated, particularly if clinical signs of thrombophlebitis reach the mid-thigh. We recommend full anticoagulation. Surgical removal of the thrombosed vein segments and associated varicosities shortens the convalescence and mitigates recurrences.[258,260,261] Unfortunately, this latter form of treatment usually results in extensive scarring. Finally, because DVT may manifest partly in the appearance of ST, patients should be examined carefully.

Surgical treatment of ST has been dominant when the ST has affected the GSV and ascended toward the saphenofemoral junction. It is thought that the incidence of DVT is three times that of normal individuals, and, in the past, with ascending thrombophlebitis of the GSV, an operation under local anesthesia to ligate and divide the vein was recommended.[262] However, gradually, anticoagulant treatment has dominated clinical practice. The advantage, of course, is that the ST is treated simultaneously by the anticoagulation, compression and rest. Nonsteroidal anti-inflammatory medications have been advocated but may have potentially severe side effects. As ST is associated with a higher risk of DVT, and because ST of the GSV when ascending to the junction leads to progression of the clot into the femoral vein, the use of low molecular weight heparins must be considered—prophylactically for 2 weeks when the clot does not threaten the deep system, but therapeutically, like for a DVT, when it does.[263] External elastic compression is recommended by most authorities on this subject.[257]

DEEP VENOUS THROMBOSIS

Varicose veins, by virtue of their low blood flow, are considered a high risk factor for DVT.[4] Without other predisposing factors, patients with varicose veins have an incidence of DVT ninefold that of the normal population.[264] Platelet aggregation is thought to occur behind valve cusps, especially when the valves are incompetent in varicose veins.[265,266] Thrombosis on the valve cusps then triggers the coagulation cascade and results in clot propagation.

Stasis of blood flow may cause activation of factors XII, XI and IX, which initiates thrombin activity to propagate thrombus formation through fibrin formation and platelet aggregation.[267] Stasis may also result in a significant amount of endothelial sloughing, with exposure of subendothelial collagen and subsequent activation of platelets.[268] An additional reason for the propensity for DVT in patients with chronic venous insufficiency (which is commonly associated

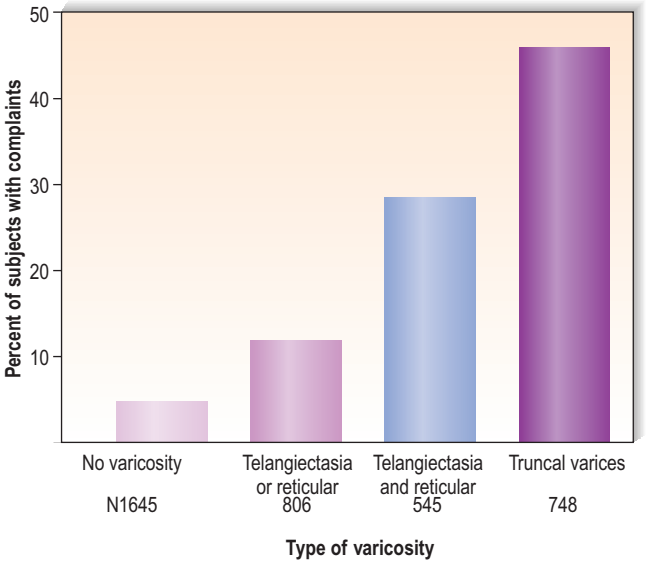


Figure 2.24 Complications according to the type of varicose vein. *N* represents the number of persons in the defined group. (Redrawn from Widmer L. Peripheral venous disorders: prevalence and socio-medical importance: observations in 4529 apparently healthy persons, Basle Study III. Bern, Switzerland, Hans Huber; 1978.)

with the presence of varicose veins) may be related to a faulty fibrinolytic system, correlated with pericapillary deposition of fibrin.[269] This hypothesis has been questioned because up to 70% of patients with idiopathic DVT have a decreased tissue plasminogen activator that probably reflects endothelial dysfunction and a decreased clearance of clotting factors.[269–272]

An increased incidence of DVT is also found in the postoperative period.[273–277] This may be related to the increased incidence of thrombophlebitis in varicose veins in the postoperative period, with an incidence estimated at 6% versus the normal 0.5% to 0.7% incidence.[278] This is of particular significance in patients less than 60 years of age. With fibrinogen scanning, DVT occurs in 56% of patients over 60 with varicose veins versus 41% in patients over 60 without varicose veins. This can be compared with 56% in patients younger than 60 years with varicose veins versus 19% in patients less than 60 without varicose veins.[279] Therefore, all patients with varicose veins who are about to undergo surgery, or who are bedridden or pregnant, should receive thrombosis prophylaxis, such as wearing a graduated support stocking, to prevent this potentially fatal, albeit rare, complication of varicose veins.

In summary, varicose veins are associated with a number of serious medical problems and are not just of cosmetic concern. The Basle study III[5] found that the incidence of the major complications of varicose veins—chronic venous insufficiency, phlebitis and pulmonary embolism—increases with the severity of the varicosity (Fig. 2.24). Even patients with minor telangiectasias and reticular veins in combination demonstrated a significant increase of these serious medical complications when compared with patients without these types of veins.

Table 2.1 Classification of Varicosities of the Lower Extremities

Group	Varicosities	Saphenous System
1	Spider bursts; telangiectatic veins	Competent
2	Mild or moderate varicosities	Competent
3	Mild, moderate or marked varicosities	Incompetent

From Heyerdale WW, Stalker LK. Ann Surg 1941;114:1042.

Box 2.8 Advantages of Ligation of Incompetent Saphenous Vein

- Continuity of the vein is interrupted at the most proximal point
- Need for cannulization is reduced to a minimum
- Number of local injections necessary for obliteration is decreased
- Period of treatment is shortened
- Adequate complete thrombosis is obtained with greater ease
- Pulmonary showers are less likely to occur

From Heyerdale WW, Stalker LK. Ann Surg 1941;114:1042.

CLASSIFICATION

A classification of varicose veins should be based on anatomic or subsequent therapeutic considerations. The first anatomic classification was proposed by Heyerdale and Stalker[280] in 1941 (Table 2.1). This classification is useful in determining when surgical ligation of the GSV is advantageous before performing sclerotherapy. The list of advantages presented by Heyerdale and Stalker still holds true today (Box 2.8). The Basle study[5] classified varicose veins into three groups:

1. Dilated saphenous veins (stem veins)
2. Dilated superficial branches (reticular veins)
3. Dilated venules (hyphenwebs).

Duffy[281] proposed a more complete classification of 'unwanted leg veins'. Because one purpose of a classification is to provide a mechanism for evaluating pathophysiology and treatment, a modification of the Duffy classification appears useful. It provides comprehensive clinical and therapeutic criteria in an effort to optimize treatment (Box 2.9 and Figs 2.25–2.30).

Varicose veins can be classified into four developmental stages. The first stage appears as a somewhat dilated blue vein in association with normal great and small saphenous veins. This stage usually occurs in teenagers with a family history of varicose veins. It is asymptomatic.

The second stage appears as a palpable, bulging, moderately dilated vein, usually in association with a larger

Box 2.9 Vessel Classification

Type 1: Telangiectasia, 'spider veins'
- 0.1–1.0 mm diameter
- Red to cyanotic

Type 1A: Telangiectatic matting
- 0.2 mm diameter
- Red

Type 1B: Communicating telangiectasia
- Type 1 veins in direct communication with varicose veins of the saphenous system

Type 2: Mixed telangiectatic/varicose veins
- No direct communication with the saphenous system
- 1–6 mm diameter
- Cyanotic to blue

Type 3: Nonsaphenous varicose veins (reticular veins)
- 2–8 mm diameter
- Blue to blue–green

Type 4: Saphenous varicose veins
- Usually over 8 mm in diameter
- Blue to blue–green

Modified from Duffy DM. Small vessel sclerotherapy: an overview. In Callen JP et al, editors. Advances in dermatology. Vol 3. Chicago: Year Book; 1988.

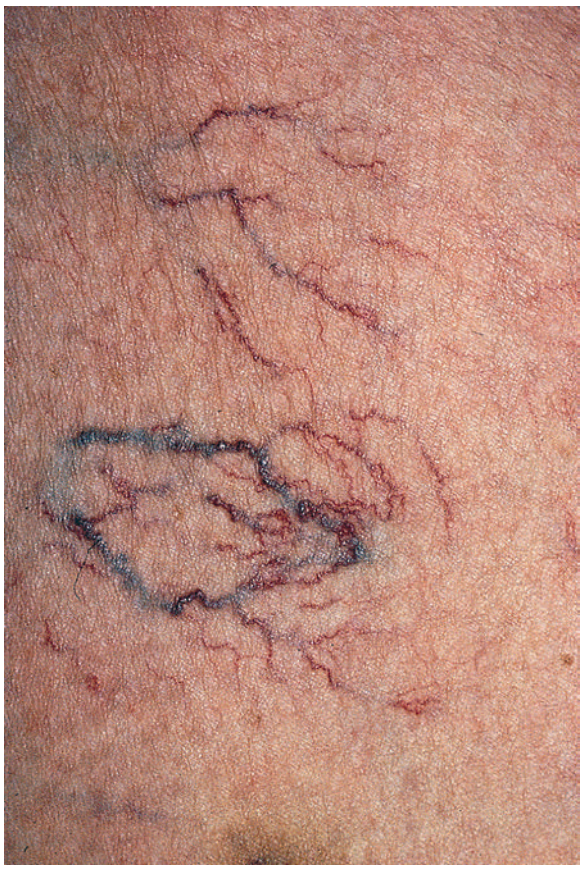


Figure 2.25 Duffy type 1 (telangiectasia) on the inner thigh of a 58-year-old woman.

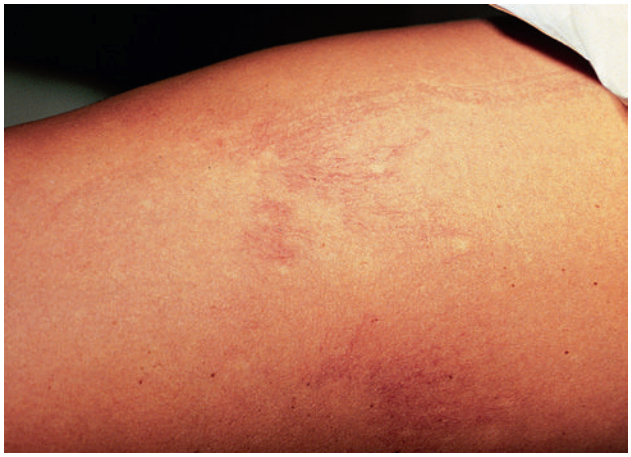


Figure 2.26 Duffy type 1A (telangiectatic matting) 6 weeks after sclerotherapy treatment on the lateral calf. Note associated reticular veins, postsclerotherapy hyperpigmentation and bruising.

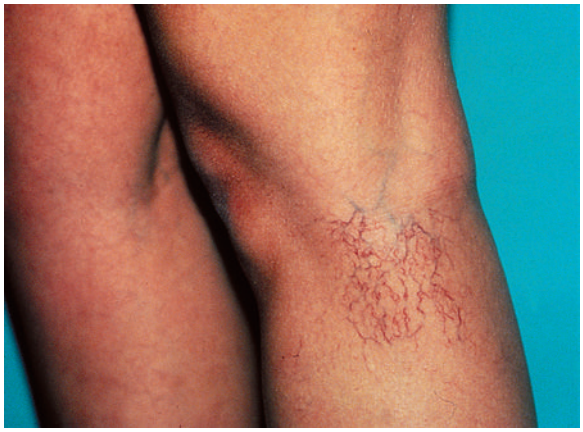


Figure 2.27 Duffy type 1B (communicating telangiectasia) in a 20-year-old woman.

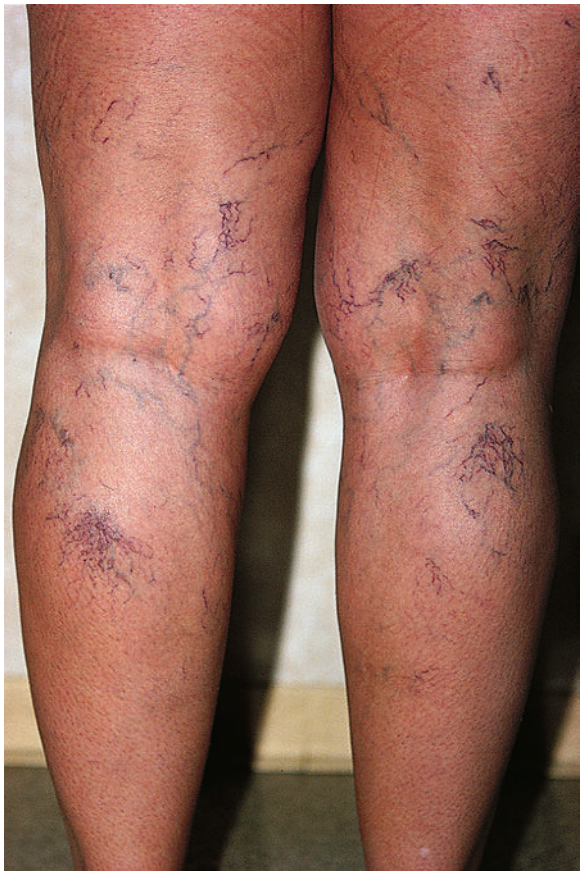


Figure 2.28 Duffy type 2 (mixed telangiectasia and varicose veins with no direct communication with the saphenous system) in a 54-year-old woman. There was no evidence (venous Doppler) of incompetence of the saphenofemoral or saphenopopliteal junctions or of perforating veins.

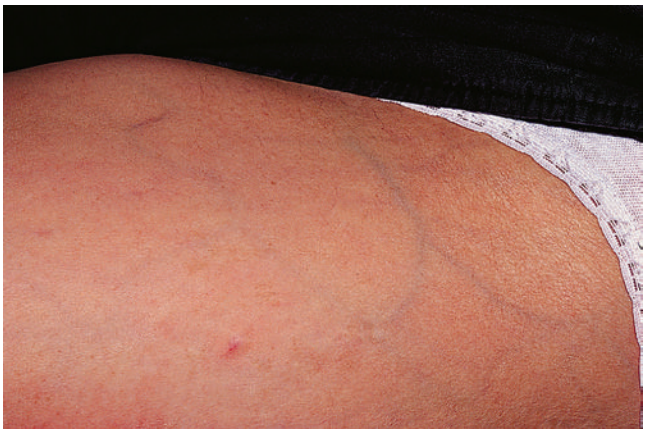


Figure 2.29 Duffy type 3 (nonsaphenous varicose (reticular) veins) located over the proximal anterolateral thigh of a 24-year-old woman.

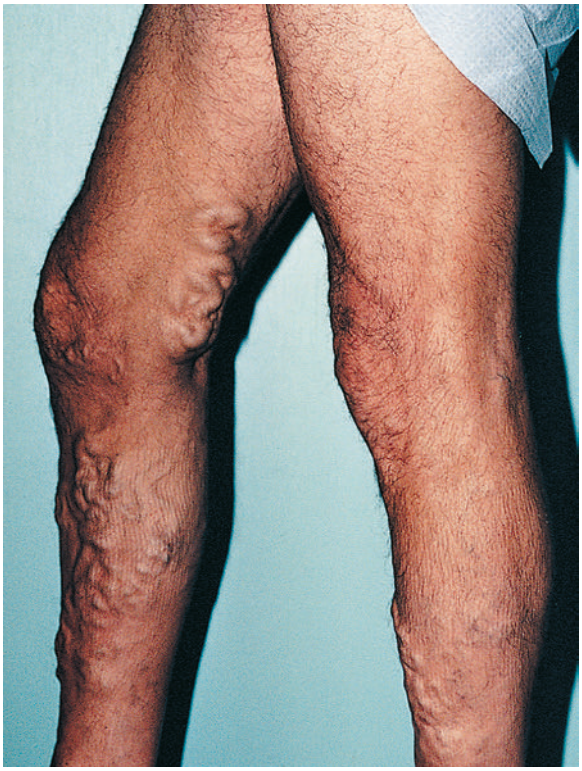


Figure 2.30 Duffy type 4 (saphenous varicose veins). Varicose great saphenous vein with incompetent valvular function throughout its length and a grossly incompetent saphenofemoral junction in a 32-year-old man.

saphenous vein. Venous Doppler examination is normal; Duplex scanning may show a dilated but competent saphenofemoral and/or saphenopopliteal junction. These veins may be symptomatic after prolonged immobilization or standing.

The third stage represents established varicose vein disease. The great and/or small saphenous veins are dilated over all or part of their length. There are associated varicose veins over the thigh and lower leg, with accompanying venules and spider veins. The varicose veins themselves may or may not be incompetent, but gross incompetence is present at the saphenofemoral and/or saphenopopliteal junctions.

The final, or fourth, stage consists of complications arising from chronic venous insufficiency and varicose veins. Perforating vein incompetence is present along with cutaneous manifestations of venous stasis disease, including ulcerations.

The development of varicose vein disease is generally progressive. Six different patterns of GSV varicosity have been described.[122] These relate to the duration of varicose vein disease (Fig. 2.31). Certain patients may experience spontaneous stabilization of the disease in the early stages. Treatment of early-stage disease may prevent the progression and cause regression of the disease process. A complete understanding of the anatomy and pathophysiology of the venous system with regard to varicose veins allows the development of a rational treatment plan.

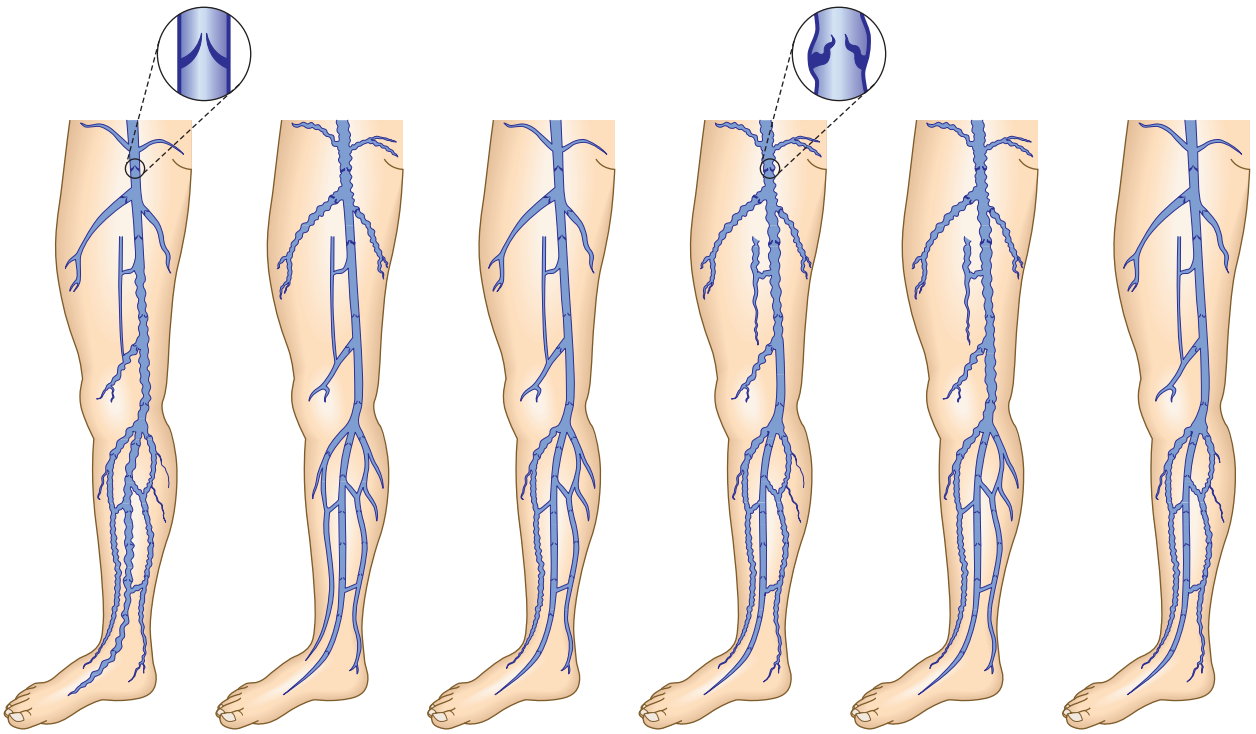


Figure 2.31 Patterns of great saphenous vein incompetence in 296 limbs with primary varicose veins. (Modified from Almgren B, Eriksson I. Acta Chir Scand 1990;156:69. © British Journal of Surgery Society Ltd. Reproduced with permission. Permission is granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

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3 Pathophysiology of Varicose Veins

Mitchel P. Goldman, with contributions by Lisa Zaleski-Larsen

Essentially, three components of the venous system of the leg act in concert: deep veins, superficial veins and perforating-communicating veins. Dysfunction in any of these three systems results in dysfunction of the other two (Fig. 3.1). When the superficial veins are placed under high pressure they dilate and elongate to accommodate an increased blood volume. Their tortuous appearance is termed *varicose*, derived from the Greek term for 'grapelike'. This term applies to both the large protruding veins within the superficial subcutaneous tissue and the smaller venectasia, or 'spider veins' that occur just beneath the epidermis.

The World Health Organization defines varicose veins as 'saccular dilation of the veins, which are often tortuous'.[1] This definition specifically excludes any tortuous veins associated with previous thrombophlebitis, arteriovenous connections or with venectasia.

HISTOCHEMICAL PHYSIOLOGY OF VARICOSE VEINS

Varicose veins differ from nonvaricose veins in physiologic function. This may occur in one or all of the histologic layers. Endothelial damage can occur in parts of a varicose vein,[2] and has been noted both ultrastructurally and physiologically by a reduction in endothelial-mediated enhancement of norepinephrine (noradrenaline) induced vasoconstriction (Fig. 3.2).[3,4]

Characterization of the endothelin receptors in varicose veins compared with those in normal veins has shown decreased contraction to endothelin-1 in both varicose and saphenous veins of patients with primary varicosities. It may be that this observation will be associated with a decrease in the number of receptors.[5]

In most investigations alterations have been found in the muscular layer, with varicose veins having a considerable degree of smooth muscle hypertrophy and a 15% increase in muscle content compared with normal veins.[6] This is thought to be a secondary response to venous hypertension. Other investigators have found that smooth muscle cells are capable of phagocytosis and decomposition of collagen fibers.[7] Smooth muscle cells from varicose veins are less differentiated compared with normal veins and demonstrate increased synthetic capacity, greater proliferation and increased migration than smooth muscle cells found in normal veins.[8] Therefore these cells may be part of the cellular basis for collagen breakdown. However, other investigators have noted a decrease in lactate dehydrogenase and creatine kinase activity in varicose versus normal veins and postulate that varicose vein weakness is the result of a thinning or damaged muscular layer.[9] This has been confirmed in a study of aging canine and human veins where a decrease in sympathetic innervation has been correlated with muscular layer thinning.[10] In addition, the protein content of varicose veins, which is predominantly smooth muscle, is reduced.[4] However, one research group has found no significant difference in the quantity of smooth muscle between normal and varicose veins.[11]

Alterations in the adventitial layer have been noted in varicose veins. Some investigators have found that varicose veins have an extremely dense and compact fibrosis between the intima and adventitia, with a diminished and atrophied elastic network and a disorganized muscular layer (Fig. 3.3).[12–15] Thickening and fibrillation of individual collagen fibers has also been noted.[2,13,16,17] This translates to a reduced compliance that may lead to poor coaptation of venous valves and increased varicose vein wall stiffness. An in vivo measurement of venous elasticity in patients with normal, 'high-risk' and varicose veins confirmed reduced elasticity in both varicose and high-risk veins.[18] In this study, individuals with high-risk veins were defined as having a family history of varicose veins, standing occupations, symptoms of venous disease and Doppler ultrasound reflux.

The described loss of tonicity of varicose veins is primarily the result of the loss of coordinated communication between smooth muscle cells. Electron microscopic studies of nonvaricose veins demonstrate the close approximation of smooth muscle cells. When veins become varicose, smooth muscle cells become vacuolated and are separated by collagen.[12,13] With increasing varicose changes intercellular collagen deposition accumulates and separates the smooth muscle cells, which then atrophy (Fig. 3.4). It is suggested that the resulting separation of smooth muscle cell hemidesmosomes causes inefficient smooth muscle contraction and increased venous distensibility.[11,13,19] However, some varicose veins are capable of constricting in response to an infusion of dihydroergotamine. This venoconstriction is even more pronounced than that occurring in normal veins.[20] The reason for this paradoxical effect is unknown, but a varicose vein appears to be a dysplastic vein characterized by malformations. Whether this is the result of continual high venous pressure or whether it is the primary etiologic event in the development of valvular incompetence is also unknown.

Elastin and collagen are known to play an important role in maintaining structural integrity of blood vessel walls. Normally when the wall is stretched, elastin generates a shortening force that opposes the traction exerted by the side branches and perivascular connective tissue and the

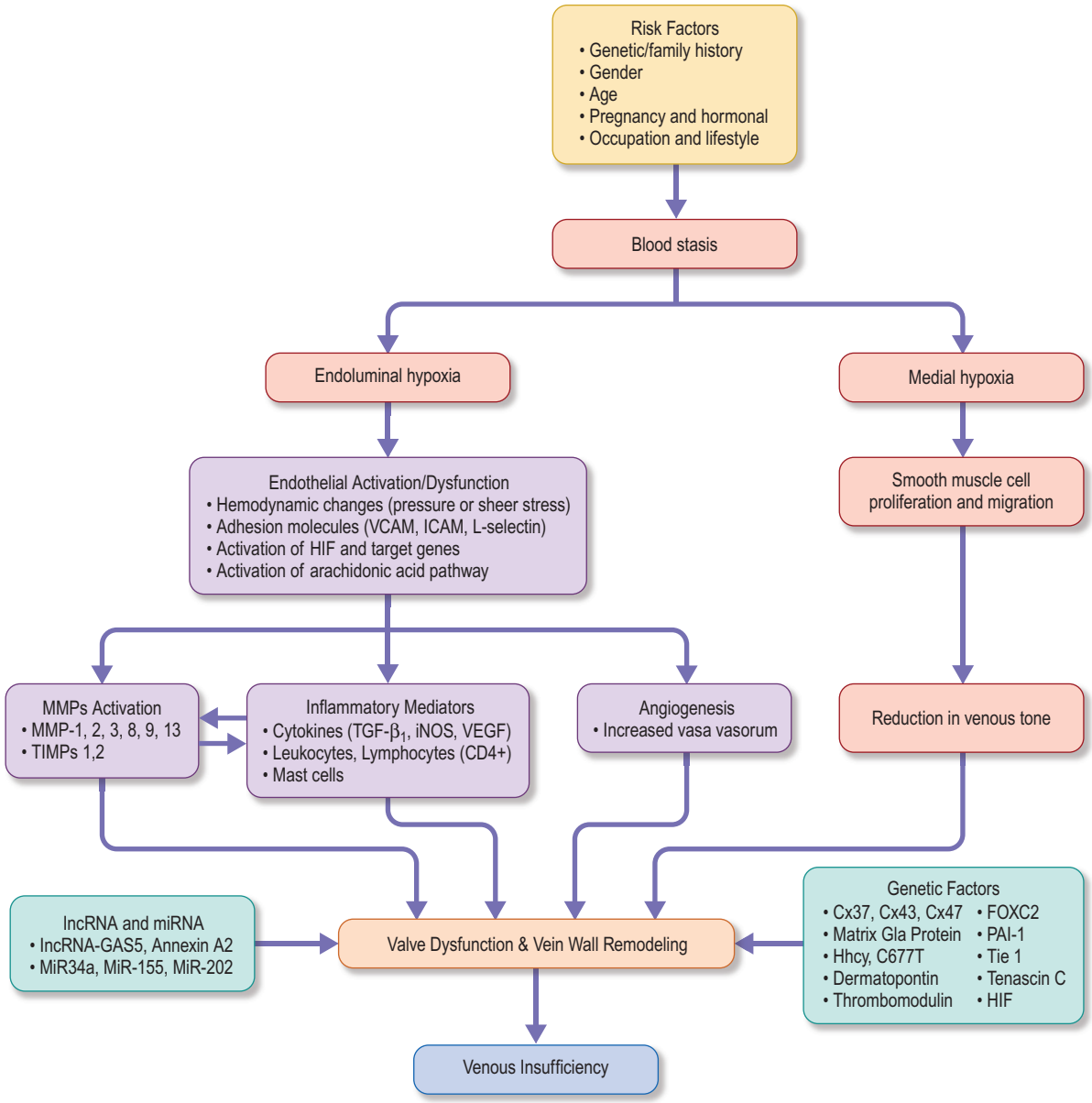


Figure 3.1 Representation of the factors involved in the pathogenesis of venous insufficiency.[56,62]

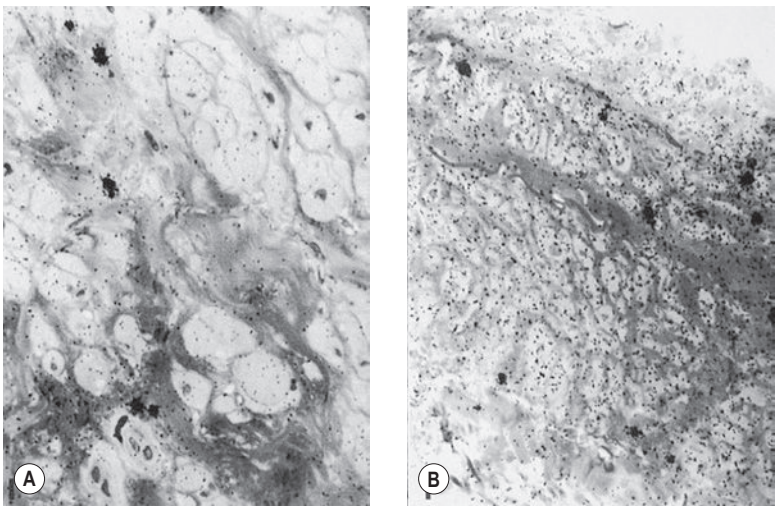


Figure 3.2 Light microscope autoradiographies of human saphenous vein strips incubated with ^{3}H-noradrenaline. In the control vein *(right),* clusters of silver grains indicative of adrenergic varicosities are seen throughout the media. Smooth muscle cells exhibit a high density of silver grains. In the varicose vein *(left),* nerve varicosities are less abundant, and smooth muscle cells are larger and have a much lower density of silver grains. Collagen is more abundant. *Bars* = 10 µm. (From Azevedo I, Albino Teixeira A, Osswald W. Changes induced by aging and denervation in the canine saphenous vein: a comparison with the human varicose vein. In: Vanhoutte PM, editor. Return circulation and norepinephrine: an update. Paris: John Libbey Eurotext; 1991.)

lengthening force caused by pressure in the lumen. Type I collagen is believed to confer tensile strength to the vessel wall, whereas type III collagen may be involved in extensibility. In dilated and morphologically normal segments of varicose veins type I collagen is present in a greater amount than type III. Furthermore, varicose veins contain more type I and type III collagen than do normal veins. It has been found that the elastin content is significantly reduced in dilated segments of varicose veins when compared with both normal veins and normal segments of varicose veins. Microscopically, the ratio of collagen to elastin appears to be significantly increased in the dilated segments of varicose veins. These findings tend to emphasize the important role of elastin in providing a retractile force that opposes development of dilation and tortuosity of the vein wall.[21]

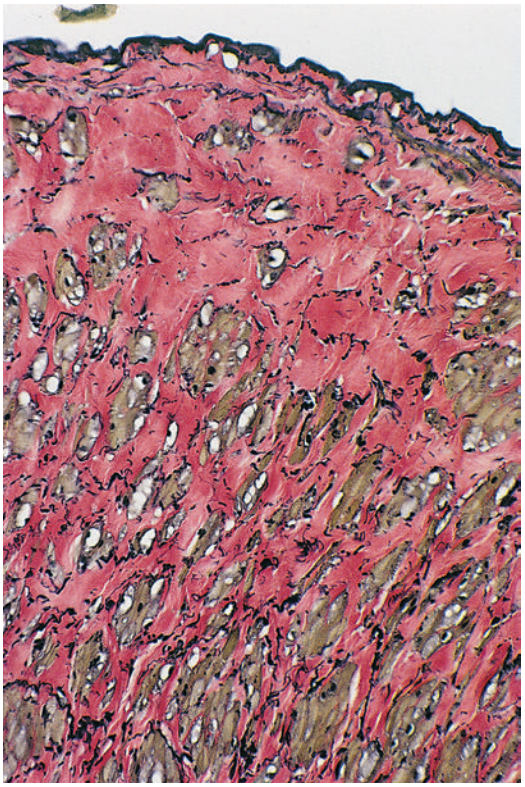


Figure 3.3 Cross-section of a tributary to the great saphenous vein in a 46-year-old man, stained with Verhoeff–van Gieson (×150). Note extensive fragmentation of elastin fibers interspersed between irregularly oriented muscle bundles with marked hypertrophy of collagen fibers. Elastic fibers stain black; collagen, red; muscle, brown–yellow.

Although collagen accumulation is thought to separate smooth muscle cells within the varicose vein wall, the collagen content of varicose veins is less than that found in normal veins.[6,22] The bulk of the varicose vein wall is made up of mucopolysaccharides and other ground substances. Varicose veins contain 67% more hexosamine (which comprises about 0.3% of normal vein dry material) than is found in normal veins.

Dysplasticity of the varicose vein wall may explain why varicose veins have an even greater susceptibility to pressure-induced distension than do nonvaricose veins. This anatomical–pathophysiologic correlation has been demonstrated by pharmacologic studies that show reduced maximal contraction of varicose veins compared with control veins.[2,19] They have also been investigated with in vitro techniques measuring distensibility as a function of infused volumes of saline.[23] However, some investigations have failed to discover a significant difference in the degree of intimal fibrosis between varicose and nonvaricose veins.[24] Therefore fibrosis of the vein wall alone is not totally responsible for the development of varicose veins.

In studying smooth muscle reactivity, the three main vasoconstrictor agents—norepinephrine, angiotensin II, and endothelin-1—were compared. In diseased vein segments, a significant reduction in response to angiotensin II and norepinephrine was seen. It was also noted that there was a reduction in response to endothelin-1. The reduction in angiotensin II affinity appeared at an early stage of varicose disease and supports the hypothesis that such an abnormality within the venous wall could play a role in the pathogenesis of primary varicose veins.[25]

A decrease in tocopherol concentration has been noted in varicose veins.[26] A significant correlation also seems

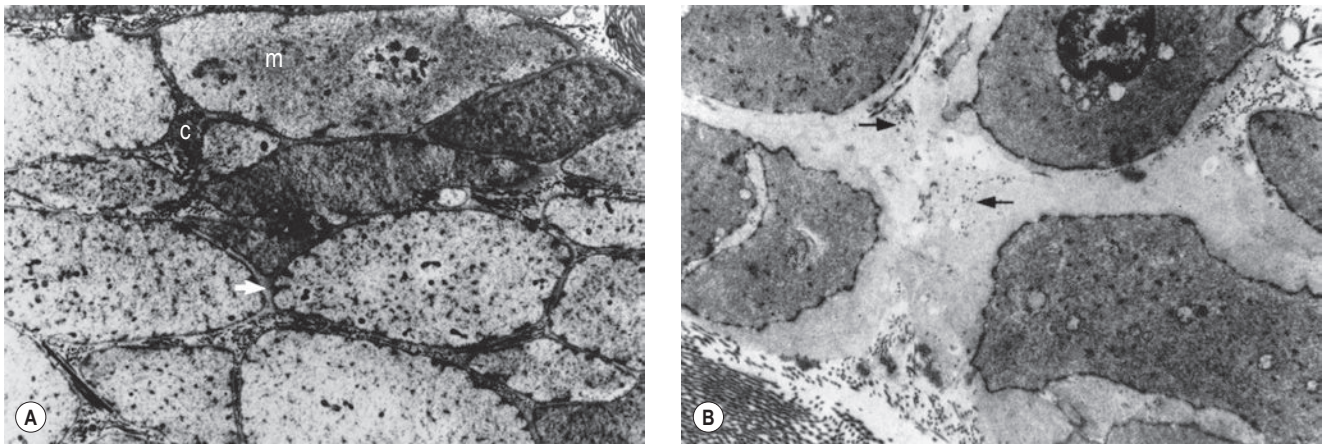


Figure 3.4 **A,** Middle muscle layer of a saphenous vein from a young subject. Smooth muscle cells *(m);* narrow perimyocytic spaces containing collagen fibers *(c).* The basilar membrane of smooth muscle is clearly visible (*arrow*). (Uranyl acetate-lead citrate, ×4000.) **B,** Muscle fibers in an aged subject showing the wide separation of dystrophic muscle cells. A few collagen fibers are visible (*arrows*). (Uranyl acetate-lead citrate, ×5000.) (From Bouissou H, Julian M, Piraggi M, Louge L. Vein morphology. Phlebologie 1988;3:1.)

to exist between the inhibition of vessel wall tissue lipoperoxidation and their tocopherol concentration independent of serum concentrations. This may be the result of the protective effect of blocking peroxidation of membrane-associated fatty acids by tocopherol and other antioxidants to prevent vein wall damage.[27] It is clear that the dysplasticity of varicose veins correlates with the changes in their pharmacodynamics and histochemistry. Varicose veins have a demonstrated loss of contractility.[28]

Varicose veins are often complicated by local inflammation and thrombosis. This may be the result of venous hypertension and an inherent histochemical abnormality in the varicose vein/endothelial wall. The formation of arachidonic acid-derived prostanoids was investigated in segments of varicose and nonvaricose veins. Venous production of prostacyclin was decreased, whereas that of thromboxane A_2 and prostaglandin E_2 was increased in the varicose vein segments, regardless of whether they were macroscopically affected or unaffected.[29] It is unknown whether this change in the cyclooxygenase pathway in the varicose vein wall is the cause or effect of its dysplasticity. In addition, histochemical examination discloses a marked increase in the activity of lysosomal enzymes,[30] acid phosphatase, β-glucuronidase and anaerobic isoenzymes (lactodehydrogenase) in primary varicose veins.[31–33] These enzyme patterns suggest a decline in energy metabolism and an increase in cellular damage in the varicose veins. It has also been found that varicose veins accumulate and metabolize norepinephrine less efficiently than normal veins.[34]

Differences in expression and microscopic localization of matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinases between normal and varicose veins may explain the variability of disease between vein segments.[35] MMP-2 has been found to cause relaxation of contracted vein segments, which could lead to progressive venous dilation, varicose vein formation and chronic venous insufficiency.[36] Whether the abnormal level and/or action of MMP is the contributing factor, or whether protracted increases in venous pressure lead to an increase in MMP expression is unknown.[37] Therefore both anatomical and biochemical abnormalities in the varicose vein wall contribute to its increased distensibility (Box 3.1).

There is conflicting evidence regarding the levels of MMP-2 in varicose veins. Increased MMP-2 and MMP-9 has demonstrated the ability to reduce contractility of the vein segment and has been proposed as a mechanism for chronic venous disease.[38] Conversely, decreased MMP-2 levels were found in varicose vein tissue in other studies that could result in extracellular matrix accumulation, hypertrophy, and atrophy in varicose veins. Increased levels of tissue inhibitors of metalloproteinase (TIMP-1) were also evident with decreased MMP-2 levels.[39,40]

The timing of MMP expression patterns are another important factor in venous disease. Alsaigh et al used microzymographic techniques in vivo to determine that a short rise in blood pressure in combination with a reduction of the fluid sheer stress resulted in early activation of MMP-1, MMP-8 and MMP-9. TIMP-1 and TIMP-2 were also found to be elevated suggesting interplay with MMPs. The damage caused by the early expression of MMPs could be the initiating factor in the inflammatory reaction resulting in venous disease. MMP may also cleave the membrane receptor vascular endothelial growth factor-2 (VEGFR-2) leaning to additional endothelial viability.[41] The shifting equilibrium of MMPs and TIMPs in varicose vein tissues may affect the ability of proteolytic enzymes to degrade components of the extracellular matrix resulting in restructuring of the vein wall.[42]

Box 3.1 Theoretical Causes of Varicose Veins

Heredity
Race
Gender
Posture
Weight
Height
Ligamentous laxity (hernia, flat feet)
Occupation
Hormones
Estrogen
Progesterone
Pregnancy
Primary valvular incompetence
Decreased number of valves
Aging
Alcohol and cigarette use
Incompetent perforating veins
Arteriovenous communication
Vein wall weakness
Vein wall metabolic dysfunction
Secondary valvular incompetence
Phlebitis
Deep vein thrombosis
Matrix metalloproteinase activation
Inflammatory mediators
lncRNA and downstream effectors
Genetic factors

Inflammatory mediators are another important component in the pathogenesis of varicosities. Transforming growth factor (TGF)-β_1 is a cytokine involved with vascular remodeling that inhibits expression of MMP-1 and collagenase synthesis and increases TIMP expression. Increased levels of TGF-β_1 and isoform nitric oxide synthetase (iNOS) have been shown to be elevated in the tortuous segments of varicosities when compared with nontortuous segments.[43]

Leukocytes use the cellular adhesion molecule L-selectin to bind to the endothelial wall and express integrins to facilitate tissue extravasation. Saharay et al demonstrated increased extravasation and degranulation of leukocytes in patients with venous hypertension.[44] Conversely Junger et al demonstrated decreased expression of L-selectin in lymphocytes in patients with chronic venous disease. [45] The difference in expression of L-selectin could be the result of differences in the disease process of venous hypertension compared with chronic venous disease.

There are a multitude of additional factors that can contribute to the inflammatory process involved with varicose veins. CD4+ T-lymphocytes were found to be significantly elevated in varicosities compared with overall-measured levels of CD4+ cells indicating a possible role in the pathogenesis of chronic venous disease.[46] Additionally, mast cells influence a variety of factors in the inflammatory cascade.

Mast cell chymase is an activator for MMP-1 and MMP-3 that can stimulate the release of TGF-β. Mast cells also secrete tryptase that can degrade Type IV collagen, elastin, proteoglycans, and fibronectin resulting in chronic venous disease.[47] Lastly, endothelium exposed to increased pressure results in increased synthesis of proinflammatory cell adhesion molecules such as VCAM, ICAM, and ELAM resulting in the inflammatory state seen in chronic venous insufficiency.[48]

Changes in RNA expression of a gene can be determined by both genetic and environmental mechanisms. Gene expression can be modified by signaling from other genes and also by regulatory elements on the same gene. MicroRNAs, long noncoding RNAs (lncRNAs), and epigenetics are additional complications with gene modification.[49,50] lncRNAs are nonprotein coding transcripts longer than 200 nucleotides that target different aspects of RNA transcription.[51] lncRNAs can target various components of the transcription reaction, transcriptional repressors or activators, and the DNA duplex to sharply control gene expression.[52] Silencing of the lncRNA-GAS5 (growth arrest specific transcript 5) promoted cell proliferation, migration and cell cycle of human saphenous vein smooth muscle cells. lncRNA-GAS5 directly binds to a calcium dependent RNA-binding protein, Annexin A2. There is evidence that Annexin A2 reduces human saphenous vein smooth muscle cell proliferation. Therefore a low expression of lncRNA-GAS5 may enable human saphenous vein smooth muscle cell proliferation and migration via Annexin A2 as a pathogenesis of varicosities.[53]

Hypoxia has also been considered as a trigger for varicose veins. Oxygenation of the outer two thirds of the saphenous vein is provided by the vasa vasorum and the inner one third by the luminal blood.[54] Acute hypoxia is a trigger for dilation of the vasa vasorum leading to increased blood flow.[55] Hypoxia-activated leucocytes and endothelium have been shown to release mediators regulating vein wall remodeling similar to those seen in varicosities.[56] In vivo studies using venous endothelial cell culture have demonstrated that hypoxia upregulated angiogenesis through the release of proangiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).[57]

Venous endothelial cells also respond to hypoxia by upregulating hypoxia-inducible factors (HIFs). HIFs are nuclear transcription factors involved with regulating genes involving oxygen homeostasis. Genes regulated by HIFs have been shown to increase the expression of proinflammatory mediators in hypoxic conditions such as VEGF, endothelial isoform of nitric oxide synthase (eNOS), prostaglandin I2 and cyclooxygenase-2.[58–60]

Hypoxia-inducible factor-1α (HIF-1α) and metallothionein (MT) also have a higher expression in varicocele and varicose veins compared with normal veins. MT is a metal-binding protein that shields against cell apoptosis under hypoxic stress. This function of MT may lead to decreased vascular cell apoptosis and contribute to the thick dilated walls of varicose veins and varicoceles.[61] The evidence for hypoxia as a causative factor in varicosities remains inconclusive because of the poor design of published in vivo studies and heterogenicity. However, similar oxygen content was found in the blood of varicose and nonvaricose veins (see Fig. 3.1).[56,62,63]

PATHOPHYSIOLOGY

Approximately 75% of the body's total blood volume is contained within the peripheral venous system.[64] The quantity of blood within the legs is a function of body position. When erect, 300 to 800 mL of extracellular and vascular fluids (the quantity varies according to the experimental method and the size of the subject measured) collects in the legs.[65–67] This includes a 15% increase of blood volume.[65] Thus the venous system, especially in the legs, is an important component of the cardiovascular system's circulatory reservoir. However, the arterial system plays an equally important role in cardiovascular adaptation to postural changes by virtue of changes in arterial resistance. In fact, studies have demonstrated that reflex changes in venous tone are not essential for this fluid shift.[68]

Venous blood pressure is determined by several factors. Among these are pressure generated by the heart, energy lost in the peripheral resistance of arterioles, hydrostatic gravitational forces, blood volume, anatomical composition of the venous wall, efficiency of one-way valves, vein wall distensibility (determined by hormonal, systemic alcohol and other factors), and contraction of venous smooth muscle as influenced by ambient temperature and sympathetic and parasympathetic nerve tone (Fig. 3.5).

Although arterial pressure is one factor in the development of venous pressure, arterial hypertension is a factor associated with the development of varicose veins in some epidemiologic studies,[69] but not others.[70] Curiously,

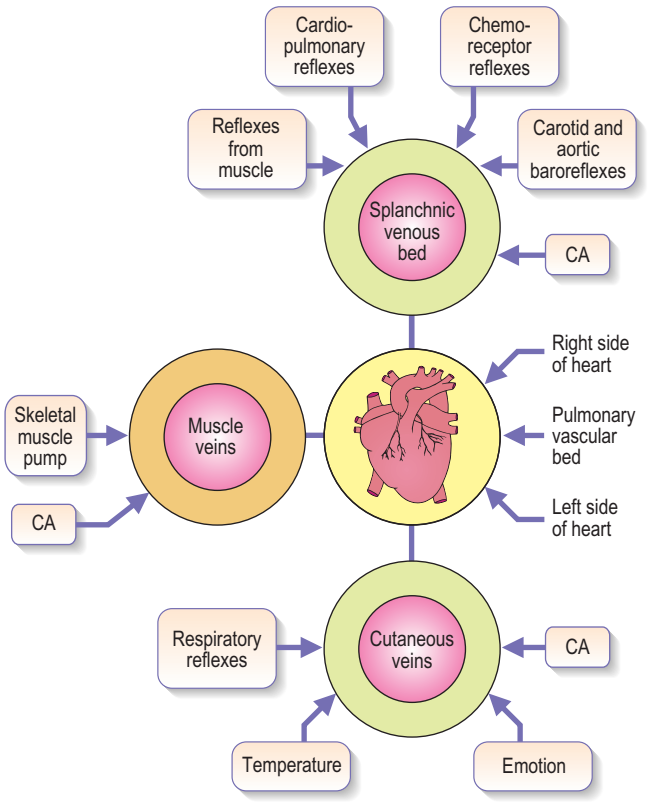


Figure 3.5 Multiple environmental and internal factors act on the venous system to influence its dilation and constriction. *CA,* Catecholamines.

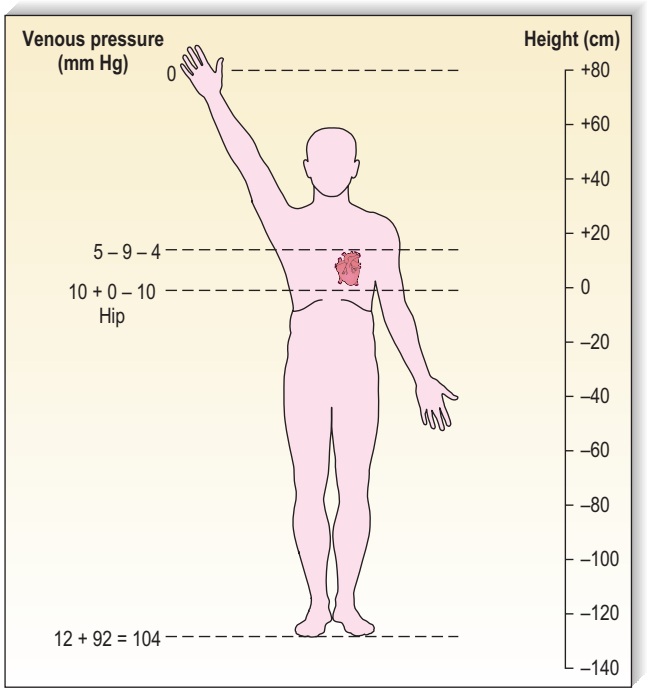


Figure 3.6 Venous pressure is that exerted by a column of blood from the heart to the location of measurement.

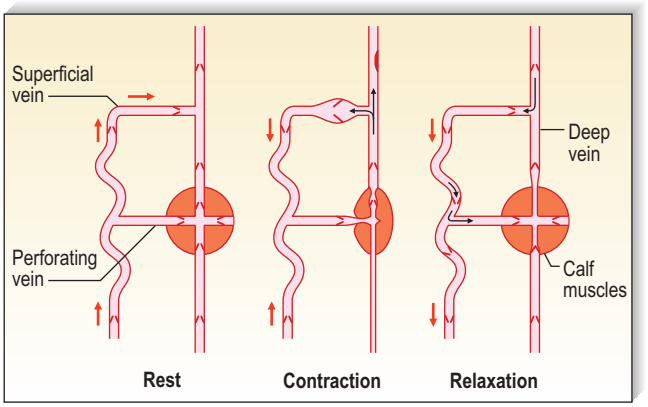


Figure 3.7 Private circulation of blood flow in primary varicose veins demonstrating a retrograde circuitous blood flow with muscle contraction and relaxation.

atherosclerotic disease has been linked epidemiologically to varicose veins, although it might be two common conditions occurring concurrently.[71,72] It is postulated that this coincidence may be related to an atherogenic risk profile, caused primarily by coexistent inactivity, obesity and hypertension.[72] At rest, in the erect position, pressure in the saphenous vein is determined primarily by the height of the column of blood from the right atrium to the site of measurement (90 to 120 mmHg at the ankle) (Fig. 3.6).[73,74] Contraction of calf muscles generates pressures of between 200 and 300 mm Hg.[75–77]

Pressure generated deep within the fascia, outside of muscles, is between 100 and 150 mmHg[77,78]; however, with muscular activity, pressure in the normal saphenous vein at the level of the malleoli falls 45 to 68 mmHg below the resting level.[79] It is reduced from 80 to 40 mmHg in the posterior tibial vein.[80] Because of the one-way valves, blood flow is directed from the superficial venous system to the deep venous system through perforating vessels (see Fig. 1.4). This has been demonstrated visually by serial phlebography of the normal lower leg.[81] The venous blood then flows towards the heart.

The venous pump in the foot is an important portion of the muscle pump of the lower leg. Weight bearing is usually necessary to propel blood up the leg. Bidirectional ultrasound velocity detector tracings of venous blood flow through the popliteal vein have demonstrated the importance of dorsiflexion of the foot when there is no weight bearing.[82] Therefore full flexion of the foot is important after sclerotherapy to maximize the efficacy of the lower extremity muscle pump.

Respiration produces alterations in intra-abdominal venous pressure. This 'abdominal venous pump' contributes to the flow of blood even when an individual is erect.[67,83] Inspiration produces a rise in venous pressure in the external iliac vein, common iliac vein and inferior vena cava when measured in both the horizontal and erect positions (6.3 mmHg and 8.7 mmHg, respectively).[83]

In the supine position, blood flows evenly along all superficial and deep vessels towards the heart. It is propelled by the relatively small *vis-à-tergo* (force from behind) from the capillaries,[80] and the respiration-induced aspiration of blood into the abdominal and thoracic veins. In contrast to deep veins, superficial veins have smooth muscle in their walls. This allows contraction of these vessels in response to cold and to drugs such as dihydroergotamine,[84,85] and allows dilation in response to topical and systemic alcohol, estrogen and light physical trauma.[80] Part of the pathophysiology of varicose veins may be a diminished response of such smooth muscle contraction, as previously described.

Regardless of its cause, chronic venous hypertension in the lower extremities causes an increase in venous diameter. This may lead to valvular insufficiency, which usually causes a reversal of blood flow from the deep veins into the superficial veins through incompetent perforating veins. This 'private circulation' may account for as much as 20% to 25% of the total femoral flow involved in a circular retrograde flow (Fig. 3.7).[86,87]

It has been found that prevalence of reflux in vein segments is correlated with signs of venous insufficiency, but in the general population approximately 12% of limbs with no disease have reflux as detected by duplex ultrasound.[88]

Venous insufficiency has been correlated with standing occupations. A study that compared symptom-free vascular surgeons with normal individuals of nonmedical vocations showed that the superficial system was by far the most common site of venous incompetence in both groups. Vascular surgeons (standing occupation) showed a greater incidence of reflux than the controls. This was true even in subgroups in which reflux was seen in the superficial veins in addition to those with reflux in the deep veins and perforating veins.[89] In patients with symptoms of venous insufficiency, reflux in the great saphenous vein (GSV) territory is found in 85% of limbs, but only 68% of limbs show true saphenofemoral junction (SFJ) incompetence. Reflux is found in 20% of such patients in the small saphenous vein (SSV) territory, and strictly nonsaphenous origin of varicosities is found in 6%.[90] One study demonstrated that 93% of the 10% of patients with nonsaphenous reflux in the study

group were women with a mean of 3.2 pregnancies.[91] This implied an association with female sex, hormones and/or number of pregnancies. Studies of causation of reflux focus on venous valves and vein walls. On one hand, an antiproteolytic milieu may favor the deposition of collagen and allow varicosities to develop[92]; on the other hand, activation of monocytes and conversion to macrophages may cause weakening or destruction of valve segments.[93]

Direction of venous flow in varicose veins has been examined by McPheeters and Rice[94] using fluoroscopy. Reversal of flow caused by incompetent perforator valves is beneficial during sclerotherapy. When a superficial varicosity is injected its venous flow is forced distally to the smaller branching veins where it is arrested (see Chapter 8).[94] Thromboembolic disease is thereby prevented.

Superficial veins respond to increased pressure by dilating. Valvular incompetence occurs and varicosities appear.[95] In addition, in muscular contraction, high compartmental pressure, which normally occurs within the calf muscle pump, is transmitted directly to the superficial veins and subcutaneous tissues drained by perforating veins.[96,97] When this occurs, venous pressure in the cuticular venules may reach 100 mmHg in the erect position.[80] This causes venular dilation over a broad area and may cause capillary dilation, increased permeability[98–101] and a subsequent increase in the subcutaneous capillary bed through angiogenesis.[99,102] This is expressed clinically as telangiectasia (venous blemishes). Histologically, cutaneous and subcutaneous hemosiderin deposition may also occur. In time this causes cutaneous pigmentation (see Chapter 2). However, some patients with chronic venous insufficiency are able to increase their venous blood flow through exercise.[103] It is postulated that various factors (e.g., sympathetic tone, temperature, tissue metabolites) compensate venous hypertension to normalize cuticular blood flow. This finding demonstrates the complexity of the superficial venous system.

A special situation develops in the area of the medial malleolus. In this area, perforating veins are not surrounded by deep or superficial fascia. Therefore any increase in deep venous pressure is transmitted directly through perforating veins to superficial connecting veins. This causes high cutaneous venous pressures and a transudation of extracellular fluid. This, in turn, leads to perivascular fibrin deposition, which has been blamed for decreased oxygenation of cutaneous and supporting tissues; this was thought to contribute to cutaneous ulceration (see Chapter 2).[99,104,105] This theory has largely been discredited; the ability of any fibrin screen to prevent oxygen diffusion has never been proven.

The effect of temperature variations on the venous system is well studied.[106,107] The cutaneous vasculature is intimately involved in thermoregulation. An increase in body core temperature results in cutaneous vasodilation. This does not occur as a result of relaxation of venous smooth muscle but is the result of the reduction in the vasoconstrictor impulses to the vein wall. Such vasodilation also occurs in varicose veins. Strain gauge venous occlusion plethysmography has shown an increase in venous distensibility associated with temperature elevation.[108] Similarly, alcohol ingestion may influence the development of varicose veins. Alcohol intake, in the same manner as increased environmental temperature, causes cutaneous vasodilation. In an examination of 136 men with primary varicose veins greater than 4 mm in diameter, it was found that a significantly increased incidence of varicose veins occurred among men who consumed 4 oz (around 120 mL) of alcohol a day.[109] In another examination of 4903 men and women with varicose veins, alcohol was found to increase the risk of varicose veins in women, and smoking increased this risk in both genders. Further experimental evaluations of these associations are warranted.[110]

In summary, pathologic development of varicose veins can be divided into four broad categories, which may overlap and contribute to each other: increased deep venous pressure, primary valvular incompetence, secondary valvular incompetence and hereditary factors (such as vein wall weakness). All of these categories coexist and are influenced by temperature, alcohol, hormonal and other vasodilatory stimuli (Box 3.2).

Box 3.2 Pathophysiology of Varicose Veins

Increased Deep Venous Pressure

Proximal

Pelvic obstruction (indirect)
Intra-abdominal pressure secondary to Valsalva, leg crossing, constrictive clothing, squatting
Obesity
Saphenofemoral incompetence
Venous obstruction

Distal

Perforator valvular incompetence
Venous obstruction

Primary Valvular Incompetence

Venous obstruction (thrombosis)
Destruction of venous valves (thrombophlebitis)
Congenital absence of venous valves
Decreased number of venous valves
Vein wall weakness

Secondary Valvular Incompetence

Deep venous obstruction
Increased venous distensibility
Hormonally induced through pregnancy, systemic estrogens, and progesterones (concentration- and ratio-dependent)

Hereditary Factors

INCREASED DEEP VENOUS PRESSURE

An increase in deep venous pressure may be of proximal or distal origin. Proximal causes include pelvic obstruction (resulting in indirect venous obstruction) such as increased intra-abdominal pressure caused by straining during defecation or micturition, wearing constrictive clothing, sitting in chairs, obesity and running, saphenofemoral incompetence and intraluminal venous obstruction. Distal causes include perforating vein valvular incompetence, arteriovenous anastomosis and intraluminal venous obstruction.

Most veins of the forearm and lower extremity remain competent even after maneuvers that induce venodilation and an increase in blood flow such as exercise, hyperemia

or postocclusion reactive hyperemia. However, veins with an inherent valvular weakness can be identified by reactive hyperemia in association with duplex flow analysis.[111] The presence of femoropopliteal reflux is associated with clinical symptoms; it has been found in up to 15% of limbs having primary varicose veins and is divided into those with superficial femoral venous reflux alone and those with isolated popliteal venous reflux.[112]

PROXIMAL ORIGIN

PELVIC OBSTRUCTION

Pelvic obstruction is an uncommon cause of varicose veins. Iliac vein compression syndrome is the phenomenon of compression of the left iliac vein by the right iliac artery overlying the fifth lumbar vertebra.[113–117] This usually occurs in women in whom it may be a cause of vulvar varicosities, but it has also been noted in men (see Chapter 5). Extravascular abdominal tumors such as ovarian and uterine carcinoma or teratoma may be causes of obstruction. More commonly it is relative pelvic obstruction that provides a mechanism for impedance of return blood flow. Relative obstruction may occur in the third trimester of pregnancy, particularly during recumbency when the gravid uterus compresses the inferior vena cava against the lumbar spine and/or psoas muscles. Phlebographic studies have shown complete obstruction of the inferior vena cava at the confluence of the iliac veins in third-trimester pregnancies.[118] Partial obstruction has been shown in earlier months of pregnancy. Some degree of compression is evident using phlebography even in the left lateral decubitus position.

INCREASED INTRA-ABDOMINAL PRESSURE

One popular hypothesis for the development of varicose veins is Western dietary and defecation habits that cause an increase in intra-abdominal pressure. A distended cecum or sigmoid colon, which is the result of constipation, may drag on the iliac veins and obstruct venous return from the legs.[119] Population studies have demonstrated that a high-fiber diet is evacuated within an average of 35 hours.[120] In contrast, a low-fiber diet has an average transit time of 77 hours. An intermediate diet has a stool transit time of 47 hours.

It is possible that the small increase in abdominal intravenous pressure caused by less than optimal bowel habits, when transmitted intravenously distally, gradually breaks down venous valves of leg veins.[121,122] Evidence in support of this hypothesis is seen in populations of people who eat unprocessed high-fiber food. These persons are free of constipation and varicose veins.[123,124] However, if this population's diet is changed to low fiber, the incidence of varicose veins increases.[119,125–128] In a diet that is intermediate between Western low-fiber and high-fiber diets, the prevalence of varicose veins is also found to be in an intermediate range.[129]

Defecatory straining induced by Western-style toilet seats has also been cited as a cause of varicose veins, in contrast to the African custom of squatting during defecation.[126] However, venous pressures of subjects measured in both the sitting and squatting positions during defecation have not shown a significant difference.[130] Venous flow has not been examined accurately in constipated and nonconstipated populations. Finally there are other dietary factors besides fiber content that may explain the differences in prevalence of varicose veins. An increased incidence of varicose veins is found in populations of people who consume diets high in long-chain fatty acids, as opposed to diets high in short-chain fatty acids.[131] Long-chain fatty acids have been shown in experimental systems to enhance blood coagulation and stimulate the development of blood clots.[132–134] Clot lysis times were slower in the population group that consumed long-chain fatty acids.[131] Accordingly the type of dietary fatty acids consumed also may predispose the development of varicose veins. In addition, the Western diet has been found to be relatively deficient in vitamin E.[135] It is hypothesized that the slight vitamin E deficiency when aggravated by pregnancy may predispose the vein wall to coagulation and fibrinolysis, thus causing the veins to become more sensitive to venous stasis and venous hypertension. Therefore although it would seem prudent to recommend a high-fiber diet for several medical reasons, it remains an unproven treatment for the prevention of varicose veins.

An association between prostatic hypertrophy, inguinal hernia and varicose veins may be caused by straining at micturition with a resultant increase in intra-abdominal pressure.[136]

Another mechanism for increasing distal venous pressure by proximal obstruction is the practice of wearing girdles or tight-fitting clothing. A statistically significant excess of varicose veins was noted in women who wore corsets compared with women who wore less constrictive garments,[137] although this finding was not confirmed by a subsequent study.[138] However, a more recent study of 20 women aged 20 to 46 who wore 'tight' jeans (degree of compression was not measured) found that in 14 of these women there was an increase in subcutaneous pressure from 10 to 15 mmHg at rest to 30 mmHg when walking as opposed to no change in pressure when wearing loose-fitting clothing. [139] This indicates that wearing tight jeans can negatively affect venous return. A similarly increased incidence was noted in women who stand at work compared with those whose jobs entail more walking and sitting,[71,73,137–143] although this has not been confirmed universally.[144,145]

Leg crossing and sitting on chairs are two other potential mechanisms for producing a relative impedance in venous return. Habitual leg crossing is commonly thought to result in extravenous compression, but this has never been scientifically verified. A decreased incidence of varicose veins has been noted in population groups that do not sit in chairs.[146,147] It is thought that sitting may produce some compression on the posterior thigh, which produces a relative impedance to blood flow. Wright and Osborn[148] have shown that the linear velocity of venous flow in the lower limbs in the recumbent position is reduced by half in the standing position and by two thirds when sitting. Alexander[147] found that the circumferential stress on the saphenous vein at the ankle was 2.54 times greater with chair sitting than with ground sitting. This may explain the increased incidence of varicose veins in men versus women in population groups in which only men sit on chairs and women sit on the floor. In this population study[146] varicose veins were present in 5.1% of men and only 0.1% of women. Finally the practical implications regarding chair sitting concern those who travel for long periods in airplanes. Pulmonary thromboembolism has occurred in many people

after prolonged air travel and has been termed *economy class syndrome*.[149] Although pre-existing venous disease, dehydration and immobility are all contributing factors, chair sitting adds another insult to the venous system.

Most[69–71,142,143,150–157] but not all[138,152,158,159] studies have found that obesity is associated with the development of varicose veins. Careful examination of some of these epidemiologic studies shows that when the patient's age is correlated with obesity, the statistical significance is eliminated.[160] Obesity was especially correlated with the development of varicose veins in women when the varicosities occurred in unison with cutaneous changes indicative of venous stasis (see Chapter 2).[156,161,162,163] This may be secondary to decreased exercise and associated medical problems specific to obesity, such as hypertension, diabetes, hypercholesterolemia and sensory impairment.[164]

Running has been demonstrated to raise the intra-abdominal pressure by 22 mmHg.[165] This increase in abdominal pressure occurs because of a reflex tightening of abdominal muscles during running, which prevents the pelvis from tipping forwards during thigh flexion induced by contraction of the iliopsoas muscle group.[166] Therefore during strenuous leg exercise elevated abdominal pressures may impede venous return. By way of comparison, a Valsalva maneuver was shown to elevate the intra-abdominal pressure by 50 mmHg or more.[165] Strenuous exercise, particularly long-distance running, is often associated with prolonged increases in limb blood flow, which theoretically could overload the venous system and lead to progressive dilation.[95] Usually dilated veins that occur in this situation are normal and do not require treatment. Finally it is commonly noted that occupations that require standing for prolonged periods have an increased incidence of varicose veins.[167] This may be exacerbated by tall height, although this factor has not been supported by other studies.[160]

SAPHENOFEMORAL INCOMPETENCE

Saphenofemoral incompetence is rarely caused by anatomical abnormalities in the saphenofemoral triangle. When it occurs, pelvic tributary veins or accessory saphenous veins may converge in such a manner that flow to the femoral vein is impeded.[168] Likewise, iliac venous incompetence caused by the congenital absence of venous valves or by damage to the valves through thrombosis may cause distal venous hypertension.

Our interest and focus on the venous valve dysfunction as a fundamental cause of distal venous hypertension began with unpublished observations using angioscopy. The angioscope provided a direct view of the internal architecture of saphenous veins. Patients taken to surgery who demonstrated preoperative reflux verified by duplex ultrasound showed a variety of pathologic lesions in the valves themselves. The first indication was a relative paucity of valves. The observation of a decrease in the number of GSV valves was reported by Cotton in 1961.[169] Next, we encountered actual valve lesions. These observations were an extension of those reported by Hoshino et al,[170] who classified valve damage in the saphenous vein into three categories ranging from stretched commissures to perforations and valve splitting.

From the preceding observations we suggest that the earliest valve defect is an increase in the commissural space, which allows reflux on the border of the vein. This may be one of the earliest causes of reflux in varicose veins. Later, thinning, elongation, stretching, splitting and tearing of the valves develop. The last stages are thickening, contraction and possibly even adhesion between valves. These observations have been confirmed by Van Cleef et al.[171] Although we have proposed that this valve damage is acquired and causes axial reflux, as well as outflow through check valves in perforating veins, others have proposed that the cause of primary venous insufficiency is an actual low number of valves in the saphenous system.[172]

The angioscopic observations could be confirmed by gross morphologic studies that, when extended to microscopy observations using monoclonal antibody labeling, have demonstrated monocytic infiltration into damaged venous valves.[173] Others have found leukocytic infiltration into varicose veins and have called attention to the fact that the cells observed released vasoactive substances including histamine, tryptase, prostaglandins, leukotrienes and cytokines.[174] Observations in patients led to the conclusions that venous hypertension was related to leukocytic infiltration on the cranial surfaces of the venous valve and venous wall, and that leukocytes there were greater in quantity than on the caudal portion of the valve leaflets and venous wall.

Therefore a model of venous hypertension was developed in which microvessels in rat mesentery were examined microscopically. Venous occlusion and subsequent venous hypertension were produced by pipette blockade of venules about 40 μm in diameter. Videomicroscopy revealed early signs of inflammation such as progressive leukocyte rolling, adhesion, subsequent migration and parenchymal cell death.

This inflammatory sequence occurred early during the phase of venous hypertension and progressed further after release of the occlusion. The model showed that venous occlusion with elevation of the hydrostatic pressure caused a highly injurious process for the surrounding tissues. It was accompanied by formation of microhemorrhages on the high-pressure side of the postcapillary venule with rolling and adhesion of leukocytes on the venular endothelium.[175]

van Bemmelen et al[176] produced a model of venous hypertension by creating arteriovenous fistulas in Wistar rats using microsurgical techniques. Valvular incompetence was seen as early as 1 day after creation of the arteriovenous fistula, and valvular structural changes were noticeable within 2 months of production of venous hypertension. Elongation of the cusps was observed. Separation and leakage of the cusps were encountered along the entire valvular free border, and, in later stages beyond 4 months, valve areas became difficult to recognize because commissures were lost and bulging of the valve sinus disappeared.

We have pursued this line of investigation and have reproduced the human observations in the animal model.[177–181]

Another model of venous hypertension has been produced by Lalka.[182] This model creates venous hypertension by ligation of the inferior vena cava, the common iliac veins and the common femoral veins. This preparation elevates rat hindlimb venous pressures compared with forelimb pressures. Myeloperoxidase assay indicates leukocyte trapping in hindleg tissues in the same way as it occurs in humans.[183]

The observations just mentioned suggest that valve damage in venous insufficiency is an acquired phenomenon

related to leukocyte and endothelial interactions and an inflammatory reaction. This observation is not universally accepted. A study on 13 valve structures from varicose GSVs showed an absence of lymphomonocyte infiltration in 85% and rare isolated 'nonsignificant' inflammatory cells in 15%.[184] However, if this hypothesis is correct, pharmacologic intervention to block leukocyte adhesion, activation and subsequent valve damage may be a possibility.

DISTAL ORIGIN

VALVULAR INCOMPETENCE

Unlike that described in the previous section, incompetence of the SFJ clearly produces distal retrograde flow into the GSV and thus produces distal venous hypertension (Fig. 3.8). The GSV then dilates, producing further distal valvular incompetence sequentially. Retrograde flow thus produced is channeled through the perforator veins back into the deep venous system. This produces a private circuit of blood flow from the femoral vein to the saphenous vein and back to the femoral vein through perforating veins.[86] It has been estimated that the total volume of flow in this circuitous route may be 20% to 25% of the total limb blood flow during exercise.[87] This paradoxical circulation can be maintained for a long time, but eventually the quantity of blood channeled by the perforator veins increases. As this happens there is hypertrophy and dilation of the superficial veins, producing valvular incompetence and localized varicose veins.

In addition to increasing superficial venous volume through perforator incompetence, retrograde flow produces an increase in acidity and potassium concentration with a decrease in venous oxygen concentration. These three factors promote vasodilation to exacerbate venous stasis.[185]

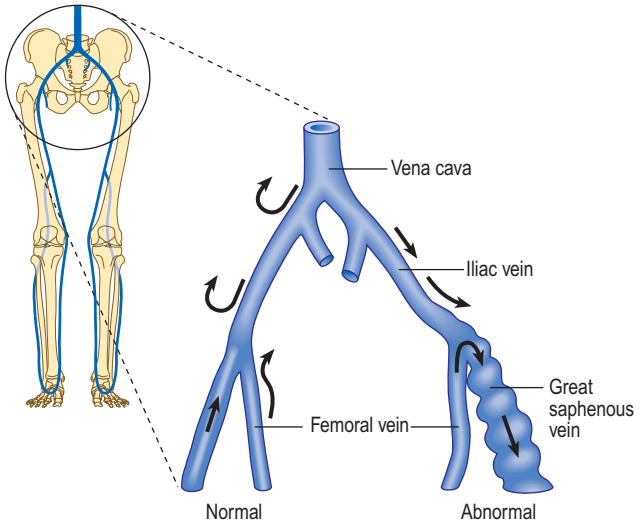


Figure 3.8 Reflux of blood from the iliac vein into the great saphenous vein occurs when the valves in the iliac vein or at the saphenofemoral junction are incompetent. With normal valvular function blood flow from a Valsalva maneuver is prevented from passing into the femoral and great saphenous veins. (From Goldman MP. Varicose and telangiectatic leg veins. In: Demis DJ, editor. Clinical dermatology. 19th ed. Philadelphia: JB Lippincott; 1992.)

Perforator incompetence in the lower part of the leg may occur from localized thrombosis in the vein following trauma. It is believed that localized thrombosis is usually masked by the local tissue injury. The valve cusps become involved by the thrombus and, after recanalization, remain functionless.[186] Dodd and Cockett[80] found on examination of 54 legs with perforator incompetence that the lower leg incompetent perforators were in communication with the soleal plexus of veins and were the channels most likely to be damaged as a result of thrombotic episodes in this region. In support of this concept, Fegan,[187] Hobbs,[188] Lofgren,[189] Beninson and Livingood[190] have all pointed out that the treatment of varicosities may have no effect on superficial venous pressure. These investigators contend that treatment of perforating veins draining the ankle and lower calf area is important.[96,137,188,191–193] The vessels may be either surgically ligated[96,174–193] or sclerosed (see Chapters 9 and 10).[188] Only then will retrograde flow under high pressure through the calf muscle pump be diverted upstream away from the skin. When this is done, a lowering of cuticular venous pressure and a decrease in dermal capillary pressure is accomplished. The excess transudation of fluid-producing edema and the associated decrease in tissue oxygenation and nutrition is halted. Quill and Fegan[194] have demonstrated clearly the narrowing of the proximal SSV after obliteration of incompetent distal perforating veins in 9 out of 11 cases. This suggests that dilation and incompetence of the saphenous vein may be caused by distal reflux and primary or irreversible abnormalities of the proximal venous wall. The finding has been confirmed through duplex examination of patients with cosmetic veins or primary varicose veins.

In a study of 500 lower limbs in 'cosmetic' patients, incompetence from below the knee extending upwards was found in 63.3%. However, only 9% were found to have perforator incompetence.[195] An additional study of 167 consecutive patients with primary varicose veins demonstrated that 31% had incompetence of the GSV but no evidence of SFJ incompetence, and 24% of limbs had incompetence of the SSV without incompetence of the SFJ.[196] Thus perforator incompetence, although important as a causative factor, is not solely responsible for varicose vein development in all patients.

Duplex scanning has contributed to knowledge regarding valvular dysfunction produced by venous thrombosis. For the most part, deep valvular insufficiency comes from direct valve destruction rather than obstruction-induced venous pressure elevation and dilation of the vein wall. Destruction of the valve cusps occurs after venous thrombosis. It follows that the extent of venous valvular incompetence is related to the extent of the original deep venous thrombosis (DVT). One could extrapolate from these observations that valvular competence might be preserved if the thrombus could be removed quickly by thrombolytic agents.[197]

Direct ambulatory venous pressure measurements and duplex examination have shown bidirectional flow through perforator veins. Exercise has been found to cause inward flow from the dilated superficial system and perforating veins into deep veins.[198] The perforator vein here functions as a drainage pipe to limit cuticular venous hypertension. This explains the dilation of re-entry perforating veins, which drain the superficial reflux into the deep venous circulation and which become competent after superficial

vein surgery.[199–202] Compression distal to perforator veins in patients with venous disease demonstrated inward flow in 55 out of 56 perforator veins examined with duplex scanning.[203] It is evident that venous hypertension is related to both perforator incompetence and valvular dysfunction.

VENOUS OBSTRUCTION

Venous obstruction may occur proximally or distally to varicose veins. An obstruction is typically produced by a thrombus that may extend proximally and distally from its origin. The thrombus may also extend into communicating or perforating veins. Depending on the extent of the thrombus venous blood may be forced into the superficial veins in either a retrograde or lateral direction. Finally it is interesting to speculate that the wearing of high-heeled shoes may lead to distal compression of the vein walls by leg muscles that are strained as a result of these shoes. When high-heeled shoes are worn, calf muscles are compressed and the gluteal muscles are used for walking.[204,205] Filho et al[206] confirmed this concept with a study comparing the venous return among women who were barefoot, or wore medium heels (3.5 cm), stiletto high heels (7 cm) or platform high heels (7 cm). The residual volume fraction (RVF) was increased in both high-heeled groups and the medium-heeled groups compared with the barefoot groups. The authors concluded that the calf muscle pump function is impaired by high-heeled shoes causing venous hypertension-like symptoms in women wearing heeled shoes for prolonged periods of time.[206]

ARTERIOVENOUS ANASTOMOSIS

Another important factor that may lead to increased venous pressure in cutaneous veins is the opening of arteriovenous communications. Arteriovenous anastomoses (AVAs) were believed to be a component in the pathogenesis of varicose veins in 1949 by Pratt[207] and by Piulachs et al[208] in 1952. Pratt hypothesized that AVAs represented the failure of closure of femoral artery branches to the saphenous system.

A clue to the presence of AVAs is often provided by the presence of varicosities in an unusual anatomical location and in the absence of detectable abnormalities of the deep venous system.[95] Physical examination often shows a lack of complete emptying of the varicose veins when the limb is elevated, during very rapid refilling of the varicose vein or venules with diascopy, during warmth over affected varicose veins and in the rare presence of a bruit or thrill over these vessels.[207] Arterial Doppler sounds are often demonstrated over varices, especially when they are associated with bright red venectasia. Between 60% and 80% of patients with congenital AVAs on the legs have associated varicose veins.[209,210]

AVAs have been demonstrated using direct operative microscopic dissection by Schalin[211] and Gius.[205] Indirect support of this theory has been provided by evaluating the oxygen content of varicose blood and skin temperature over varicose veins.[212–216] These studies estimate that AVAs occur in 64% to 100% of patients with varicose veins. However, at least one study has found no difference in varicose vein blood oxygen levels.[217] These authors postulated that oxygenation of venous blood is also related to metabolic activity, blood flow, blood volume in the varicosity, body position and intravenous pressure. This was confirmed indirectly by measuring skin oxygen levels in patients with and without varicose veins. In this study no significant difference could be found.[218] An additional study of 39 patients with varicose veins failed to show pulsatile flow or any significant change in mean venous O_2, in comparison to controls.[219] However, Pratt[207] estimated that AVAs occur in 24% of varicose veins and in 50% of patients with recurrent varicose veins after surgical ligation and stripping.

Schalin[220] has demonstrated AVAs with thermography (Fig. 3.9). He reviewed the role of arteriovenous shunting in the development of varicose veins and concluded that the recurrent and varying flow of arterial blood transmitted to veins over years causes the venous wall to distend. Schalin made his observations using operative microscopy and demonstrated that AVAs connect to varicose veins at the convex curves. Although AVAs are difficult to detect radiographically in association with varicose veins,[221] rapid venous filling is commonly seen in arteriograms of limbs with severe venous stasis.

Opening of the AVA may occur through developmental or functional abnormalities of vasa vasorum of the venous wall. In one scenario an association of excessive alcohol consumption in male patients with varicose veins was proposed as a cause of arteriolar dilation and new capillary formation, which may act like multiple AVAs.[109] Alternatively, opening of the AVA may be caused by proximal venous hypertension breaking down the capillary barrier.[221] Once dysfunction of the AVA is established, shunting of arterial blood directly into the venous system further increases venous dilation. Whether AVAs are the cause or the result of varicosities is still unknown. Despite this, common observations tend to support the concept of AVA-induced varicosities. Varicose veins may recur after anatomically correct sclerotherapy that obliterates all perforating veins. This may result from an AVA distal to the point of injection. Also, the bright red color of some leg telangiectasias may be caused by an underlying AVA. Finally, cutaneous ulceration after sclerotherapy treatment may also be related to injection of venules and their associated AVAs (see Chapter 8). Therefore the AVA is important as either an etiologic or associated factor in the cause and treatment of varicose veins, but it is not the primary cause of all varicose veins.

PRIMARY VALVULAR INCOMPETENCE

Primary valvular incompetence is a serious precursor of varicose veins because, by definition, such valves are permanently damaged, absent or incompetent. As originally suggested by William Harvey,[222] an incompetent valve causes distension of the distal vein by gravitational back pressure and may produce a varicosity. Many factors may be responsible for the development of valvular incompetence, including developmental abnormalities and destruction of the venous valves. Direct venoscopic evaluation in 25 patients with varicose veins disclosed that the GSV was valveless from the SFJ to the upper calf, where the first normal valve appeared.[223] Regional differences occur in varicosities.

Congenital valvular agenesis is a very rare cause of varicose veins.[224–228] Multiple case reports and a series of 14 patients have been described.[224,229] Such patients have partial or complete absence of deep vein valves in the lower extremities. Familial occurrence in two pedigrees suggests a simple dominant mode of inheritance. Clinically such patients are

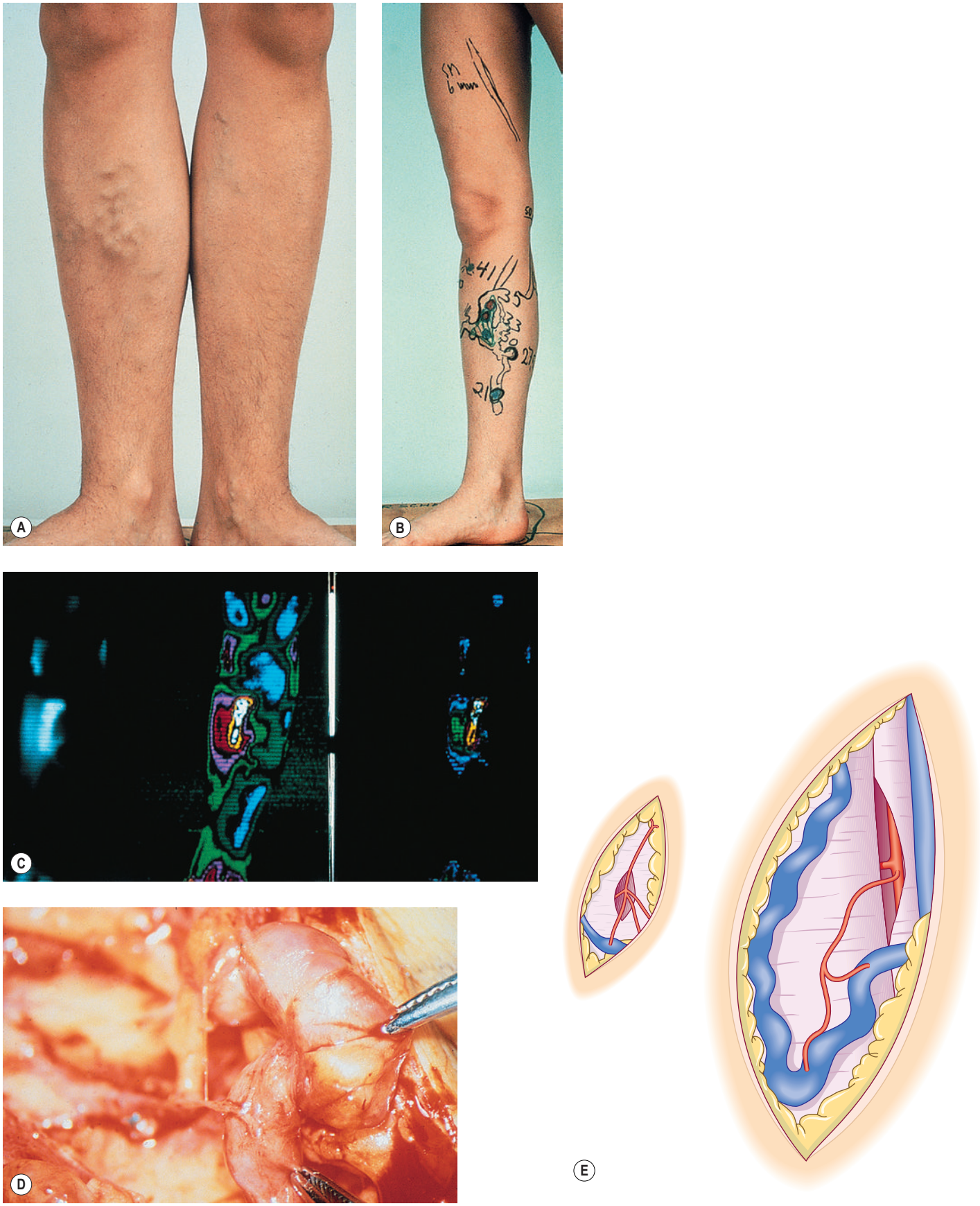


Figure 3.9 **A,** Use of an operation microscope in cautious dissection of a 27-year-old woman identified two small pulsating vessels at the medial calf; **B,** 33–35 cm above the floor; **C,** corresponding to a thermographically hot (35° C) varicosity. **D,** These arteries joined the meandering (tortuous) vein at the convex bends. No alternative arterial runoff was identified. **E,** illustrates the connection of the arteries with the varicose vein. (Courtesy Lars Schalin, MD.)

detected by development of venous insufficiency at an early age. Interestingly, signs and symptoms invariably occurred only after puberty. The most serious physical finding was cutaneous ulceration in the typical medial malleolar area. The most notable physical finding was ankle edema occurring during the day that was completely resolved at night or during rest. Another common sign was marked orthostatic hypotension from venous pooling in the legs. In these patients, wide variations in the number of valves were seen. They ranged from complete agenesis in both lower extremities to agenesis in only one leg or even partial agenesis. Therefore, although rarely reported, valvular agenesis may be found to some degree on careful examination of some patients. Its diagnosis is critical before performing injection sclerotherapy because a major complication of injecting veins without valves is a possible progression of venous fibrosis and thrombosis to the deep venous system. This could worsen venous insufficiency even to the extent of jeopardizing the viability of the limb.

Scientific evaluation of the relative significance of valvular deficiency in relation to the development of varicose veins is not as clear as valvular agenesis as a cause for varicose veins. An autopsy study of 44 limbs disclosed four with varicose veins that had normal valves in the femoral vein and the SFJ. Valves were absent proximal to the SFJ in three of the four varicose vein limbs. This was statistically significant when compared with nonvaricose vein limbs.[230]

Another autopsy study demonstrated a lower number of venous valves in the left internal iliac vein compared with the right iliac vein. This could explain the relative increased incidence of left-sided varicose veins; the relative obstruction caused by the right iliac artery may be unimportant (Villavicencio JL, personal communication, 1989). Anatomical studies do not define the functional significance of venous valves. In a radiographic functional study of external iliac and femoral valves performed on 12 male volunteers with and without varicose veins, subjects with a family history of varicose veins were found not to have femoral or external iliac valves.[231] Conversely those men without a family history of varicose veins did have such valves. Another study of 54 normal adults and 19 children of patients with varicose veins confirmed these findings. Venous Doppler examination showed that incompetent iliofemoral valves were present in 16% of the normal adults and in 32% of the children of patients with varicose veins.[232] These studies lend support to the theory of descending sequential valvular incompetence as a pathogenic mechanism for the development of varicose veins. Interestingly, a Nigerian study found that Caucasians show a relative deficiency of venous valves relative to Africans.[233] However, this cannot explain the lack of difference in the incidence of varicose veins between black and white people in America.

Despite the studies just mentioned, other studies have unfortunately failed to show a convincing association between the absence of iliofemoral valves and the presence of GSV incompetence.[234] In addition, veins that have been reversed (thus rendering their valves incompetent) and used as arterial grafts fail to elongate or dilate. They certainly do not develop into varicose veins.[235] Finally, at least one study demonstrated a competent saphenofemoral valve in up to 50% of GSVs with incompetent distal valves, suggesting that reflux progresses distal to proximal in these patients.[236,237] Therefore primary valvular deficiency, with or without increased transmural pressure, is best thought of as a contributory factor and not as an absolute causative factor in all patients with varicose veins.

Light-microscope findings of the venous valve in varicose veins consist of multiple dystrophic changes. There is a proliferation of collagen fibers and smooth muscle cells, in addition to distortion and tearing of elastic fibers in the cusp. This translates to intimal thickening and tortuosity (Fig. 3.10).[238]

Common mechanisms for the destruction of these valves are DVT and thrombophlebitis. DVT is estimated to precede the development of varicose veins in as many as 25% of patients.[239] Incompetence of the veins may also occur because of destruction of the valves by the inflammatory process of thrombophlebitis.[240–242] In addition to spontaneous DVT, thrombophlebitis may occur as a result of chemical or mechanical trauma or inflammatory bowel disease. Thrombophlebitis may also occur postsurgically in association with various malignancies, as a result of hormonal elevations associated with birth control pills, the postpartum period or even smoking.[242]

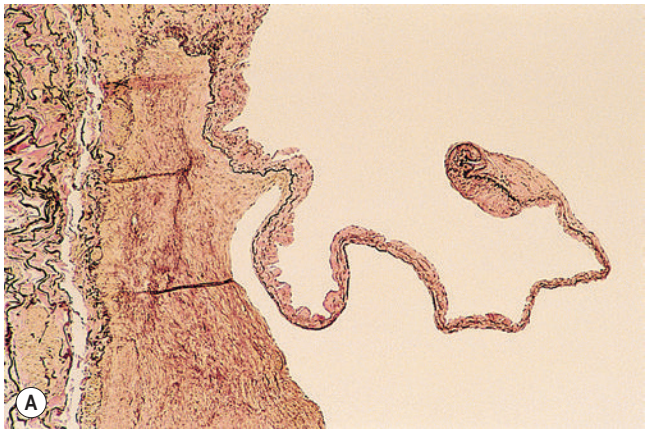
Finally, chronic venous dilation may in itself cause valvular fibrosis. Venous dilation increases tension on the cusps of the valves, which causes them to project into the lumen of the vein as rigid flanges (Fig. 3.11). The resultant turbulence of blood flow is thought to cause sclerosis and contraction of the valve and also its eventual disappearance. This has been noted on histologic examination of varicose veins removed at surgery or postmortem operations.[243]

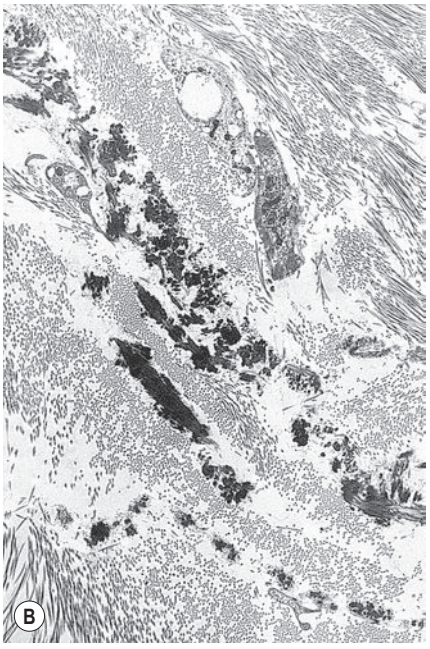
SECONDARY VALVULAR INCOMPETENCE

Secondary valvular incompetence is a common cause of varicose veins. In this situation the valves are normal, but become incompetent because of dilation of the vein wall. Secondary valvular incompetence may occur as a result of destruction of the valvular system after DVT or because of the expansion in the diameter of the vein. This latter process may occur through an increase in venous volume, obstruction in venous return or a hormonally induced increase in venous distensibility.[244] Thrombotic destruction of venous valves usually begins in the venous sinuses such as in the soleal sinuses. Here the thrombus may spread to the posterior tibial vein and subsequently into the ankle communicating veins.[80] Organization and recanalization of the thrombus destroys the valves.[80] An even more dangerous event occurs when the thrombus spreads proximally as a precursor to the development of a pulmonary embolism.

EFFECTS OF PREGNANCY

Pregnancy is typically associated with secondary valvular incompetence. Many epidemiologic studies have found a significantly increased incidence of varicose veins in women who have been pregnant.[72,142–144,159] However, some epidemiologic studies have failed to confirm this association when the effect of age is controlled.[70,138] An additional study confirmed that the GSV diameter increases during the first pregnancy, but does not increase further in subsequent pregnancies.[245] Varices are often first noted during pregnancy and are exceedingly rare before puberty.[246] Population studies have found that only 12% of women with





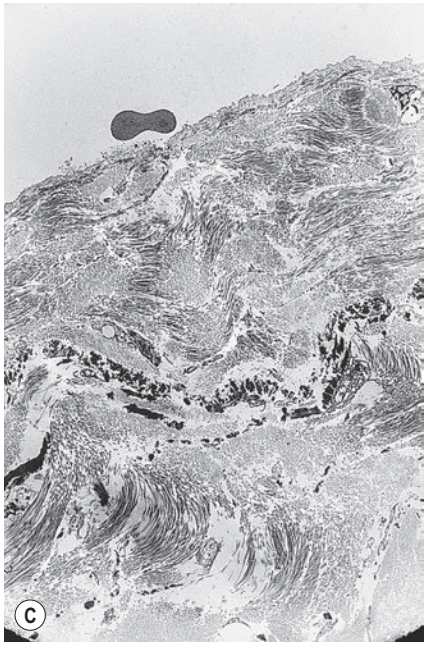


Figure 3.10 **A,** Valve cusp in a varicose vein. Intimal thickening is marked with thinning of the tunica media (elastic stain, Verhoeff–van Gieson, ×20). **B,** Protofibrils are proliferative with a complex course in a varicose vein. (Electron microscope stained with silicotungstic acid uranyl acetate.) **C,** Elastic fibers are torn with an aberrant course. (Electron microscope stained with silicotungstic acid uranyl acetate.) (Reproduced from Obitsu Y, Ishimaru S, Furukuva K, Yoshihama I. Phlebology 1990;5:245.)

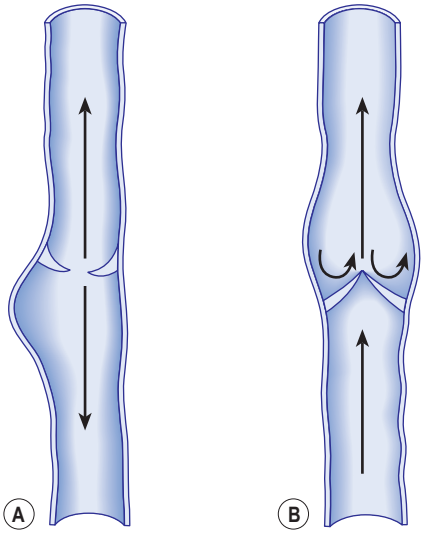


Figure 3.11 **A,** Diagram of eccentric dilation beneath the valve cusps in a varicose vein. **B,** Normal valve shown for comparison. (From Cotton L. Varicose veins. Gross anatomy and development. Br J Surg 1961;48:589. © British Journal of Surgery Society Ltd. Reproduced with permission. Permission is granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

varicose veins have never been pregnant.[247] It has been suggested that in addition to hormonal effects (discussed later), increased total blood flow in the iliac veins from the uterine and ovarian veins may explain the occurrence of varicose veins in early pregnancy.[248] Pregnancy is accompanied by an increase in plasma volume to 149% of normal shortly before parturition.[249] Blood flow through the uterine veins increases 4- to 16-fold in the first 2 months of pregnancy and doubles again during the third month.[250] Although uterine obstruction to venous flow and an increase in iliac blood volume and flow are measurable physiologic factors in pregnancy, it is obvious that factors other than venous congestion are important in the development of varicose veins.

Serial duplex scanning and air plethysmography determinations have revealed that women with no known venous disease can experience significant increases in common femoral vein and SFJ diameters without developing venous reflux. This is also true of women in pregnancy who have demonstrated prepregnancy venous obstruction.[251]

Femoral vein obstruction by the gravid uterus may lead to secondary valvular incompetence through an increase in proximal venous pressures. The obstructive effects of the uterus do not develop during pregnancy until the second

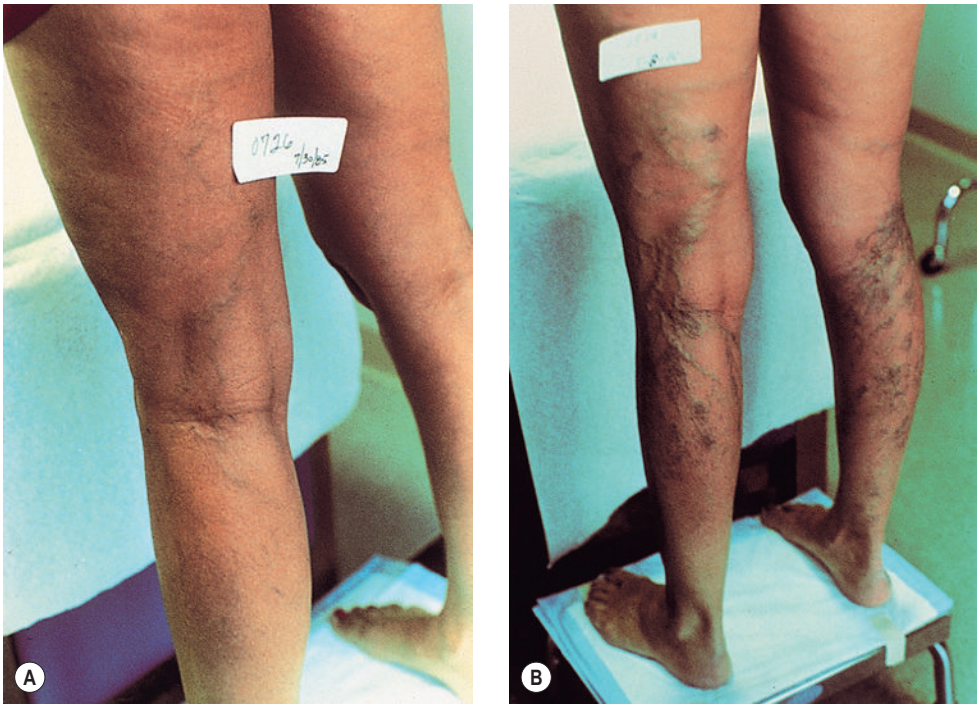


Figure 3.12 Woman, 33 years old. **A,** Before pregnancy. **B,** 20 weeks into pregnancy with a 15-lb weight gain. Note the dramatic increase in the size and number of varicose veins. (Courtesy Anton Butie, MD.)

and third trimesters.[252] A sequential study of 50 gravid women through the first, second and third trimesters using Doppler ultrasound demonstrated that femoral venous flow was obstructed in 72% of erect patients in the second trimester, and in 86% of patients in the third trimester.[253] An additional study of femoral blood flow in 61 pregnant patients demonstrated that the most significant decrease in femoral blood flow occurred when the head of the fetus became engaged during the latter part of the third trimester.[254] However, a study of venous capacitance and outflow in pregnant women at term, 1 week, 6 weeks and 3 months after delivery demonstrated a decrease that persisted until 3 months after delivery.[255] Other factors affect venous function in pregnancy.

The effect of the gravid uterus on the impedance of femoral blood flow may be influenced by hereditary factors. Although some investigators have not found a consistent relationship between the presence or absence of varicose veins and obstruction to venous flow,[253] others have measured venous pressure in the popliteal vein in pregnant patients in the third trimester and found a marked increase in venous pressure, but only in those women with varicose veins.[256] Therefore both an increase in blood volume and an obstruction of venous return are responsible for the development of varicose veins in pregnancy. These two factors do not account for the development of smaller telangiectasias and venectasias; nor do these factors account for the development of varicose veins in the first trimester.

In pregnancy hormonal factors are primarily responsible for venous dilation. As many as 70% to 80% of patients develop varicose veins during the first trimester, when the uterus is only slightly enlarged (Fig. 3.12). In the second trimester, 20% to 25% of patients develop varicose veins, and 1% to 5% of patients develop them in the third trimester.[257–259]

Varicose veins of the legs are first apparent as early as 6 weeks into gestation at a time when the uterus is not yet large enough to significantly impede venous return from the leg veins. In contrast, vulvar varices usually develop in the third trimester, but may appear late in the first trimester.[248,260] Furthermore, Mullane[259] notes that symptoms of varicose veins can be the first sign of pregnancy and can occur even before the first missed menstrual period. This confirms the observations of many multiparous women and argues for a profound influence of progesterone on venous dilation and valvular insufficiency. Siegler[261] states that 40% of all pregnant patients are affected and maintains that all women will develop varicosities if they have a sufficient number of pregnancies. Berg[262] estimates that 30% of primigravidas and 60% of multigravidas suffer varicose changes in the veins during pregnancy. In support of this theory is Mullane's patient who developed varicose veins for the first time during her eleventh pregnancy.[259] An evaluation of venous refilling times in primiparae and multiparae patients with varicose veins demonstrated no difference between the two groups.[263,264] Another study examining the CEAP (clinical, etiology, anatomy, pathophysiology) classification of 583 women and the prevalence of GSV reflux found no correlation with the reflux patterns and the number of pregnancies.[265] Therefore the first pregnancy likely represents the most important injurious factor, with each subsequent pregnancy producing minor deterioration of venous function.[245,266]

Findings show that venous distensibility increases in both forearm and calf veins with the progression of pregnancy, particularly after the thirteenth week.[267] The increase in distensibility is greater in the calf than in the forearm and returns to normal by the eighth postpartum week.[267]

Incompetence of the saphenous veins may occur because of excessive dilation of the vein when there is sufficient

separation of the valve cusps.[241] Interestingly, retrospective studies have shown that 40% to 78% of patients note the development of varicosities during the second pregnancy rather than during the first.[13,258,259] Rose and Ahmed[13] postulate that veins that become subclinically varicose after the first pregnancy become clinically obvious after the second pregnancy. As previously mentioned, this impression has been confirmed with photoplethysmography evaluation of venous refilling times.[263]

The pregnant state is associated with elevations of multiple hormones. Estrogen produces a relaxation of smooth muscle and softening of collagen fibers in general, which may explain the increased distensibility of veins.[268,269] It has been reported that increased distensibility of vein walls occurs as a result of estrogen therapy.[270,271] McCausland[258] believes that the progesterone level and more importantly the estrogen/progesterone ratio is primarily responsible for increased venous distensibility. Supporting this theory is the marked venous distensibility demonstrated in women who are given a synthetic progesterone.[272] A study in 1946 reported that the administration of an estrogenic substance, Diovocylin (CIBA, Basel, Switzerland), to 27 pregnant patients with either varicose or telangiectatic veins in weekly doses throughout pregnancy actually produced an amelioration of the smaller and larger types of vein, and a reduction of peripheral edema and subjective complaints in the majority of patients.[273] This was confirmed in a subsequent study of 34 patients treated with 0.05 mg of oral ethinyl estradiol two to four times daily.[274] Presumably administration of this substance altered the progesterone/estrogen ratio (No mention was made of feminization of male babies on follow-up examination.) An additional study has demonstrated a complete relief of symptoms in 13 of 15 patients with 'angiectids' (small, intradermal, raised, bluish mats of blood vessels) in pregnancy using diethylstilbestrol (E.R. Squibb, Aliso Viejo, CA) in doses ranging from 50 to 150 mg daily.[275] In this regard, the degree of pain and disability caused by the angiectid was frequently related to the level of subnormal estrogen. Symptomless angiectids were correlated with low normal amounts of estrogen and progesterone. Therefore the hormonal factors responsible for the development or exacerbation of varicosities in pregnancy may very well be related to the estrogen–progesterone balance. Hormonal influences may also explain why varicose veins that develop in pregnancy resolve postpartum (Fig. 3.13).

A practical model to represent the growth of varicose veins during pregnancy is to observe that in certain women a number of leg veins grow in diameter and length as pelvic veins do. This process, useful for the development of the embryo, is useless in these leg veins, which can be considered as ectopic pelvic veins in the lower limbs. Their involution is exactly parallel to involution of pelvic veins and begins immediately after the woman gives birth. It is logical to consider that these veins are submitted to the influence of hormones and have the same receptors.

One additional hypothesis to explain the development of varicose veins in pregnancy is the development of AVAs. Venous volume with correction for capillary filtration was found to be larger in pregnant women with varices than in pregnant women without varices or in nonpregnant women. This may indicate the presence of arteriovenous malformation.[276]

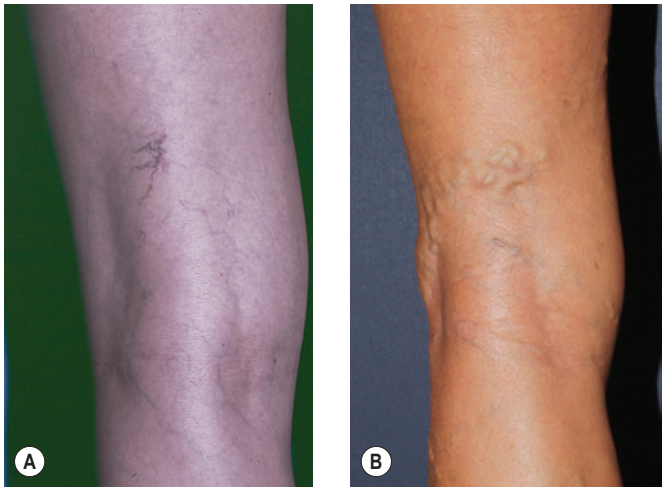


Figure 3.13 **A,** Twenty-eight-year-old woman in her sixth month of pregnancy. Note prominent varicose, reticular and telangiectatic veins on the right posterior thigh and calf; **B,** 6 months after delivery. Note near complete resolution of all new veins without treatment.

In pregnancy, two factors operate to dilate leg veins: increased venous distensibility from hormonal stimulation, and increased venous pressure from obstruction by the gravid uterus and an increased blood volume. Sumner[277] estimated that 80% to 90% of varicose veins tend to regress during the puerperium. He advises physicians to wait 6 to 12 weeks after delivery before performing surgery or sclerotherapy, to allow time for the varices to regress. This not only enhances treatment efficacy, but also allows the physician to make a more accurate assessment of the true extent and severity of the disease.

The hormonal influence on the venous system extends beyond pregnancy. Studies have demonstrated that the increase in venous distensibility is different for different oral contraceptive agents. Oral contraceptives with a high progestogen component appear to increase venous capacitance and may induce venous stasis, whereas coagulability is partially enhanced by estrogen-dominant contraceptives.[278] The effect of systemic estrogen and progesterone can be demonstrated with photoplethysmography, venous Doppler tensiometry and biomicroscopy. With these evaluations, women taking a low-dose oral contraceptive agent (0.020 mg ethinyl estradiol plus 0.150 mg desogestrel) undergo observable microcirculatory changes without clinical evidence of varicose or telangiectatic vein development. When women take a higher estrogen oral contraceptive (0.030 mg ethinyl estradiol plus 0.075 mg gestodene), significant capillaroscopic changes and a significant impairment of photoplethysmography occur, associated with clinical signs and symptoms such as orthostatic edema, itching, heaviness and slight pain in the lower limbs.[279] A retrospective evaluation of 2295 patients who took various concentrations and types of oral contraceptives determined the existence of a significant relationship between the intensity of symptoms and functional symptomatology, and the dosage of estrogen and progesterone.[280] Epidemiologic evaluations concerning the use of oral contraceptives demonstrate a trend, but do not prove a statistically significant risk for their use in the development of varicose veins.[142,281] In addition, alterations in

leg vein distensibility were not found in the first half of pregnancy or during oral contraceptive therapy with estrogen-dominant ethyl adrianol (10 mg) by means of ascending phlebography.[282]

Finally, it has been noted by Gallagher[283] in his practice of 20,000 patients that the incidence of minor asymptomatic varices decreases after menopause. This is correlated with a fall in estradiol production and plasma concentration. Therefore neither estrogen nor progesterone seems to be an independent factor influencing venous capacitance; the proportional concentrations of either one may be more important.

MENSTRUAL CYCLE EFFECTS

A change in venous distensibility occurs during the menstrual cycle,[272,278] being higher during the luteal phase than during the follicular phase.[278] This increase in distensibility correlates most closely with progesterone levels.[272] However, studies on vein distensibility do not distinguish between relaxation of smooth muscle and alteration in the viscoelastic properties of the venous wall. These studies do not exclude the possibility that the increased distensibility may result from the reduction in vasoconstrictor tone. Therefore it is difficult to make recommendations regarding the timing of sclerotherapy within the menstrual cycle or the necessity to discontinue oral contraceptives during sclerotherapy.

Recent studies measuring progesterone and estrogen receptors in varicose GSV from men and women demonstrate an increase in both estrogen and progesterone receptor–positive cells only in women with varicose veins. There was no difference between men with and without varicose veins and women without varicose veins.[284,285] These gender differences may be hormone related or related to the presence of younger premenopausal females in the varicose vein patient group. Thus women may be innately predisposed to developing varicose veins in addition to being susceptible to the systemic effects of these hormones.

Of more clinical concern is postpartum thrombophlebitis and its attendant dangers of pulmonary embolism and eventual development of the postphlebitic syndrome.[286] The reported incidence of thrombophlebitis in pregnancy ranges from 0.35%, with a 0.085% incidence antepartum and 0.27% postpartum,[287] up to 3.6% when mild cases are included in statistical analysis.[288] Multiple factors are responsible for the increased incidence of thrombophlebitis in this group of patients. In late pregnancy, blood volume is increased, the uterus impedes venous return and elevated hormone levels produce an increased distensibility of veins with resulting valvular incompetence. In addition, multiple factors are present at childbirth, including increased clotting factors and a hormonal environment conducive to clotting that appear to predispose this physiologic milieu to the development of thrombophlebitis.[289,290] Therefore graduated elastic support hosiery should be worn before, during and immediately after delivery.[286]

CONSTITUTIVE ELEMENTS AND PROGRESSION OF VARICOSE VEINS

Whatever the mechanism or the origin of the disease, fundamental lesions remain the same. All or several can be observed in a patient, and the description of the case uses them as bricks to build up the pathophysiologic model with which the therapeutic decision will be taken (Tables 3.1 and 3.2).

Although each individual lesion has its proper treatment, the relative importance of its proximal position, distal (ascending theory) versus proximal (descending theory), for the development of valvular incompetence can lead

Table 3.1 Therapeutic Options for Each Elementary Lesion

Lesion	Consequences	Conservative Treatment	Interventional Treatment
Valvular incompetence	Reflux Hypertension	Compression Phlebotropic drugs	Suppression of vein, restoration of competence
Venous wall remodeling	Dilation	Phlebotropic drugs	Suppression
Varicose reservoir	'Siphon'	Compression	Suppression
Calf muscle pump	Inefficacy	Physiotherapy	Compression
Vein wall, microcirculation	Symptoms, decompensation	Phlebotropic drugs	No biochemical alterations

Table 3.2 Pathophysiologic Background

Lesion	Consequences	Superficial System	Deep System
Valvular incompetence	Reflux, hypertension	+++	+++
Vein wall remodeling	Dilation, tortuosity	+++	±
Varicose reservoir	'Siphon'	+++	±
Obstruction	Hypertension	±	++
Calf muscle pump	Inefficacy	+	+++
Reduction of vein wall compliance	Dynamic obstruction	±	+
Tissue alterations	Multiple	+++	+++

to different treatment approaches. Contrary to the classic descending approach (crossectomy) it has been shown that in patients with a large varicose reservoir and a reflux of the GSV, ablation of the varicose reservoir by phlebectomy can correct the saphenous reflux in more than 66% of cases and provide satisfactory midterm (4 years) clinical results.[291] These findings are consistent with the evaluation of systematic color-flow duplex scan images showing the pattern of varicose veins in a cross-sectional study of untreated patients, which showed a predominance of early lesions in tributaries rather than in the saphenous trunk.[292] It seems that the progression of varicose veins can be ascending, descending, or a combination of both directions, either in different subsets of the disease or even in the same patient, consecutively or simultaneously. As this natural history issue of varicose veins is likely to strongly influence the long-term results of the treatment, follow-up studies in treated patients and also in untreated subjects from the general population are clearly needed.

HEREDITY

Although development of varicose veins can usually be ascribed to one of the previously mentioned pathologic states, postmortem examination may not disclose the apparent source of the high-pressure leak from the deep to the superficial system.[293] Therefore other inherent factors such as vein wall weakness, increased primary valvular dysfunction, agenesis and other genetic factors may enhance the development of varicose veins.

In an extensive study in France, 134 families were examined. Of these, 67 were patients with varicose veins plus their parents, and 67 were controls without varicose veins plus their parents. A total of 402 subjects was examined. The results demonstrated the prominent role of heredity in the development of varicose veins ($P < 0.001$). For the children, the risk of developing varicose veins was 90% when both parents were afflicted. When only one parent was affected, the risk of developing varicose veins was 25% for males and 62% for females. The overall risk of varicose vein development was 20% when neither parent was affected by varicosities.[294]

A familial tendency toward the development of varicose veins has been described in many population groups.[141–143,160,163,295–299] This may also be demonstrated by the development over time of varicose veins bilaterally when patients with unilateral varicose and telangiectatic veins are followed for 10 years.[298] A limited study of 50 patients with varicose veins in Great Britain disclosed a simple dominant type of inheritance.[300] Only 28% of patients had no family history of varicose veins. In Scandinavia, questionnaires completed by 124 women with varicose veins disclosed a 72% prevalence of varicose veins of an autosomal type in the women's siblings.[296] Of these cases 28% were of a recessive pattern. Troisier and Le Bayon[301] examined 154 families with 514 descendants. They found that if both parents had varicose veins, 85% of children had evidence of varicose veins, whereas 27% of the children were affected if neither parent had varicose veins and 41% of the children were affected if one parent had varicosities. These authors concluded that the inheritance of varicose disease is recessive. However, some studies have not found a significant familial tendency.[145,302]

A first twin study found that 75% of 12 monozygotic pairs were concordant with regard to varicose veins versus 52% of 25 dizygotic same-sexed pairs.[303] But the definite proof regarding the influence of heredity came in 2005 from a large study of 2060 unselected pairs of female twins aged from 18 to 80 years,[304] which showed that the concordance rate for varicose veins phenotype was significantly ($P < 0.001$) higher for monozygotic (67%) than for dizygotic twins (45%). In the same study, a significant linkage of varicose veins to a marker of the *FOXC2* region of the chromosome 16 was found, suggesting *FOXC2*, a gene already known for its role in the embryogenesis of the lymphatic system, is implicated in the development of varicose veins. These findings were replicated in another study where *FOXC2* was found to be associated with venous valve failure and reflux.[305]

Although these studies provide a clear demonstration of the role of genetic factors in the pathogenesis of varicose veins, they also demonstrate that environmental factors play an important role as well, because the concordance rate in monozygous twins is far from 100%. Other studies have found more of a multifactorial inheritance. In a detailed study from Sweden of 250 probands of patients with varicose veins requiring treatment, the overall frequency of varicose veins in female relatives was 43%, compared with 19% in male relatives.[306]

The absence of venous valves in the external iliac and femoral veins has been shown to be a marker of varicose veins in a limited radiographic study of 12 male volunteers, some with and some without varicose veins,[231] and in a venous Doppler study of 54 patients with varicose veins.[307] In addition, a simple dominant mode of inheritance has been reported in 14 patients with either partial or total congenital absence of venous valves of the leg.[213,308] This genetic predisposition may be the result of multiple factors and the subsequent development of varicose veins may depend on one or more occupational or hormonal factors.

Congenitally weak or nonfunctioning venous valves may be an initiating factor in the altered venous hemodynamics that lead to the formation of varicose veins.[309] The argument against this theory is that valvular cusps consist of a fibrous tissue core covered by endothelium. This structure has been demonstrated to be extremely strong in experimental models.[310] In fact, it has been estimated experimentally that valves will not rupture at the physiologic pressures to which a valve might be subjected during life. Therefore it is more likely that alterations in the vein wall, and not valve strength, are responsible for the development of incompetence.

Rose and Ahmed[13] postulated that an inherited alteration in vein wall collagen and/or elastin, or an increase in vein wall collagen deposition with separation of smooth muscle cells (as previously described), is a major etiologic precursor to the development of varicose veins. They reasoned that increased venous pressure should lead to hypertrophy of the vein wall, as demonstrated in arterialized venous bypass coronary grafts,[310–314] and not the dilation associated with varicose veins. Accordingly, dilation of varicose veins, at times only in certain areas of the vein, must be caused by a vein wall defect—not merely by the presence of high venous

pressure. A generalized increase in venous distensibility was found in superficial forearm and hand veins in patients with a saphenous varicosity as compared with patients without varicosities.[315,316] Abnormal distensibility curves were found to be similar regardless of the age and sex of the patient. This may be related to a reported decrease in collagen content in the saphenous veins of patients with varicosities, which occurs even in vein segments that are not varicose.[22,32] The decrease in venous distensibility may also be related to a constitutional decrease in venous α-adrenergic receptor responsiveness in patients with varicosities. Patients with varicose veins require significantly higher doses of norepinephrine for vasoconstriction than do control subjects. This finding applies to both varicose and normal veins in the same individual.[317] The neural regulatory network in the saphenous vein also consists of acetylcholinergic and peptidergic neurons, in addition to both circulating and endothelium-derived vasoactive substances.[318] Thus neural and hormonal factors are important regulators of venous distensibility.

The decreased collagen content in varicose vein walls has been related physically to its viscoelastic properties, with varicose veins breaking at lower pressures than normal veins.[319] This effect may occur in certain patients from a genetic defect affecting the biosynthesis of certain collagen types. One example is Ehlers-Danlos syndrome, type IV (vascular type) in which patients have a deficiency in collagen type III normally present in the skin, arteries and gut. These patients also frequently have varicose veins.[320] In addition, patients with previous hernia surgery also have an increased incidence of varicose veins suggesting that ligamentous laxity may be a risk factor.[163] However, this theory does not explain why correction of proximal valvular dysfunction with a tourniquet can correct abnormal venous pressures distally if it is the vein wall that is abnormally distensible.[321]

Generalized dystrophic changes in the vein wall were confirmed histologically through biopsy of normal dorsal foot veins in 97.3% of patients with varicose veins.[322] The generalization of venous wall changes from superficial to deep veins was also demonstrated.[22] The authors speculate that this generalized trend may allow improvement of sclerotherapy techniques by choosing a stronger sclerosing agent when a peripheral venous biopsy demonstrates severe dystrophy (see Chapter 9).

Another interesting relationship is the recently described association of varicose veins with the ABO blood group system. Numerous studies have demonstrated a relationship between blood groups of the ABO system and DVT of the lower limbs.[323–326] These studies indicate an increased incidence of DVT in patients with blood type O, particularly when associated with pregnancy or the use of oral contraceptive agents.[326] However, one study found an increased incidence of thromboembolism in people with blood group A.[327] A study of 569 French men and women showed the risk of varicose veins in patients with type A blood to be double that of patients with all other blood groups.[328] Varicose veins were defined as the presence in the standing position of a permanent dilation with reflux of at least one leg vein with a diameter of 3 mm or more. The risk of varicose veins persisted after adjustment for age, sex, paternal or maternal history and a personal history of DVT. No association was found between Rhesus factor and varicose veins. Therefore, a patient's blood group may be taken into account when assessing the need for prophylactic treatment of varicose veins or assessing the risk of postoperative venous thrombosis.

Various genetic factors have more recently been correlated with chronic venous disease. Connexins are gap junction proteins involved in physiologic and developmental processes. Connexin 37 (Cx37) has been associated with venous valve development and could be a future target for valvular malfunction.[329] Matrix Gla protein (MGP) is a vitamin K–dependent Gla-containing protein that binds to calcium ions and acts as an inhibitor of vascular mineralization.[330] Cario-Toumaniantz et al demonstrated an increased mineralization of nonvaricose and varicose smooth muscle cell cultures with decreased MGP levels.[42] Variations in the gene expression of Tenascin C and dermatopontin were also found within varicose veins as another possible contributor to the pathogenesis of varicose veins. Tenascin C induces MMPs and modulates cell matrix attachment, whereas dermatopontin interacts with decorin to regulate collagen fibrillogenesis.[42]

Thrombomodulin (TM) is an integral membrane protein on endothelial cells that is a co-factor in the thrombin-induced activation of protein C to downregulate the coagulation cascade. TM bound to thrombin also has a simultaneous procoagulant effect by inhibiting fibrinolysis by cleaving thrombin-activatable fibrinolysis inhibitor into its active form.[331] Le et al found a specific TM DNA mutation of a −1208/−1209 TT deletion to be increased in patients with varicose veins. This mutation has an effect with the proliferative function of TM.[332]

An increase in serum homocysteine levels has been associated with the CEAP class severity of primary chronic venous disease. The highest levels of homocysteine were seen in C4–6 chronic venous disease raising the possibility that homocysteine may play a role in promoting chronic venous disease complications.[333] Sam et al also found a statistically significant increase in hyperhomocysteinemia (HHcy) in patients with CEAP 2–6 chronic venous disease in comparison to the average population at 39% to 5%, respectively. Higher levels of homocysteine were noted with the higher CEAP levels. The highest homocysteine levels were seen in patients with the most common genetic mutation for HHcy, a methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism. Patients with this C677T polymorphism were also correlated to have a higher CEAP class severity.[334]

Plasminogen activator inhibitor type 1 (PAI-1) is a serine protease that inhibits fibrinolysis through the inhibition of tissue plasminogen activator and urokinase.[335] The PAI-1 4G/5G gene polymorphism is an addition or deletion of a guanosine in the promoter region of the PAI-1 gene and has been associated with chronic venous insufficiency. A 3.25-fold increase in the risk for development of chronic venous insufficiency has been associated with the 4G allele.[336,337]

Tyrosine kinase with Ig and ECG homology domains (Tie1) is an enzyme-linked receptor that phosphorylates angiopoietin. Tie1 may play an integral role in hemodynamics, stabilization of capillary vessels, remodeling and deterioration of vessels.[337] Wang et al found a decreased expression of Tie1 in varicose veins compared with normal

veins that could play a role in the pathogenesis of varicose veins.[338]

Studies on varicose and normal veins using gene expression profiling based on cDNA microarray analysis suggest that pathways associated with fibrosis and wound healing may be altered in varicose veins.[339] Whether the upregulated varicose vein genes are a sequel to the changes in the varicose vein wall rather than a primary contributing factor to varicose pathogenesis awaits additional study.

AGING

The incidence of varicose veins increases with age (Table 3.3),[340] therefore vein wall damage should also be more pronounced in the veins of older patients (Fig. 3.14). Superficial venous reflux also increases with age (Fig 3.14A).[88,341] An autopsy study of the popliteal vein in 127 persons demonstrated diffuse changes with an increase in connective tissue in the media, which became most pronounced in the fifth decade and progressed in later years. This is associated with the loss of muscle cells in the media.[342] The finding correlated with an abnormality in the physical property of axial tension testing in 93 specimens of saphenous veins from 22 patients harvested during coronary bypass surgery.[343] One study of 31 normal veins and 41 varicose veins in patients and autopsy samples ranging in age from 25 to 92 years failed to disclose an age-related difference.[344] The latter study concluded that varicose veins were a predetermined disease unrelated to aging effects.

In conclusion, the influence of both genetic and environmental factors in the development of varicose veins has been clearly demonstrated. Although the *FOXC2* gene is likely to be involved, the heredity of varicose veins appears to be multigenic. Identification of the different components is crucial for the understanding of the pathogenesis of the disease. However, environmental factors also play a crucial role; as they are strongly associated with the lifestyle of industrialized countries, an improvement of their understanding can lead to a better primary prevention of the disease. Finally, progression of varicose veins is far from being fully understood, although therapeutic interventions targeted at secondary or tertiary prevention are widely advocated to patients all over the world. Follow-up studies exploring the natural history of varicose veins will be of great benefit and importance.

Table 3.3 Development of Varicose Veins (Percentage of Study population)

	Age (years)			
	10–12	14–16	18–20	29–31
Telangiectasia	0	3.7	12.9	50.4
Reticular	10.2	30.3	35.3	74.3
Perforating	0	4.1	5.2	25.7
Tributary varicose	0	0.8	5.0	17.7
Truncal varicose	0	1.7	3.3	12.5
Junctional reflux	0	12.3	19.8	26.5

Adapted from Schultz-Ehrenberg U, Reich-Schupke S, Robak-Pawelczyk B, et al. Prospective epidemiological study on the beginning of varicose veins (Bochum Study I-IV). Phlebologie 2009;38:17.

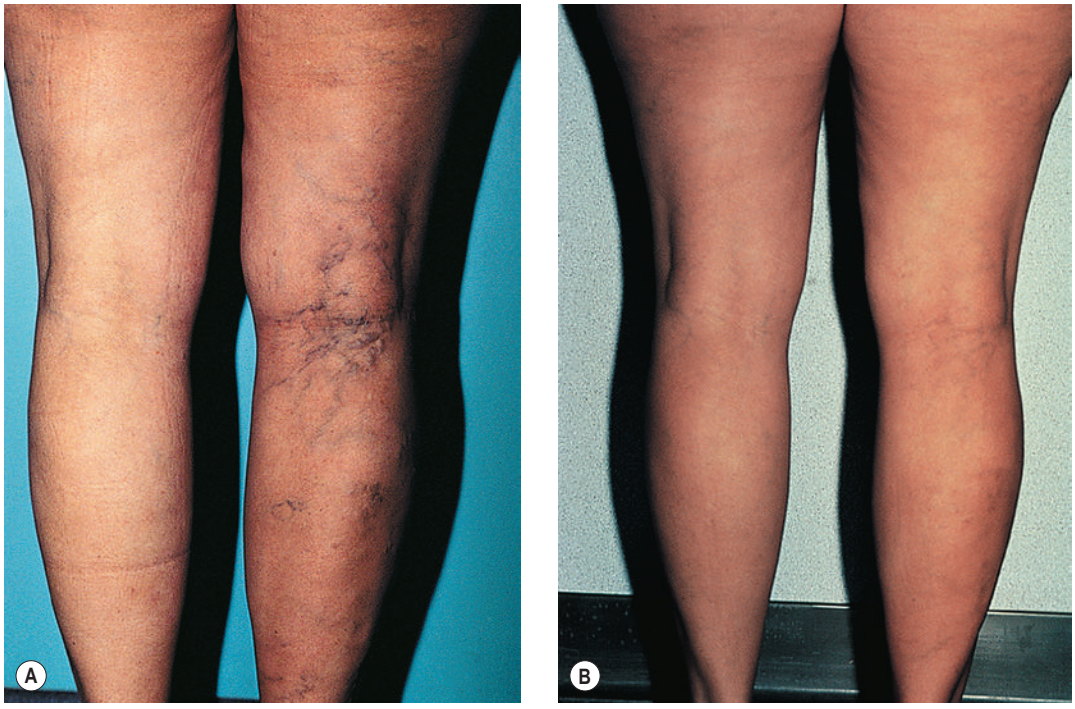


Figure 3.14 Female triathlete with no smoking history and rare alcohol use demonstrating the effect of age over a 22-year span. **A,** On the left, age 42. **B,** On the right, age 64.

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4 Pathophysiology of Telangiectasias

Mitchel P. Goldman, with contributions by Lisa Zaleski-Larsen

The term *telangiectasia* was coined in 1807 by Von Graf to describe a superficial vessel of the skin visible to the human eye.[1] These vessels measure 0.1–1 mm in diameter and represent an expanded venule, capillary or arteriole. Telangiectasias that originate from arterioles on the arterial side of a capillary loop tend to be small and bright red and do not protrude above the skin surface. Telangiectasias that originate from venules on the venous side of a capillary loop are blue, wider, and often protrude above the skin surface. Sometimes, telangiectasias, especially those arising at the capillary loop, are red at first but with time become blue, probably because of increasing hydrostatic pressure and backflow from deep veins.[2,3]

CLASSIFICATION

Redisch and Pelzer[4] classified telangiectasias into four types based upon clinical appearance (Fig. 4.1):

1. Sinus or simple (linear)
2. Arborizing
3. Spider or star
4. Punctiform (papular)

Papular telangiectasias are frequently present in patients with collagen vascular disease. Spider telangiectasias are red and arise from a central filling vessel of arteriolar origin. Red linear telangiectasias occur on the face (especially the nose) or legs. Blue linear or anastomosing telangiectasias are found most often on the legs.

Raymond-Martimbeau and Dupuis[3] proposed another classification based on the relationship between telangiectasias and superficial as well as deep veins. Using duplex ultrasound, they evaluated 525 consecutive patients with 884 zones of telangiectasia without underlying saphenous or perforator vein incompetence. They found that 8.8% of the telangiectasias joined the deep venous system, 12.6% joined the superficial venous system, 71.2% were directly connected to reticular veins and 7.4% had no obvious connection. This is in contradistinction to the reports of very high incidence of arterial venous anastomoses for leg telangiectasias.[5]

The actual etiology of telangiectasias may be identical to that of varicose veins.[6] However, the findings of Raymond-Martimbeau and Dupuis[3] suggest that valvular damage occurs with subsequent venous hypertension that is transmitted to epidermal vessels, which then elongate and dilate. Our research has implicated a leukocyte–endothelial interaction that relates intercellular adhesion molecule-1 and monocytes to adherence and migration of cells.[7] Valve and vein wall damage is produced by monocytes in the interstitial tissue.[8] Thus, pharmacologic treatment of telangiectasias may be possible in the future.

This chapter discusses the pathophysiology and anatomy of telangiectasias occurring on the lower extremities.

PATTERNS

Two common patterns of telangiectasias on the legs of women, besides red or blue streaks, are the parallel linear pattern, usually found on the medial thigh (Fig. 4.2), and the arborizing or radiating cartwheel pattern, seen most often on the lateral thigh (Fig. 4.3).[9] These two subsets of telangiectasias seem to run in families and may form anastomosing complexes as large as 15 cm in diameter. The arborizing type on the lateral thigh usually appears with 'feeding' reticular veins (see Fig. 1.11). These complexes have been termed *venous stars*, *sunburst venous blemishes* and *spider leg veins* by various authors.

PATHOGENESIS

The pathogenesis of each type of telangiectasia is somewhat different. Multiple factors may play a role in the development of new blood vessels or the dilation of existing blood vessels (see Chapter 3). Acquired telangiectasias probably result from the release or activation of vasoactive substances, such as hormones and other chemicals. Conditions associated with increased or activated vasoactive substances include anoxia, infection and certain physical factors that result in capillary or venular neogenesis.[4,10,11] One common area for the development of telangiectasia is the medial thigh. This has been thought to be, in part, a result of pressure exerted by crossing the legs. A report on tissue atrophy in a woman with associated telangiectasia at the site of pressure where her legs crossed suggests that intermittent pressure results in subcutaneous tissue loss or atrophy.[12] Unfortunately, to our knowledge, no formal studies on tissue pressure have been performed. Box 4.1, an extension of observations made by Shelley[13] as well as Anderson and Smith,[14] lists the major etiologies associated with telangiectasias arising on the lower extremities.

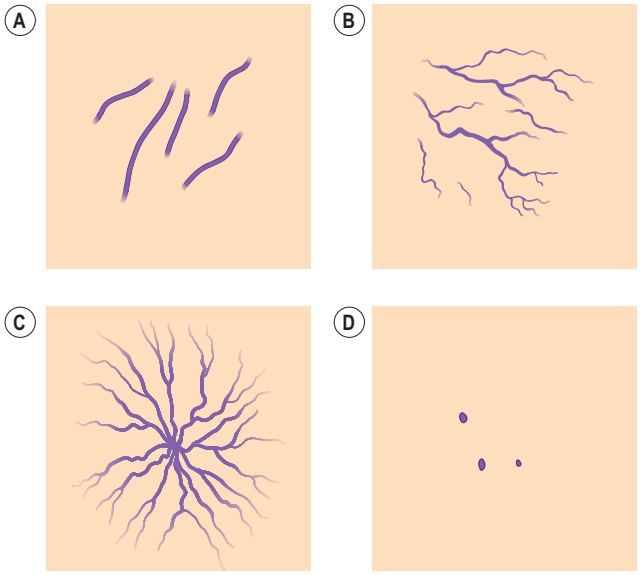

Figure 4.1 Four types of telangiectasias. **A,** Simple. **B,** Arborized. **C,** Spider. **D,** Papular. (Adapted from Reddish W, Peltzer RH. Am Heart J 1949;37:106.)

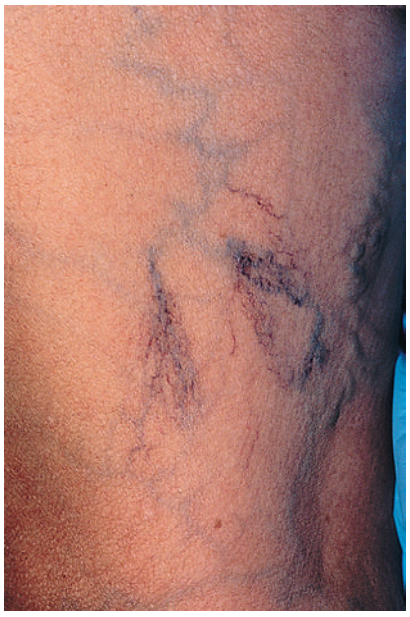

Figure 4.2 Typical appearance of telangiectasia located at the medial thigh in a 54-year-old woman. Note the feeding reticular vein proximal to the telangiectasia.

INCIDENCE

The incidence of varicose and telangiectatic leg veins in the general population is presented in Chapter 2. The relationship between varicose veins and spider leg veins (telangiectasias) is profound. The anatomy and pathophysiology of telangiectasia is presented in Chapters 1 and 3. Telangiectasias increase in incidence with advancing age.[15] Among neonates, the prevalence of telangiectasias is 3.8%, with 26% occurring on the legs.[16]

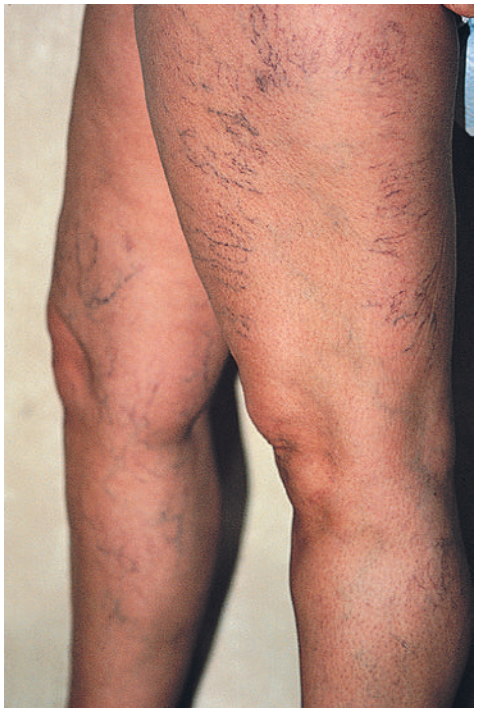

Figure 4.3 Common appearance of cartwheel or radiating telangiectasia pattern on the lateral thigh of a 42-year-old woman. Note the feeding blue reticular vein at the distal aspect of the telangiectatic pattern.

Two surveys have detailed the characteristics of patients seeking treatment of unwanted spider leg veins. Duffy,[17] in a nonrandomized survey of his patients, reported a 90% family history of varicose or telangiectatic leg veins. Patients included three sets of identical twins with similar-appearing leg telangiectasias. Sadick,[18] in a nonrandomized survey of 100 patients seeking treatment, found a 43% family history of varicose or telangiectatic leg veins. Both surveys found that one third of the patients first noted the development of these veins during pregnancy. Among this subset of patients, veins became most severe after the third pregnancy.[17] Between 20% and 30% of patients developed these veins before pregnancy, and 18% of women noted the onset of the veins while taking oral contraceptives. Both authors concluded that the development of leg telangiectasia is probably a partially sex-linked, autosomal dominant condition with incomplete penetrance and variable expressivity.

PATHOPHYSIOLOGY

Multiple conditions—inherited, acquired and iatrogenic—are involved in telangiectasia formation.

GENETIC/CONGENITAL FACTORS

Numerous genetic or congenital conditions (listed in Box 4.1) display cutaneous telangiectasia. The pathogenesis of the development of telangiectasia in these syndromes is unknown. Genetic syndromes associated with leg telangiectasias include nevus flammeus [alone or as a component of Klippel–Trénaunay syndrome (KTS)], nevus araneus,

Box 4.1 Causes of Cutaneous Telangiectasia of the Lower Extremities

Genetic/congenital factors

Vascular nevi

- Nevus flammeus
- Klippel–Trénaunay syndrome
- Nevus araneus
- Angioma serpiginosum
- Bockenheimer syndrome

Congenital neuroangiopathies

- Maffucci syndrome
- Congenital poikiloderma (Rothmund–Thomson syndrome)
- Essential progressive telangiectasia
- Cutis marmorata telangiectatica
- Diffuse neonatal hemangiomatosis

Acquired disease with a secondary cutaneous component

Collagen vascular diseases

- Systemic lupus erythematosus
- Dermatomyositis
- Progressive systemic sclerosis
- Cryoglobulinemia

Other

- Telangiectasia macularis perstans (mastocytosis)
- Human immunodeficiency virus [human T-lymphotropic virus, type III (HTLV-III)]

Component of a primary cutaneous disease

Varicose veins
Keratosis lichenoides chronica

Other acquired/primary cutaneous diseases

- Necrobiosis lipoidica diabeticorum
- Capillaritis (purpura annularis telangiectodes)
- Malignant atrophic papulosis (Degos disease)

Hormonal factors

Pregnancy
Estrogen therapy
Topical corticosteroid preparations

Physical factors

Actinic neovascularization and/or vascular dilation

Trauma

- Contusion
- Surgical incision/laceration

Infection

- Generalized essential telangiectasia
- Progressive ascending telangiectasia
- Human immunodeficiency virus (HTLV-III)

Radiodermatitis
Erythema ab igne (heat/infrared radiation)

(Modified from Goldman MP, Bennett RG. J Am Acad Dermatol 1987;17:167.)

angioma serpiginosum, Bockenheimer syndrome (diffuse genuine phlebectasia), congenital neuroangiopathies (especially Maffucci syndrome), congenital poikiloderma, essential progressive or generalized telangiectasia, cutis marmorata telangiectatica and diffuse neonatal hemangiomatosis.

NEVUS FLAMMEUS

Nevi flammei (port-wine stains) affect 0.3–1% of the population,[19,20] with women being twice as likely to be affected as men.[21,22] Cases are usually sporadic, but a 10% familial incidence[21] and an autosomal dominant inheritance have been described.[23–26] Lesions occur in various shapes and sizes on any part of the body. They most commonly occur on the face but may cover large areas of the body, including an entire arm, leg or trunk (Fig. 4.4). Lesions often overlay the distribution of peripheral nerves. Nevi flammei are usually macular and vary in color depending upon the extent and depth of vascular involvement. Lesions become progressively nodular and darker with time and may ulcerate and bleed from minor trauma.

Histologic examination shows a collection of thin-walled capillary and cavernous vessels arranged loosely throughout the superficial and deep dermis (Fig. 4.5). These vessels represent dilations of postcapillary venules within the superficial dermis, with a mean depth of 0.46 mm.[27] In infancy, histopathologic changes of cutaneous vasculature are minimal. With advancing age, however, these lesions usually undergo progressive ectasia and erythrocyte stasis.[27] Although rare, cavernous hemangiomas arising from

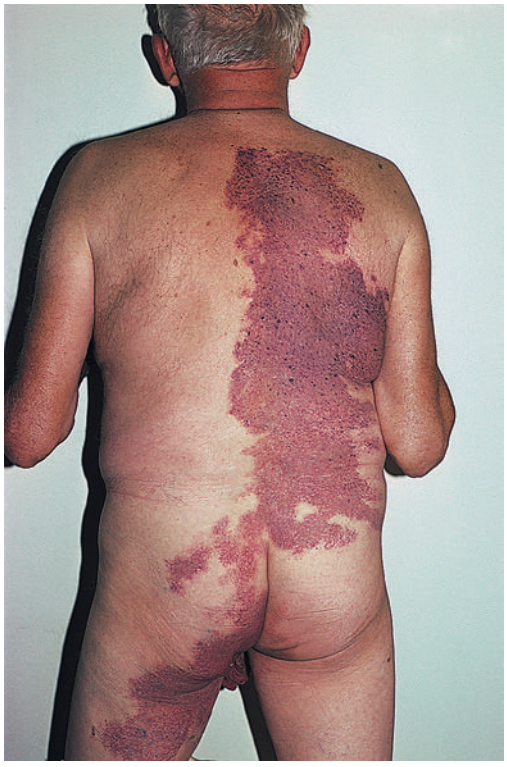

Figure 4.4 Nevus flammeus in a 68-year-old man without any associated soft tissue abnormalities. Note that the lesion extends down the posterior thigh.

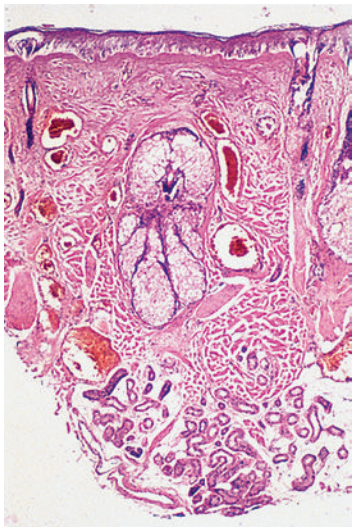

Figure 4.5 Histologic section of a nevus flammeus taken from the forehead of a 66-year-old man immediately after treatment with an argon laser. Note the location of the enlarged blood vessels within the middle and deep dermis. Because this lesion has just been treated, the overlying epidermis demonstrates thermal changes, and the vessels are thrombosed. (Hematoxylin and eosin stain; original magnification, ×80.) (Courtesy Richard Fitzpatrick, MD.)

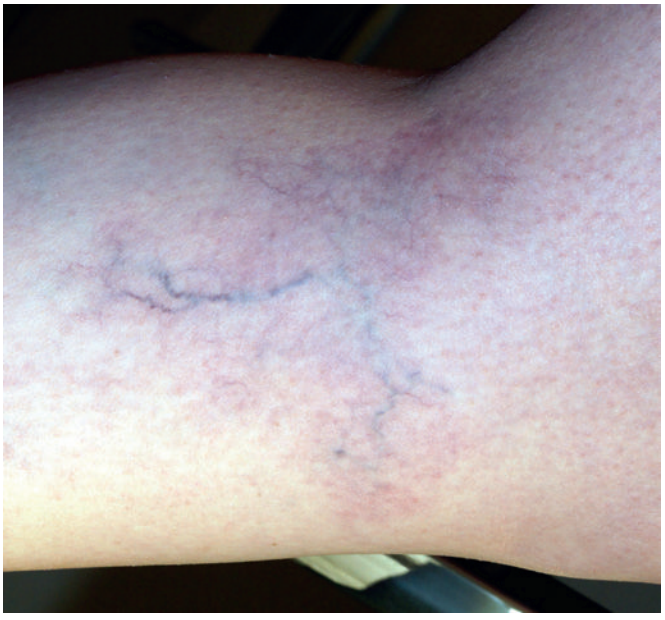

Figure 4.6 Example of a light colored angioma with typical hyperdilated telangiectasias. Sclerotherapy may improve this aspect dramatically, although the angioma could require an additional laser treatment after 2 months.

arteriovenous malformations may occur within the lesions.[28] There may also be evidence of other vascular malformations or neovascularization.[27] Further, some lesions on the legs may be associated with prominent telangiectasias and reticular varicose veins (Fig. 4.6).

A nevus flammeus can also be a component of a larger congenital vascular disease, with the most common that involves the leg being KTS.

KLIPPEL–TRÉAUNAY SYNDROME

In KTS (Fig. 4.7), the cutaneous vascular abnormality is associated with underlying varicose and telangiectatic veins with or without significant abnormalities of the deep and superficial system or arteriovenous anastomoses (AVAs). In addition, hypertrophy of soft tissue and bone may occur with overgrowth of the involved extremity (Figs 4.8 and 4.9).

The cause of KTS is unknown. Its prevalence in newborns is estimated to be 1:25,000.[29] There is no uniformly apparent hereditary factor.[30] One study of 14 affected patients suggests an autosomal dominant inheritance,[31] but some authors speculate that an atresia, agenesis or compression of the deep venous system by fibrotic tissue is the cause.[32] Other authors suggest that a congenital weakness of the venous wall, in combination with vascular hypertension from an abnormal venous system, leads to the development of KTS.[33] Baskerville et al[34] studied 49 patients with KTS and found that 68% had a superficial, embryologic venous channel on the lateral aspect of the thigh (Fig. 4.10). Histologic and venous flow studies suggest that, because these veins are usually present at birth and avalvular, KTS is caused by a mesodermal abnormality during fetal development that leads to persistence of arteriovenous communications, causing the triad of a nevus flammeus, soft tissue hypertrophy and varicosities.[35] This entire patient population had clinical varicose veins, and 88% had pain and limb swelling. Twenty-two percent had severe hemorrhage from varicose vein rupture, and 6% had a history of superficial thrombophlebitis. Baskerville et al[34] recommended surgical excision–avulsion of symptomatic superficial varices. Villavicencio,[36] building upon his experience with 14 patients, also recommended surgical excision followed by sclerotherapy to treat patients with intractable symptoms.

Servelle[37] presented his findings on 786 patients with KTS. He found venographic evidence for obstruction in most patients and postulated that changes seen in KTS are manifestations of this obstruction. In addition to cutaneous and soft tissue findings, Servelle noted a 36% incidence of varicose veins in his patient population. Concomitant malformations of the deep venous system (avalvulia, aneurysmata, aplasia, lateral marginal veins) have been found in up to 94% of patients.[38] Servelle recommended surgical intervention to the deep venous system and cautioned against treating superficial varicosities, owing to the potential for increased outflow obstruction.

When associated with KTS, cutaneous telangiectasias, venulectasias and varicose veins occur in the distribution of the underlying vascular malformation of soft tissue and bone. Some patients have a persistent embryologic lateral limb bud vein. The large drainage capacity of this vein may limit venous hypertension. In this instance, microcirculatory change, rather than large vessel change, may account for limb hypertrophy.[39] Thus, because KTS can be composed of a variable venous system, sclerotherapy treatment must be performed only after a thorough vascular evaluation.[40] Extensive pure venous malformations without other sequelae have also been reported and are distinct from KTS.[41] These lesions represent dilated venous tumors involving both skin and muscle. Coagulation studies are abnormal in 88% of patients.

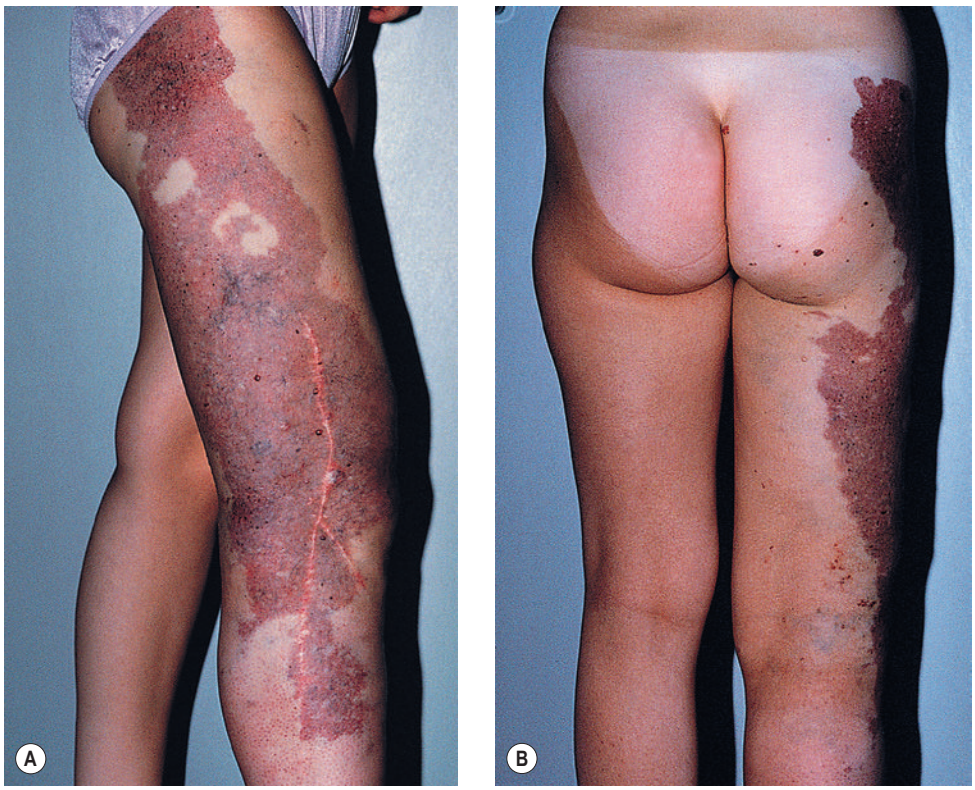

Figure 4.7 Adolescent female, 16 years old, with Klippel–Trénaunay syndrome and associated varicose veins and nevus flammeus of the right lower extremity from the toes to buttock.

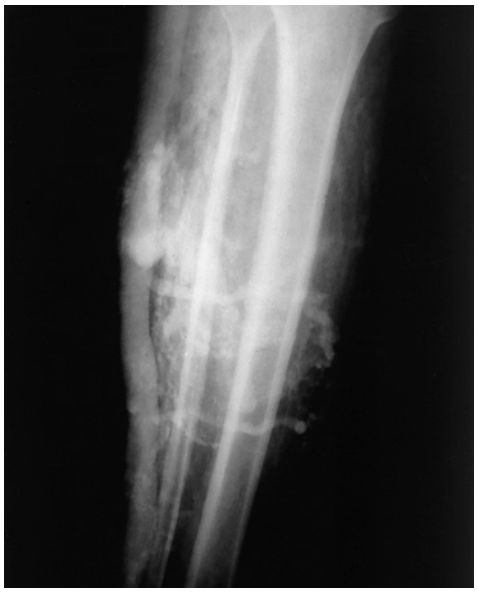

Figure 4.8 Venogram film of the right calf (anteroposterior projection) of the patient shown in Fig. 4.7. There are multiple dilated collateral dermal venules and a grossly enlarged lateral accessory saphenous vein along the posterolateral aspect of the calf, which is avalvular. The deep venous system is absent. (Courtesy Christopher Sebrechts, MD.)

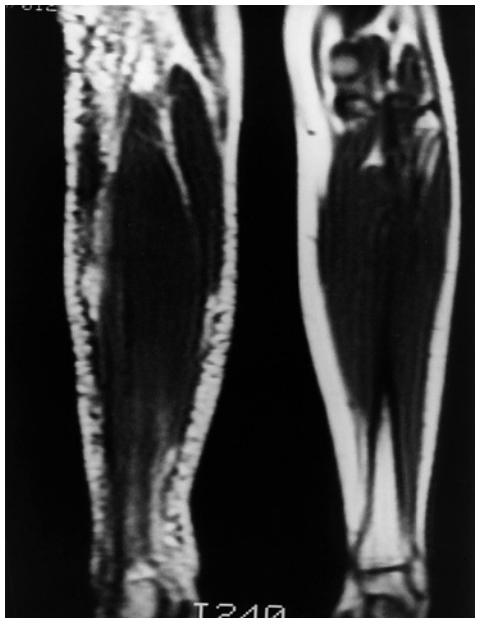

Figure 4.9 Coronal T1-weighted magnetic resonance image of the calves (repetition time 500, echo time 20) of the patient shown in Fig. 4.7. Multiple small collateral vessels in the subcutaneous fat of the right calf are shown as a spaghetti-like accumulation of dermal venulectases. Note the enlarged lateral accessory vein present along the posterolateral aspect of the right calf.

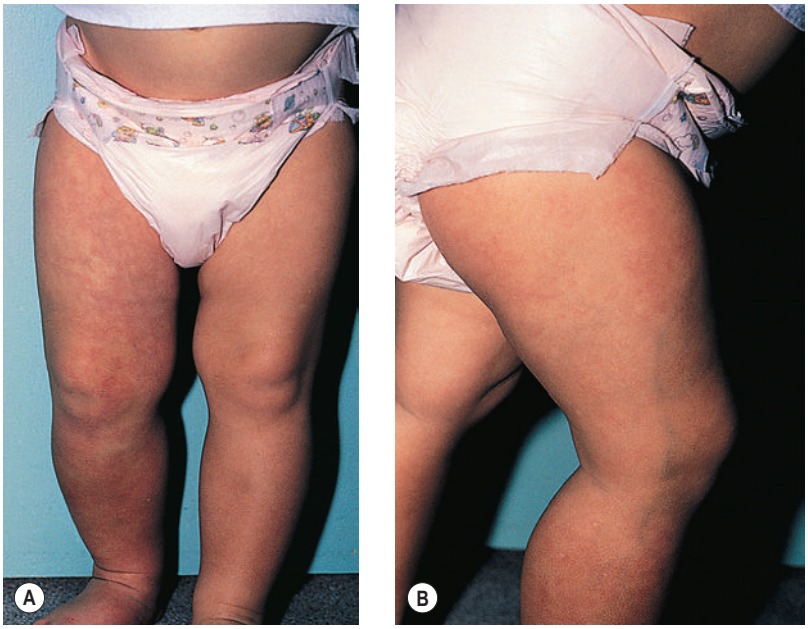

Figure 4.10 **A,** One-year-old girl with Klippel–Trénaunay syndrome on the right leg manifesting as a port-wine stain on the medial calf and thigh, elongation of the affected limb (note bent knee to compensate for the 1-cm increased length) and soft tissue hypertrophy noted as increased diameter of the affected limb. **B,** Lateral view demonstrating a prominent lateral varicosity 6 mm in diameter that was incompetent through its entire length with Valsalva-positive incompetence.

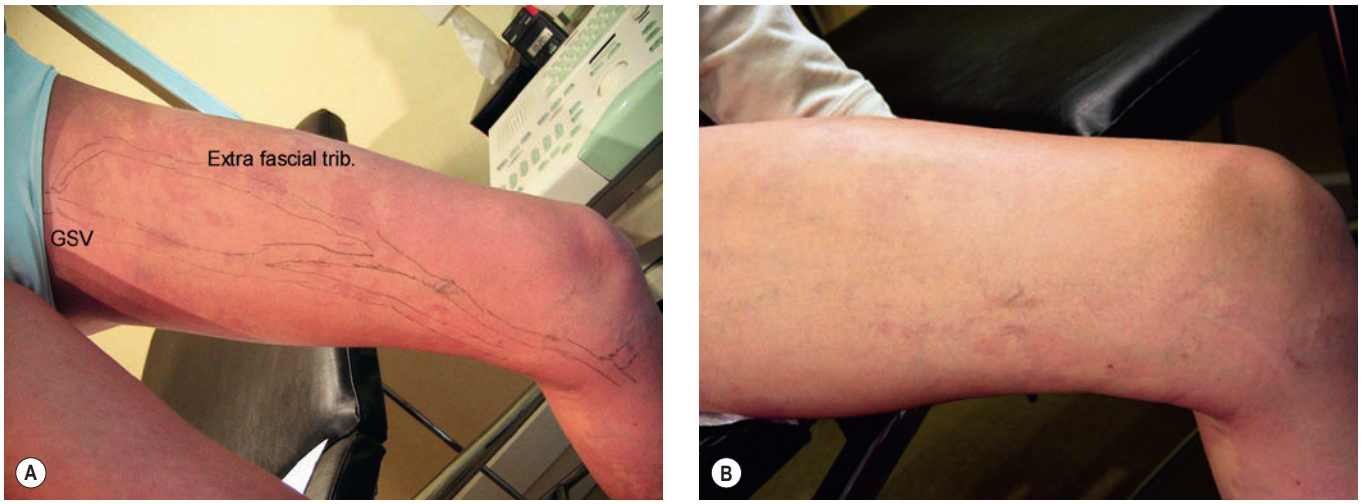

Figure 4.11 Case report. Telangiectasias, varices and livedo associated with a venous malformation of the left lower limb. In this 12-year-old girl, the saphenous system is hypertrophic and the deep system is hypotrophic. Both systems are competent, but blood flow is predominantly superficial. Both limbs have the same length and circumference. The limb is not symptomatic. The patient's complaint is mostly related to the existence of telangiectasia clusters. Three sessions of injection of 0.5% polidocanol foam in telangiectasias have improved the lesions enough to satisfy her. No treatment other than compression and microsclerotherapy is scheduled at present; evolution of superficial veins—for example, the possible appearance of reflux—will dictate the patient's management.

Most venous angiodysplasias demonstrate associated telangiectasias (Figs 4.11 and 4.12).

Proteus syndrome is a congenital hamartomatous condition that may have overlapping features with KTS.[42] In 1983, Wiedemann et al[43] described Proteus syndrome as consisting of partial gigantism of the hands or feet, hemihypertrophy, pigmented nevi, soft tissue tumors, macrocephaly and other hamartomatous changes. Patients with Proteus syndrome can also demonstrate prominent capillary hemangiomas, telangiectasia and varicosities.[44–47] Clinical findings are usually evident at or shortly after birth. This condition may represent a somatic mutation that influences the local regulation or production of tissue growth factors.[48]

Sclerotherapy to nontruncal varicose and telangiectatic veins can restore some degree of venous competency and relieve symptoms. In addition to experiencing a heavy, tired feeling of the affected limb, patients may have recurrent bleeding from cutaneous vascular blebs. These vessels are easily traumatized, with trauma occasionally leading to cutaneous and soft tissue infections. Sclerosing these vessels is helpful and has been practiced for more than 60 years.[49]

A complete discussion of the surgical management of KTS or the vascular component of Proteus syndrome is beyond the scope of this text. But, in short, if an incompetent feeding varicose vein is found alone with an intact deep

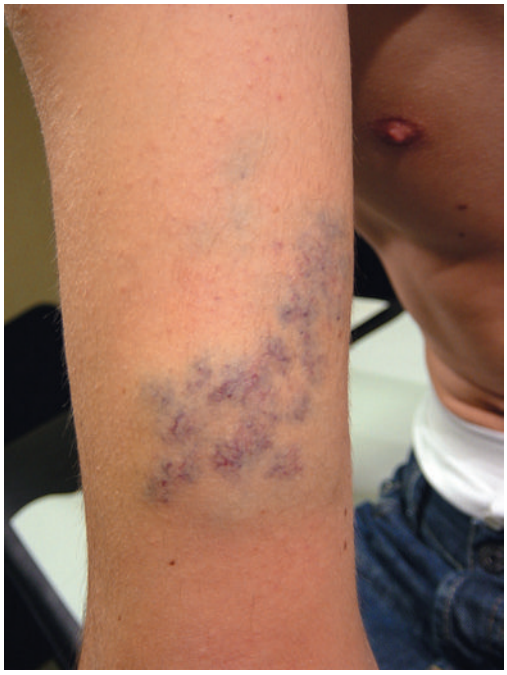

Figure 4.12 Telangiectasias associated with venous dysplasia of the upper limb in an 18-year-old man.

venous system, the former can be avulsed safely. This procedure is often combined with sclerotherapy to distal varices. Foam sclerotherapy can be an important treatment modality, although dozens of treatment sessions may be required to minimize the volume of injected foam. Care must be taken to ensure adequate venous return from the remaining vessels. Treating perforating veins is usually quite difficult because there may be hundreds of connections between the superficial and deep venous systems.[40]

Laser coagulation or photocoagulation is reserved for cutaneous ectasia, which usually occurs within the nevus flammeus. These manifestations are treated not for cosmetic reasons but to prevent bleeding and infection (Fig. 4.13) (see Chapter 13).

NEVUS ARANEUS

Nevi aranei (spider telangiectasias) may occur as a component of a number of congenital and acquired diseases. They are found in up to 15% of the normal population and increase in number during pregnancy, liver disease and multiple other conditions.[50] Ninety-nine percent of nevi aranei occur superior to the umbilicus.[50,51]

Lesions appear as bright red macules composed of a central red dot, with fine blood vessels radiating from the center (Fig. 4.14). The central vessel may pulsate, indicating

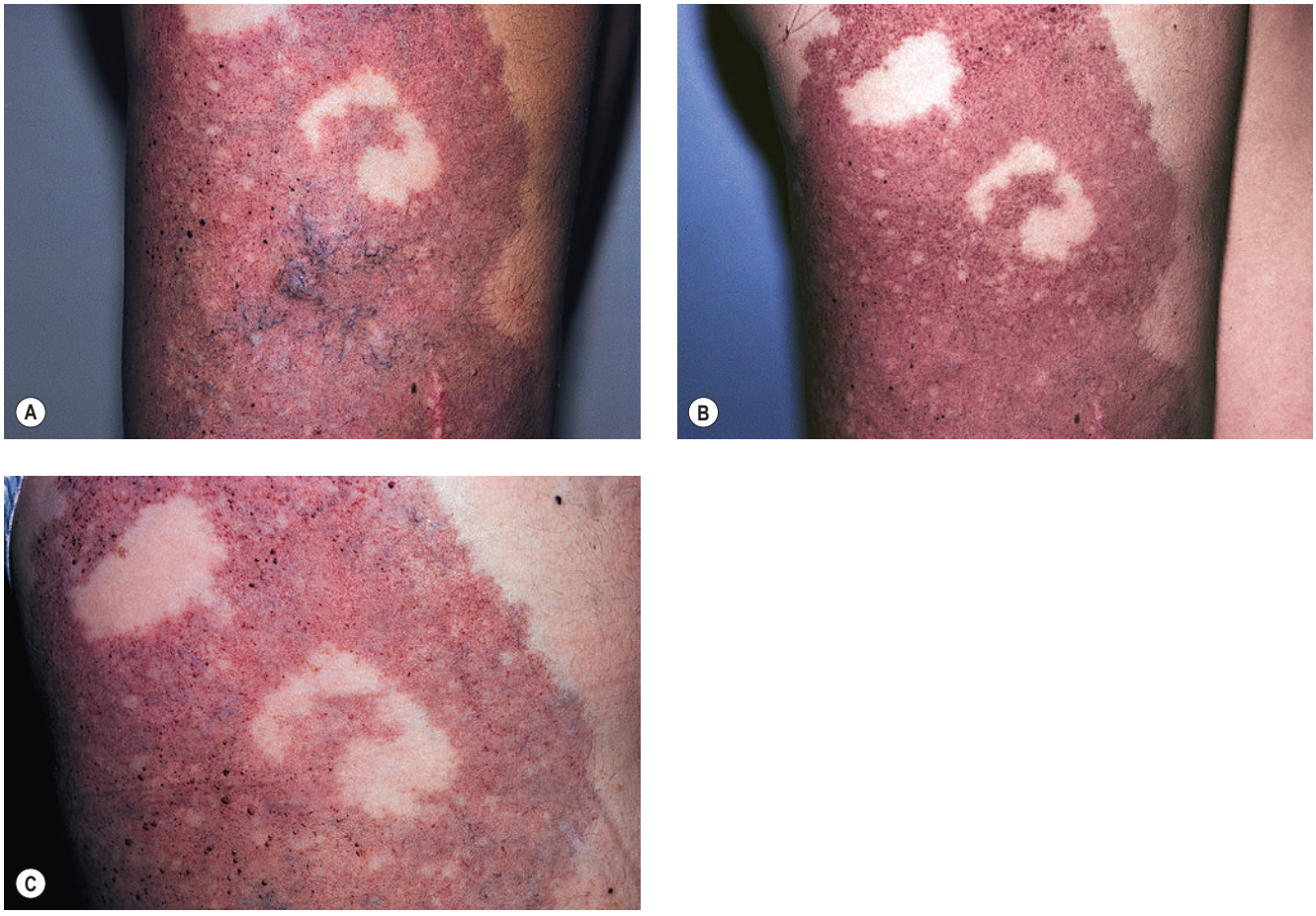

Figure 4.13 Before **(A)** and after **(B)** treatment of a section of the nevus flammeus and associated superficial varicosity of the patient shown in Fig. 4.6. The reticular veins were treated with polidocanol 0.75% (6 mL total) followed by multiple impacts with an SPTL-I pulsed-dye laser (Candela, Wayland, MA) at 8 J/cm^2. **C,** Clinical appearance 5 years after last sclerotherapy/laser treatment. Note the recurrence of venules and vascular ectasia.

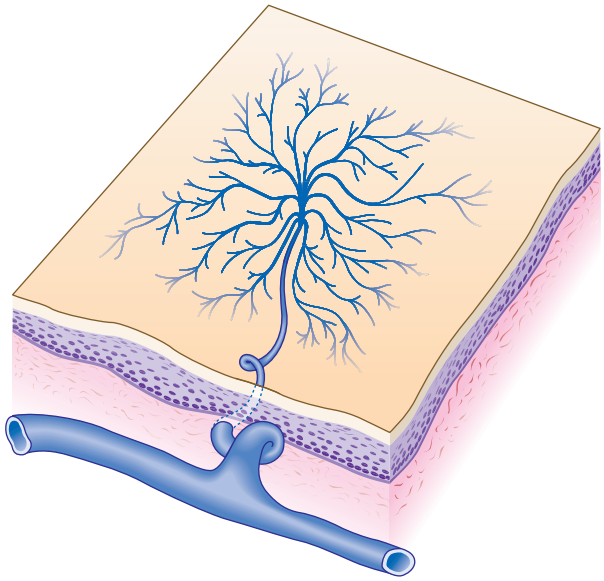

Figure 4.14 Schematic diagram of a nevus araneus (arteriolar spider) showing the origin at a dermal arteriole with coiled extension to the superficial dermis and branching horizontal 'arms'.

its arteriolar origin. Point compression of the central dot blanches the radiating vessels. One genetic disease with this form of telangiectasia is ataxia telangiectasia, which may have lesions distributed within the popliteal fossae.[52,53]

Vascular spiders arise from the terminal arteriole (see Fig. 4.14).[4] Within the spider telangiectasia, blood pressure is lower than systolic pressure but higher than venous pressure. One measurement demonstrated its pressure to be 85 mmHg when systolic pressure was 120 mmHg.[54] The vessels arise within the deep dermis and push their way up into the superficial dermis as a space-occupying lesion. The central arteriole connects to dilated venous saccules with radiating venous legs in the papillary dermis.[50] Detailed histologic studies have provided little understanding of the factors responsible for the initial growth of nevi aranei.[55]

Because spider telangiectasias are composed of a central arteriole, sclerotherapy as treatment usually produces ulcerations (see Chapter 8). Therefore, recommended treatment involves fibrosing the central feeding arteriole via the pulsed-dye laser (PDL) at 585 nm or 595 nm, continuous wave lasers at 511 nm to 577 nm, intense pulsed light (IPL) or electrodesiccation (see Chapter 12).

ANGIOMA SERPIGINOSUM

Angioma serpiginosum is a rare nevoid disorder of the upper dermal vasculature. The disease usually occurs on the lower extremities in women and has its onset in childhood. Although most cases are sporadic, one family study suggests an autosomal dominant inheritance.[56] Lesions appear as small erythematous puncta, which occur in groups. The lesions enlarge as new puncta form at the periphery, while those in the center fade. This results in a reticular or serpiginous pattern and has been reported in a mosaic pattern.[57] A dilation of the subpapillary venous plexus may lead to telangiectasias. Histologic examination shows a number of ectatic capillaries in the superficial dermis. Endothelial cells are vacuolated, appear hyperplastic and have an increased number of interendothelial junctions. Capillary walls are thickened with prominent basal laminae and a 'heavy' precipitation of fine fibrillar material. The deeper dermis is unremarkable.[58] Therefore, angioma serpiginosum may represent a type of capillary nevus. Rho et al[59] reported a nearly complete resolution of an angioma serpiginosum case with the 532-nm potassium titanyl phosphate (KTP) laser after two treatment sessions.

BOCKENHEIMER SYNDROME (DIFFUSE GENUINE PHLEBECTASIA)

Diffuse genuine phlebectasia was first described by Bockenheimer[60] in 1907. One review has documented 40 cases in the literature.[61] This rare syndrome represents a deep venous malformation that is rarely present at birth, usually first manifesting in childhood. Multiple large venous sinusoids or cavernous hemangiomas develop, usually on an extremity. These frequently thrombose, hemorrhage and ulcerate and may ultimately progress to a gangrenous infection. Unilateral localization is common. Secondary cutaneous telangiectasia develops in response to venous hypertension. Late manifestations are soft tissue and/or bone hypotrophy or hypertrophy.

Compression therapy is generally beneficial to prevent manifestations of both venous hypertension as well as thromboses. Surgical excision and phlebectomy have produced varying results, generally with recurrence.[62,63] Sclerotherapy has been successful in one of two cases.[64,65]

MAFFUCCI SYNDROME

Maffucci syndrome is a congenital, nonfamilial dysplasia consisting of vascular malformation and dyschondroplasia. Patients have single or multiple hemangiomas, varicosities and telangiectasias of the legs. Dyschondroplasia and enchondromas occur as bony nodules on the fingers, toes and extremities. Patients have unequal bone growth and slow union of easily sustained fractures. The distribution of vascular lesions often does not correspond to that of the skeletal lesions. In addition to hemangiomas, lymphangiomas and lymphectasias may be present.

The syndrome affects all races, affects men and women equally, and has no evidence of a familial tendency.[66] Twenty-five percent of patients have symptoms manifest within the first year of life; 78% manifest symptoms before puberty.[66] From 25% to 30% of patients develop malignancies, including chondrosarcoma, angiosarcoma, lymphangiosarcoma, glioma, fibrosarcoma, pancreatic carcinoma and ovarian teratomas.[66–69] Surgical excision or sclerotherapy to treat symptomatic vascular lesions is helpful.[36]

CONGENITAL POIKILODERMA

Congenital poikiloderma (Rothmund–Thomson syndrome) is a rare neurocutaneous syndrome that has its onset in the first year of life. There appears to be a female predominance. Although an autosomal dominant inheritance pattern has been demonstrated, 70% of cases show a familial recessive inheritance.[70] A fine telangiectatic network first appears on the cheeks and progresses within 1 year to involve the head, arms, buttocks and legs. There may be associated scaling of the skin and lichenoid papules. Affected patients often have sparse hair as well as soft and translucent skin. Dwarfism, cataracts, dental abnormalities, mental

retardation, hypogenitalism, diabetes mellitus and osteosarcoma may also occur.[70,71]

ESSENTIAL PROGRESSIVE TELANGIECTASIA

Essential progressive telangiectasia (EPT) is a rare entity that has been reported in association with bronchogenic carcinoma,[72] angiokeratomas,[73] chronic sinusitis[10] and autoimmune disorders.[74] However, EPT is most commonly an isolated entity. EPT has been reported to be associated with small varicose veins that occur many years after disease onset.[75]

Histochemical examination establishes the vessels in EPT to be venular in origin.[76] Lesions appear as blue to bright red telangiectasias 0.1–0.4 mm in diameter. There may be associated peritelangiectatic atrophy of the subcutaneous tissue. Lesions most commonly appear on the feet and distal leg but rarely involve the entire leg.

The treatment of these lesions is often fraught with complications because many of the telangiectasias are intimately associated with arterioles. This leads to frequent recurrence of lesions after treatment. However, cautious treatment with sclerotherapy, PDL, or, best, IPL is usually successful (see Chapter 13).[75,77]

CUTIS MARMORATA TELANGIECTATICA CONGENITA

Cutis marmorata telangiectatica congenita is a rare congenital cutaneous vascular anomaly consisting of a sharply demarcated, reticulated vascular network of blue–violet venules associated with telangiectasias, with or without varicose veins. There have been about 300 cases reported to date in the world literature. The typical clinical findings consist of persistent cutis marmorata, telangiectasia, phlebectasia, occasional ulceration and atrophy, and an associated nevus flammeus may be present. The cutis marmorata component is neither transient nor related to temperature. Telangiectasias may not appear in the first 2 years of life.[78–80] Lesions are most prominent on the lower extremities but may involve any cutaneous surface. Involvement may be unilateral or bilateral. Atrophy and ulcerations of the overlying skin may occur over time.[81] Lesions have been reported to improve spontaneously in up to three fourths of patients within the first 2 years of life.[80]

Most cases of cutis marmorata telangiectatica congenita occur sporadically, and two thirds of the approximately 300 reported cases occurred in women.[78–80,82] The pathogenesis is most likely multifactorial; genetic (autosomal dominant inheritance)[83,84] and teratogenic factors are most commonly cited.

Histologic examination demonstrates an abnormal dilation of capillaries and veins.[85,86] Associated congenital abnormalities have been reported in up to 50% of patients; these include structural defects of the musculoskeletal system, ocular and dental malformations and also arteriovenous malformations.[87] Nevus telangiectaticus and hypertrophy or atrophy of the affected limbs are also reported.[88]

DIFFUSE NEONATAL HEMANGIOMATOSIS

Diffuse neonatal hemangiomatosis (DNH) is a rare congenital vascular disorder, presenting in infancy with multiple cutaneous and/or visceral hemangiomas. Multifocal lymphangioendotheliomatosis with thrombocytopenia is a newly described disorder with a much higher mortality rate than infantile hemangiomas. A proposal to split diffuse neonatal hemangiomatosis into multifocal infantile hemangioma with or without extracutaneous disease has been proposed to prevent confusion of these conditions and their different risk profiles.[89] The combination of hepatic and cutaneous hemangiomas occurs twice as often in girls as in boys.[90] Hemangiomas are usually present on the skin and may be associated with large areas of telangiectasias and venulectasias (Fig. 4.15).

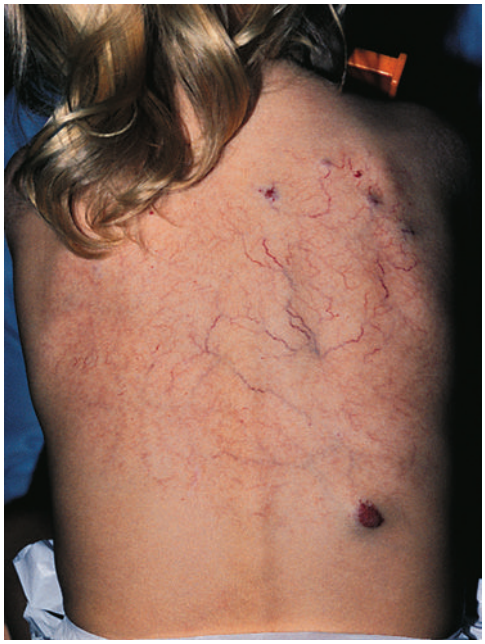

Figure 4.15 Diffuse neonatal hemangiomatosis on the back of a 2½ -year-old girl. The telangiectatic component was present at birth. Within the first few months, cutaneous hemangiomas began to appear. A large mediastinal hemangioma was also noted surrounding the esophagus. Systemic treatment with corticosteroids did not result in any notable decrease in the size of the internal or cutaneous hemangiomas. The patient was still well at age 13 years.

Infants with multifocal infantile hemangiomas with extracutaneous disease may die as a result of high-output cardiac failure resulting from arteriovenous shunting of blood flow through the hemangiomas. Recognition of the cutaneous component, which may be minimal in some infants, will help to prevent confusion of high-output cardiac failure with a congenital heart disease.[91] Earlier treatments consisted of systemic steroids, selective embolization or surgical excision.[66] However, oral propranolol has emerged as the new treatment of choice, offering a low side effect profile with excellent cosmetic results.[92–95] Selective sclerotherapy of the telangiectasias may be performed for cosmesis.

ACQUIRED DISEASE WITH A SECONDARY CUTANEOUS COMPONENT

Telangiectasias that occur as a component of an acquired or primary cutaneous disease evolve from multiple factors. When associated with collagen vascular diseases, relative tissue anoxia may cause the appearance of telangiectasias, especially in acral areas. Alternatively, circulating cryoglobulins may also lead to acral telangiectasias. Periungual

telangiectasias are particularly common in systemic lupus erythematosus and progressive systemic sclerosis. In addition, various vasculitic factors or other immunologic factors associated with these diseases may lead to the appearance of telangiectasias, particularly in areas where other physical factors (such as actinic damage) are prominent.

In some conditions (e.g., mastocytosis), a component of the disease itself, such as the release of mast cell vasoactive factors including histamine or heparin, may lead to the development of telangiectasias.[96,97] Histologic studies in a patient with unilateral facial telangiectasia macularis eruptiva perstans demonstrated an accumulation of mast cells.[98]

COMPONENT OF A PRIMARY CUTANEOUS DISEASE

VARICOSE VEINS

Varicose veins lead to the development of telangiectasias, most likely through associated venous hypertension with resulting angiogenesis, vascular dilation[50] or an increased distensibility of the telangiectatic vein wall (see Chapter 3). Although telangiectasias associated with varicose veins may first appear as erythematous streaks, they turn blue with time. Blue telangiectasias have an average oxygen concentration of 68.7%, versus 75.86% for red telangiectasias.[99] Thus, the decrease in oxygen content of blue telangiectasias probably represents their association with the venous portion of the capillary loop. The relatively low oxygen concentration of red telangiectasia is possibly related to the backflow of venous blood into the capillary loop. Often telangiectasias are directly associated with underlying varicose veins, so the distinction between telangiectasias and varicose veins becomes blurred.[50]

Bihari et al[100] demonstrated that some leg telangiectasias have a high flow consistent with AVAs. They found a high flow in 5 of 22 limbs studied with Doppler flow analysis. They speculate that telangiectasias associated with AVAs account for the fast refilling of the former, as well as for their bright red color, the arterial pulsation seen in some, and the occurrence of ulceration with injection of dilute solutions (see Chapter 9).

Corona phlebectatica (Fig. 4.16) is defined as a fan-shaped intradermal telangiectasia on the medial or lateral aspect of the foot.[101] An evaluation of 411 limbs with great saphenous vein (GSV) incompetence demonstrated corona phlebectasia in 204 patients (49.6%).[102] The frequency of corona phlebectasia was significantly greater in limbs with skin changes such as pigmentation and dermatitis than in limbs with normal skin (77.2% versus 40.6%). Blue telangiectasias were also more frequently observed in limbs with skin changes. Therefore, the degree of venous hypertension is directly related to the development of both the telangiectasias comprising the corona phlebectasia as well as their blue appearance. Researchers in one epidemiologic study evaluated 3072 members of a general population to determine whether corona phlebectatica could be used as a marker to predict more severe stages of chronic venous disease (CVD).[103] Those with corona phlebectatica were classified as having either 'mild' involvement (up to one half of the foot edge involved) or 'severe' (entire foot edge involved). Approximately 50% of the population with C1–C6 stages of disease [clinical, etiology, anatomy and pathophysiology (CEAP) classification; see Chapter 2] demonstrated mild corona. However, severe corona was associated with more advanced stages of CVD (C4 and C5). Thus, the authors conclude that although mild corona phlebectatica is not a good marker to differentiate between different stages of CVD, severe corona does frequently signify more advanced stages of CVD.

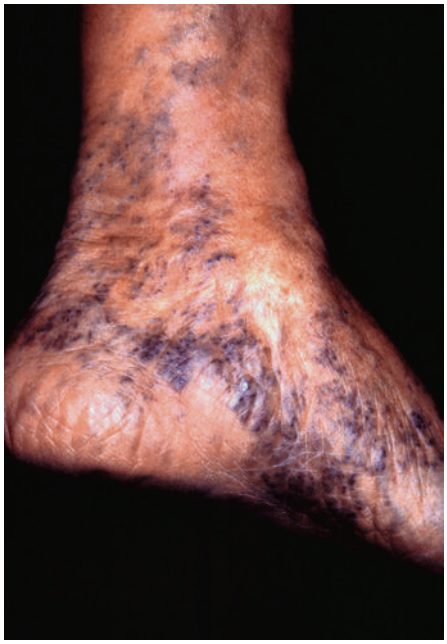

Figure 4.16 Severe corona phlebectatica around the scar of a healed ulcer. Medial malleolus of a 70-year-old woman with chronic venous insufficiency and postthrombotic syndrome (C5s Es Asdp Pr). See Table 5.1 for further information on the clinical, etiology, anatomy and pathophysiology (CEAP) classification for chronic venous disease.

Corona phlebectatica has been categorized into four components: venous cups (veins), blue telangiectasias (intradermal venules), red telangiectasias (superficial venules) and stasis spots (capillaries). In a study of 262 patients with CVD, investigators found stasis spots and blue telangiectasias to have a linear association with CEAP severity. Stasis spots had the highest specificity, and blue telangiectasias were more sensitive for predicting the CEAP severity level. The relationship of red telangiectasias and venous cups was not shown to have a clear association with CEAP severity.[104]

Telangiectasias have been shown by multiple investigators who used various techniques to be associated with underlying reticular veins. Tretbar[105] studied 100 patients with telangiectasias (0.1 mm in diameter) with venous Doppler and found that the telangiectasias were connected with associated 'feeding' reticular veins. These veins were separate from any truncal varicosities that may have been present. All blue reticular veins demonstrated reflux that did not appear to originate from the GSV or small saphenous veins (SSV). In patients with blue reticular veins, 50% demonstrated reflux from incompetent calf perforating veins. Weiss and Weiss[106] confirmed these findings with Doppler examination of 700 patients. They noted audible reflux in 88% of patients

whose telangiectasias were associated with a 'feeding' reticular vein. In addition, they confirmed that enhanced therapeutic efficacy with decreased postsclerotherapy hyperpigmentation occurred when the reticular veins were treated before distal telangiectasias were treated.[107] Duplex scanning has also demonstrated telangiectasias to be associated with 'feeding' reticular veins.[108,109] Somjen et al[109] found that 89% of telangiectasias had closely situated incompetent reticular veins. Furthermore, Raymond-Martimbeau and Dupuis[3] found that 71.2% of telangiectasias had direct connections to reticular veins. Finally, direct radiographic imaging and duplex examination have shown connections between telangiectasia and both the deep and superficial venous systems.[3,110] Importantly, 2 of 15 telangiectasias examined were found to connect directly to the deep venous system without any obvious cutaneous sign. Mariani et al[111] evaluated 200 telangiectatic areas with a 10-MHz probe duplex ultrasound and transillumination. They found that 100% of telangiectasias in 106 female patients were connected to reticular veins (1–3 mm in diameter). In 73.5% of the telangiectatic areas, one or more incompetent perforator veins were present.

Only one author has reported a lack of importance of reticular veins with telangiectasias.[112] In this singular 'treatise', successful eradication of telangiectasias was not dependent upon simultaneous eradication of reticular veins. However, the author failed to recognize that placing a Doppler probe over a vessel such as a reticular vein will extinguish the sound of reflux. Even 'light' pressure on a Doppler probe can generate hundreds of pounds per square inch and accounts for the fact that even the largest axial veins can be closed with light finger pressure.

The relationship between telangiectasias and reticular veins emphasizes the importance of postsclerotherapy compression when treating telangiectasias (see Chapter 8). It is clear that treatment of the feeding varicosity results in treatment of the distal telangiectasia (see Chapters 9 and 12). Perhaps a more appropriate term instead of *feeding veins* would be *back pressure recipient veins*. When no apparent connection exists between a telangiectasia and deep collecting or reticular vessels, the telangiectasia may arise from a terminal arteriole or arteriovenous anastomosis.[1]

Telangiectasias may be associated with underlying venous disease even when there are no other clinical abnormalities. Thibault et al[113] evaluated 83 patients with spider leg veins using duplex and Doppler examinations. They found that 23% of these patients without clinically apparent varicose veins had incompetence of the superficial venous system. In addition, 1.2% had incompetence of a perforator vein. Nineteen patients, each with one clinically abnormal leg and one clinically normal leg, were also evaluated. Interestingly, 37% of clinically normal legs demonstrated incompetence of the superficial system. The abnormal legs in this group had a 74% incidence of incompetence of the superficial system, and 21% had saphenofemoral incompetence. This study demonstrates the need for both a clinical and noninvasive diagnostic workup in patients who have spider veins and reinforces the view that spider veins arise from underlying varicose veins through venous hypertension.

Engelhorn et al[114] similarly advocated ultrasound mapping of the GSV in women with telangiectasias, even in asymptomatic patients. This study evaluated 269 limbs of women with telangiectasias (CEAP class C1); exclusion criteria included the presence of concomitant varicosities, overlying skin abnormalities including ulcerations, and limb edema. Venous reflux was present in 46% of the 269 extremities, with 44% of patients having reflux of the GSV. Seven percent of the extremities had reflux of the SSV, 5% had reflux of both the GSV and SSV, and only 2% had reflux isolated solely to the SSV. Seventy-eight percent of these telangiectatic limbs were symptomatic. Interestingly, reflux prevalence was similar in symptomatic (47%) and asymptomatic (44%) extremities. Because treatment of telangiectasias with sclerotherapy is rarely effective if one fails to also detect and treat any underlying incompetent superficial veins, the authors advocate pretreatment saphenous vein ultrasound mapping, even in asymptomatic patients.

A proposed mechanism for the development of leg telangiectasia associated with underlying venous disease is that preexisting vascular anastomotic channels open in response to venous stasis.[115] Venous stasis with resulting venous hypertension leads to a reversal of flow from venules back to capillaries. The resulting capillary hypertension leads to opening and dilation of normally closed vessels. Consequently, relative anoxia as a result of reversed venous flow leads to angiogenesis. Merlen[1] stated that capillaries and venules have an enhanced neogenic potential and a remarkable tendency toward neogenesis in a hypoxic atmosphere.

In addition, Braverman[116] distinguished between the arterial and venous sides of the microcirculation on the basis of ultrastructural characteristics of the vascular basement membrane, which appears homogeneous in arterial vessels and multilaminated in venous vessels. With this finding, he demonstrated changes from arterial to venous vessels in various cutaneous disorders, such as psoriasis, within 48 to 72 hours. It is postulated that this change occurs as a result of changes in circulation pressure. Thus, the development of venulectasias and telangiectasias in venous hypertension may represent the conversion of preexisting capillaries into venules.

KERATOSIS LICHENOIDES CHRONICA

Prominent telangiectasias on the feet and legs have been described in patients with keratosis lichenoides chronica,[117] a condition not usually associated with telangiectasias.[118] Severe pruritus was also present in these patients, and, although the authors ascribed the development of the telangiectasias and lichenoid papules to the same process, it appears to be equally likely that both physical manifestations could be caused by chronic rubbing and scratching. Thus, it is difficult to separate the development of telangiectasias into primary versus secondary processes in this disease.

OTHER ACQUIRED PRIMARY CUTANEOUS DISEASES

As with telangiectasias of acquired cutaneous disease, telangiectasias of primary cutaneous disease rarely affect the legs, with the obvious exception of varicose veins. Other cutaneous diseases associated with telangiectasias are necrobiosis lipoidica diabeticorum, capillaritis (purpura annularis telangiectodes; Majocchi disease) and malignant atrophic papulosis (Degos disease).

Progressive pigmented purpuric dermatitis (Schamberg disease), pigmented purpuric lichenoid dermatitis (Gougerot–Blum capillaritis), lichen aureus and purpura annularis telangiectodes (Majocchi disease) share the common pathogenic denominator of dilation of the superficial papillary dermal capillaries with occasional endothelial proliferation. These conditions are manifested by punctate purpuric lesions and telangiectasias, predominately on the lower legs. Most patients do not have manifestations of venous hypertension. Capillary microscopy in 12 patients with pigmented purpura disclosed ectatic dilated venules in the subpapillary plexus.[119] Iwatsuki et al[120] found fibrinoid degeneration and occlusive damage with swollen endothelia in three of eight patients with this condition. Upon direct immunofluorescence examination, each of the eight patients had evidence of C3, C1q and fibrin within papillary vessels. These findings suggest an immunologic etiology.

Treatment of telangiectasias caused by an acquired or primary cutaneous disease is usually best accomplished by treatment of the acquired disease itself. The telangiectatic component of these lesions is usually asymptomatic and requires no treatment except for cosmesis. In that case, electrodesiccation or the tunable continuous dye laser, PDL or IPL may be the treatment of choice (see Chapter 13).

HORMONAL FACTORS

PREGNANCY AND ESTROGEN THERAPY

The hormonal influence on the development of telangiectasias is well known, but a survey of 61 phlebologists by the International Union of Phlebology demonstrated many different opinions regarding the role of hormones and telangiectasia.[121] Seventy-two percent of responders thought that hormones have a causal or worsening effect on telangiectasia, and 38% thought that hormones may have an effect on sclerotherapy treatment; however, only 25% recommended that patients stop hormone therapy before treatment.

Pregnancy is perhaps the most common physiologic condition that leads to the development of telangiectasias. Corbett[54] first suggested this in 1914. Bean[50] has estimated that almost 70% of women develop telangiectasias during pregnancy, the majority of which disappear between 3 and 6 weeks postpartum (Fig. 4.17). Pregnant women often develop telangiectasias in the legs within a few weeks of conception, even before the uterus has enlarged to compress venous return to the pelvis.[122,123] Also, pregnant women and those taking birth control pills have been shown to have an increase in the distensibility of vein walls.[124] This increase in distensibility has also been noted to fluctuate with the normal menstrual cycle.[125] It was found that leg volume was greatest just before ovulation and during menses. The increased distensibility did not fully correlate with one specific hormone but was related to both estrogen and progesterone levels or ratios.

Hormonal stimulation may lead to the development of telangiectasias independently of the effect on venous distensibility. Paradoxically, estrogen has been found to be beneficial in controlling symptoms of venous distensibility during pregnancy (see Chapter 3).[126] Thus, some hormonal influence is involved in the development of varicose veins and their associated telangiectasias in women (see Chapter 3),

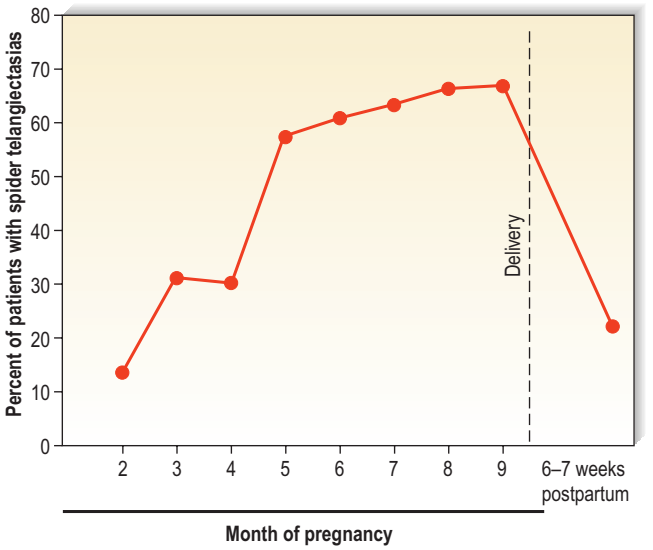

Figure 4.17 Incidence of spider telangiectasias in white pregnant women as a function of the duration of pregnancy. (From Bean WB. Vascular spiders and related lesions of the skin. Springfield, IL: Charles C Thomas; 1958.)

but the exact hormonal mechanism for telangiectasia development is unknown.

Davis and Duffy[127] reported an apparent association of estrogen excess states with the development of telangiectatic matting after sclerotherapy of spider leg veins. In their selected patient population of 160, 29% of women who developed 'new' telangiectasias were taking systemic estrogens or became pregnant, compared with 19% of patients on hormones who did not develop telangiectatic matting. One additional patient noted the disappearance of both spider veins and telangiectatic matting after taking the antiestrogen tamoxifen citrate (Nolvadex; AstraZeneca, Wilmington, DE). Biopsies of these patients were not performed.

Estrogen acts by entering its target cell and associating with an extranuclear receptor protein. This complex then enters the nucleus and modulates RNA synthesis.[128] Because endothelial cells have been found to possess estrogen receptors, they may be potential target cells.[129] Sadick and Neidt[130] assayed 20 patients with leg telangiectasias for estrogen receptors. Interestingly, they failed to find any evidence of such receptors in their patient population. Sadick and Urmacher[131] also assayed patients with telangiectatic matting for estrogen receptors and again found no evidence of their presence. They postulated that estrogen receptors are not present in increased numbers in leg telangiectasias. The measurement technique was not sensitive enough to ascertain their presence or that estrogen acts on endothelium through an indirect pathway. This pathway may be a stimulation of angiogenic factors (see Chapters 3 and 8) or an increase in vascular distensibility.

The hormonal influence on telangiectasia neogenesis has been noted in 17 of 46 reported cases of unilateral nevoid telangiectasia syndrome.[132,133] Another study noted this in 10 of 15 reported cases. In these female patients, the telangiectasias did not occur until triggered by pregnancy or puberty and correlated with high serum estrogen levels. Of

the remaining five cases, four were associated with alcoholic cirrhosis and one was congenital. There was no association with the development of varicose veins. Progesterone receptors have also been reported in two patients with unilateral nevoid telangiectasia in one of the patients' receptors developed following metastases from a carcinoid tumor of the stomach.[134,135]

MALIGNANCY

Although exceptionally rare, cutaneous patches of telangiectasias can represent metastases of an underlying malignancy.[136–138] When this phenomenon does occur, the most common associated malignancy is breast cancer. However, there have also been at least two reported cases of cutaneous metastases from prostate carcinoma presenting as telangiectatic patches.[139,140] Reddy et al[139] reported a man who presented with an asymptomatic nontender, nonblanching telangiectatic patch on his chest. The patch had been enlarging since its onset 3 months previously. A biopsy from the patch showed ectatic papillary dermal blood vessels within which were aggregates of prostate-specific antigen–positive adenocarcinoma cells. Similar histologic findings were seen in lesional tissue from the other reported case of telangiectatic cutaneous metastases of prostate cancer.[140] Interestingly, the former patient had been diagnosed with prostate cancer 12 years before the appearance of the telangiectatic patch; he subsequently died as a result of metastatic prostate cancer 6 months after presenting with the telangiectasias. The authors speculate that the telangiectatic cutaneous metastases resulted from hematogenous dissemination of the neoplastic cells; the intravascular prostate-specific antigen–positive tumor cells found within the lesional skin biopsy support this theory. Regardless of the mechanism, cutaneous metastases of an underlying systemic malignancy usually herald advanced disease and a grave prognosis.

TOPICAL CORTICOSTEROID PREPARATIONS

A common form of iatrogenic telangiectasias may occur from the use of high-potency topical steroid preparations. Leyden[141] first reported the development of rosacea associated with telangiectasias in 10 patients who regularly used topical fluorinated steroids on the face. Katz and Prawer[142] demonstrated clinical cutaneous vascular dilation and network development within 2 weeks of treatment with superpotent topical steroids (betamethasone dipropionate in an optimized vehicle and clobetasol ointment). This type of steroid-induced telangiectasia probably reflects the loss of perivascular ground substance, allowing distention of existing vessels, or the capillary elongation and distortion generated to meet the requirement of the hyperplastic epidermis.[143] Accordingly, covert vascular visualization has been shown to represent the early changes of cutaneous atrophy that occur as a result of steroid use.[144] Interestingly, facial telangiectasias have been reported to develop in association with long-term application of a topical corticosteroid to the scalp.[145] In this report, the long-term use of betamethasone valerate lotion allowed percutaneous absorption of a sufficient amount to spread locally from the scalp to the face through the dermal vasculature. Therefore, topical application of corticosteroid preparations can induce the development or appearance of telangiectasias. There has been a rise in incidence with the use of illicit topical bleaching preparations that are hydroquinone-adulterated with high-potency topical steroids such as clobetasol.

PHYSICAL FACTORS

ACTINIC NEOVASCULARIZATION AND VASCULAR DILATION

Physical factors are commonly responsible for acquired telangiectasia. Telangiectasias are noted to appear after many types of physical trauma. The most common form of physical damage to the skin is that caused by sun exposure.[146,147] Telangiectasia on the face is probably a manifestation of persistent active arteriolar vasodilation caused by weakness in the vessel wall, resulting from degenerative elastic changes or weakness in the surrounding connective tissue caused by chronic sun exposure. Alternatively, ultraviolet B (UVB) exposure has been shown to elevate epidermal tumor necrosis factor (TNF),[148] which promotes angiogenesis by various mechanisms that may also induce dilation of existing vessels.[149] Vascular endothelial growth factor (VEGF) has also been shown to be elevated in the epidermis following UVB exposure, with an increase in the number of cutaneous blood vessels.[150] Finally, the aging process itself may lead to vessel dilation. Perivascular veil and adventitial cells are believed to be responsible for the synthesis and maintenance of the peripheral portion of vascular walls in the dermis.[116] These cells decrease in number with aging, correlating with a histologic thinning of vascular walls.[151] Thus, both direct and indirect ultraviolet light as well as the aging process contribute to the development of telangiectasia.

Ultraviolet-induced telangiectasias most often arise from arterioles and are seen frequently in individuals with fair complexions, often on the nose (especially on the ala and nasolabial crease). A similar mechanism for the pathogenesis of type 1 telangiectasias may also apply to their occurrence on the legs. An examination of more than 20,000 Americans[152] demonstrated the presence of fine telangiectasias in 17.3% of men and 11.6% of women with low sun exposure, compared with 30.1% of men and 26.2% of women who reported high sun exposure. More significantly, 15.5% of men and 40.9% of women with actinic skin damage were shown to have spider leg veins, compared with 6% of men and 28.9% of women without actinic skin damage. Solar-induced damage to cutaneous and subcutaneous tissue is a significant etiologic factor in the appearance of telangiectasias (Fig. 4.18).

TRAUMA

Contusion

Various forms of physical trauma may lead to the growth of new blood vessels. Contusion injuries are a common mechanism for the development of a localized growth of telangiectasias (Fig. 4.19). In these cases, neovascularization probably results from epidermal and endothelial damage, which induces the release of angiogenic factors, including fibrin.[153] Trauma also causes a rapid change in the permeability of cutaneous blood vessels through the release of various mediators.[97] The increased permeability of endothelium may lead to angiogenesis through multiple mechanisms.[154]

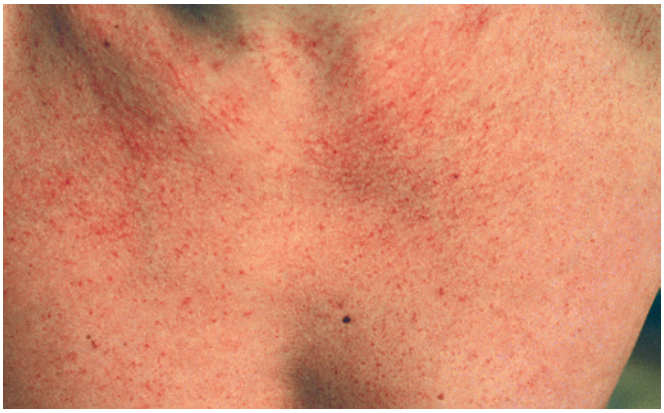

Figure 4.18 Extensive distribution of fine red telangiectasias on the chest of a severely sun-damaged 50-year-old woman.

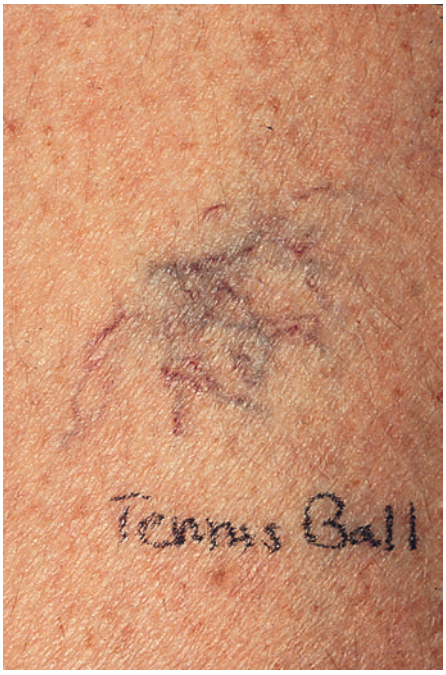

Figure 4.19 Posterior thigh of a 35-year-old woman hit with a tennis ball 1 year previously. The resulting telangiectatic mass developed shortly after resolution of the bruise.

A solitary giant spider angioma with an overlying pyogenic granuloma was described in a patient with alcoholic cirrhosis.[155] The authors postulated that local mechanical irritation led to a reactive proliferation of endothelial cells. When the central pyogenic granuloma was removed, the surrounding spider telangiectasia disappeared.

Surgical Incisions or Lacerations

Surgical incisions or cutaneous lacerations are common events that require physiologic neovascularization. Here, angiogenesis is a prerequisite for the progression of wound healing.[153] Fibrin deposition appears to play a prominent role in wound healing by stimulating new blood vessel growth.[153,156] The resulting formation of blood vessels has been demonstrated to represent a dilation and extension of existing blood vessels.[97] Unfortunately, some postsurgical

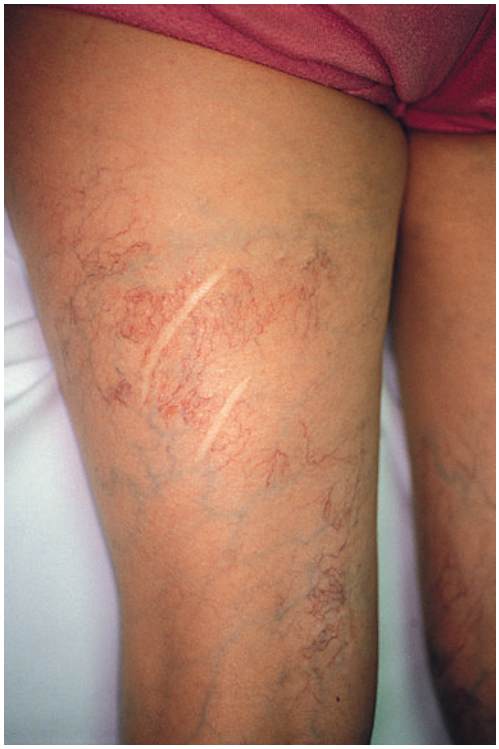

Figure 4.20 This woman underwent an extensive ligation and stripping of her varicose veins at 18 years of age. She developed numerous telangiectasias around the surgical sites within weeks of the surgical procedure. This photograph was taken 22 years after the surgical procedure.

patients develop an exaggerated angiogenic response manifested by cutaneous telangiectasias. Although this may occur at sites of ligation for vein stripping (Fig. 4.20), the most common surgical event that leads to telangiectasia development is the skin flap procedure. When a skin flap is under excessive tension, telangiectasias may develop at the edge of the flap. This excessive blood vessel growth may be induced by mechanical forces on the wound. Histologic examination demonstrates the orientation of vascular fiber networks along lines of tension. This orientation may be related to the activation of cell growth through stretching.[157] Thus, the vascularization of skin flaps and grafts supports the concept of an epidermal stimulus for vasculogenesis.[158,159]

INFECTION

Generalized Essential Telangiectasia

Generalized essential telangiectasia (GET) is a benign form of telangiectasia of unknown etiology. It often begins in late childhood as extensive linear telangiectasias of the legs. It is more common in girls, but estrogen and progesterone receptors in the vascular lesions have not been found to be elevated.

Various infections have been associated with the development of the form of telangiectasia just described. Bacteria may stimulate endothelial proliferation in vitro.[160] In 1926, Becker[161] reviewed a series of patients with generalized telangiectasia and associated this phenomenon with syphilitic infection. Of these patients, 16 had evidence of systemic syphilis and 4% had evidence of a focal infection. Ayres

et al[10] later described a patient with generalized telangiectasia and a sinus infection. Resolution of the sinusitis with antibiotic treatment resulted in the disappearance of the telangiectasia.

GET is difficult to treat because of the recurrent progressive nature and generalized distribution. Tetracycline, minocycline, doxycycline, acyclovir and ketoconazole have been shown in some studies to improve GET.[162,163] Compression stockings have been shown to halt the progression of the lesions, with speculation that hypostasis of the limbs may be involved in the pathogenesis.[154a,164] Last, the long-pulsed 532 neodymium-doped yttrium aluminium garnet laser has resulted in nearly complete resolution of the telangiectasias after six treatment sessions, with a partial relapse noted at 6-month follow-up.[164]

Progressive Ascending Telangiectasia

Progressive ascending telangiectasia is a distinct entity with telangiectasias on the lower extremities that is related to occult infections and has responded to antibiotic and antifungal drugs. Shelley[13] and Shelley and Fierer[165] described two cases of EPT that resolved after empirical treatment with tetracycline and ketoconazole, respectively. Electron microscopy studies in one patient demonstrated focal fibrin clots in some of the dilated vessels, which disappeared within 1 month of ketoconazole therapy.[165] The authors postulated a microbial-induced focal intravascular coagulation as the causal factor in the pathogenesis of this rare form of acquired telangiectasia. Perez et al[166] described a case that had been resistant to systemic antibiotic and antifungal drugs that was successfully treated with a 585-nm flashlamp-pumped PDL.

Human Immunodeficiency Virus

Immunosuppressed populations are frequently infected with a wide variety of bacterial, fungal and yeast species. The first report of neovascularization in immunosuppressed patients was in an HIV-positive patient with hemophilia who had numerous telangiectasias on the shins; the telangiectasias resolved after treatment with tetracycline.[167] Unfortunately, the specific infection involved is usually difficult to identify because a myriad of infections occur in immunosuppressed patients. Also, a survey of homosexual men with and without lymphadenopathy demonstrated that 47% had focal telangiectasias in a broad distribution across the anterior chest.[168] The presence of telangiectasias was significantly, although not exclusively, associated with HIV seropositivity. Telangiectasias in this group did not appear to be related to underlying bacterial or fungal infection or to sun exposure. The authors postulated that this clinical finding might have been a direct manifestation of HIV infectivity.

Although not telangiectatic, bacillary angiomatosis (also known as *epithelioid angiomatosis*) is a disease most often characterized by multiple reddish cutaneous papules. Tissue sections of these lesions demonstrate weakly reactive gram-negative bacilli. The cutaneous lesions resolve with antibiotic therapy. Thus, this new entity confirms an infectious etiology for the stimulation of vascular proliferation.[169]

In summary, circumstantial evidence indicates that a systemic or localized infection promotes the development of neovascularization. Because this clinical association is so rare, when the ubiquitous occurrence of infections in humans is considered, its pathophysiology remains obscure.

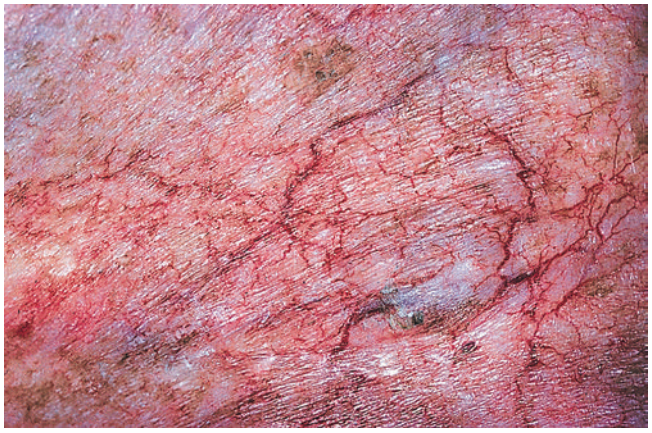

Figure 4.21 Telangiectasia on the lateral neck of a patient treated with radiation for laryngeal carcinoma 20 years previously.

RADIODERMATITIS

Therapeutic radiation therapy may lead to the development of telangiectasias (Fig. 4.21). Chronic radiodermatitis has noticeably decreased with the advent of megavoltage equipment and better technique. Megavoltage radiation beams are more penetrating than the older, lower-energy beams; this minimizes the radiation dose to the skin. However, at least 5% of patients receiving therapeutic radiation therapy develop cutaneous telangiectasias.[170] The fundamental pathology of chronic radiodermatitis is fibrosis of the vessels with occlusion and varying degrees of homogenization of the connective tissue. Residual superficial blood vessels are usually dilated.[171]

Prevention of radiodermatitis has been examined using different modalities. *Calendula officinalis* is a phytotherapy derived from a medicinal plant shown to have a multitude of properties, including bactericidal, fungistatic, virucidal and antiseptic. Schneider et al[172] evaluated 51 patients comparing *Calendula officinalis* with essential fatty acids for the prevention and treatment of radiodermatitis in patients with head and neck cancer. The *C. officinalis* group had an average radiodermatitis grade of 1, whereas the essential fatty acids group had an average radiodermatitis grade of 2. Additional studies are needed to confirm these results.

The use of phototherapy with an indium gallium aluminum phosphorus laser operated at 660 nm is currently under investigation as a preventative measure for radiodermatitis in patients with breast neoplasms. This low-powered laser has been shown to promote tissue repair by stimulating neocollagenesis and reducing inflammation. Additional investigations are needed to verify the ability to prevent radiodermatitis.[173]

ERYTHEMA AB IGNE

Infrared radiation or heat exposure can lead to the appearance of telangiectasia. Erythema ab igne is a localized dermatosis that occurs as reticular pigmentation and telangiectasia produced by repeated exposures to heat. It is commonly seen on the legs of women who sit close to heating units in countries without central heating; recently,

there have been reports of erythema ab igne appearing on the anterior thighs in patients exposing these sites to heat generated by laptops.[174–177] Histologic findings include epidermal atrophy, vasodilation, a dermal mixed cellular infiltrate and an increase in melanophages as well as free-lying melanin granules.[178]

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5 Noninvasive Examination of the Patient Before Sclerotherapy

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Before sclerotherapy is performed, the examiner must obtain a focused history and perform a meticulous physical examination, including inspection and palpation (level 1). This combination places the patient into a proper clinical classification, and this, in turn, will dictate therapy. For example, primary venous insufficiency is characterized by telangiectasias, reticular varicosities and varicose veins without the stigmata of chronic venous disease. In contrast, the latter has characteristic hyperpigmentation, edema, ulceration or scarring from healed ulcers. The presence of chronic disease findings prompts the examiner to be more insistent regarding further evaluation.

Confirmatory diagnostic testing is performed after the history is taken and the physical examination is performed. The handheld continuous-wave Doppler historically was a routine part of the physical examination, but it is being replaced by compact, portable duplex ultrasound visualization. At present, the vascular laboratory (level 2) provides a reliable tool for acquiring anatomic and functional information that not only confirms the diagnosis but also formulates treatment. Elements of the diagnostic vascular laboratory have become part of a routine physical examination.[1] This approach has been confirmed in the guidelines of the Society for Vascular Surgery and the American Venous Forum.[2,3]

Invasive testing such as phlebography and ambulatory venous pressure (AVP) (level 3) measurements, while of historical significance, have been relegated to a secondary role as large amounts of data are obtained from duplex ultrasound. The level of diagnostic testing performed is dictated by the severity of the clinical condition.

MEDICAL HISTORY

A focused history is the beginning of every evaluation for any patient with a suspected vascular disorder. Obtaining a clear understanding and detailed description of the symptoms is the first step. Recording of the patient's concerns and reasons for seeking treatment should also be done at this time because patients concerned by pain at first interrogation may focus on esthetics in subsequent sessions following treatment of primary sources of reflux. Symptoms of venous insufficiency have been termed *nonspecific*. However, patients with clear symptoms of venous insufficiency typically do not ascribe these to varicose veins. Symptoms include aching, tiredness and far-ranging discomfort in the legs, relieved by sitting and leg elevation. Such discomfort increases as the day progresses, with standing and with increased vein stretching. In women, symptoms are exacerbated on the first days of a menstrual period because elevated progesterone levels cause increased vein swelling. Symptoms may also begin in pregnancy. It has been said that for males with varicose veins the lack of progesterone or estrogen results in fewer symptoms.

The magnitude of symptoms is not dependent upon the size of the varicosities. Telangiectasias and reticular varicosities may cause symptoms identical to those of gross varicose veins. Because symptoms are due to pressure of dilated veins on somatic nerves, it is not surprising that some patients experience burning near varices. This is classically thought to be ischemic neuropathy, but it may be capillary pressure–related. A sudden disabling pain that develops on standing or sitting with legs dependent and is relieved by muscular activity is termed *venous claudication*, a misnomer.

Several studies have suggested that a family history of varicose veins is common in this patient population.[4–6] In patients with severe manifestations of chronic venous disease, a history of deep venous thrombosis is obtained in less than one third of patients.[7,8] Nonetheless, a personal and family history of a diagnosis of venous thrombosis should be requested. If present, it is important to clarify the way in which this diagnosis was confirmed (phlebography, venous duplex or simply clinically). Patients should be prompted to recall specific aspects of their medical history, such as traumatic fractures, leg swelling, need for systemic anticoagulation, illness requiring bed rest, or major surgical intervention.

CEAP CLASSIFICATION

An international ad hoc committee of the American Venous Forum developed the CEAP classification for chronic venous disease in 1994 (Table 5.1; see also Chapter 2) with the goal of stratifying clinical levels of venous insufficiency. The four categories and descriptors selected for classification were clinical manifestations (C), etiology (E), anatomy (A) and underlying pathophysiology (P). The CEAP classification has been endorsed worldwide, despite its acknowledged deficiencies. It has been adopted as the standard in many clinics in Europe, Asia, South America and the United States for categorizing chronic venous disorders, guiding treatment decisions and predicting prognosis. Its weakness is the

Table 5.1 CEAP Classification Scheme

Clinical Classification

C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins—separated from reticular veins by a diameter of 3 mm as the upper limit of size of a reticular vein
C3	Edema
C4a	Pigmentation, eczema (stasis dermatitis)
C4b	Lipodermatosclerosis, atrophie blanche (livedoid vasculopathy)
C5	Healed venous ulcer
C6	Active venous ulcer

Each clinical class is further characterized by a subscript for the presence of symptoms (S, symptomatic) or their absence (A, asymptomatic). Symptoms include aching, pain, tightness, skin irritation, heaviness and muscle cramps, as well as other complaints attributable to venous dysfunction.

Etiologic Classification

Ec	Congenital
Ep	Primary
Es	Secondary (postthrombotic)
En	No venous etiology identified

Anatomic Classification

As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified

Pathophysiologic Classification

Basic CEAP

Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

Advanced CEAP

Same as Basic with the addition that any of 18 named venous segments (below) can be used as locators for venous pathology.
All items listed in C should be repeated.

Venous Segments

Superficial Veins

1	Telangiectasias/reticular veins
2	GSV above knee
3	GSV below knee
4	SSV
5	Nonsaphenous veins

Deep Veins

6	IVC
7	Common iliac vein
8	Internal iliac vein
9	External iliac vein
10	Pelvic: gonadal, broad ligament veins, other
11	Common femoral vein
12	Deep femoral vein
13	Femoral vein
14	Popliteal vein
15	Crural: anterior tibial, posterior tibial, fibular veins (all paired)
16	Muscular: gastrocnemial, soleal veins, other

Perforating Veins

17	Thigh
18	Calf

GSV, Great saphenous vein; SSV, small saphenous vein; IVC, inferior vena cava.

inability to distinguish between levels of smaller superficial veins. The CEAP classification was revised in 2004[9] and is now referred to as *advanced CEAP.*[10]

Within the CEAP classification, the clinical assessment is described as follows:

- C0: no visible or palpable signs of venous disease
- C1: telangiectatic and reticular veins (see definitions in Chapter 2)
- C2: varicose veins
- C3: edema
- C4a: pigmentation and/or eczema
- C4b: lipodermatosclerosis and/or atrophie blanche
- C5: healed ulcer
- C6: active ulcer

The descriptor A is added for asymptomatic patients, and the designation S is used in case of symptoms.

All clinical features must be reported in the advanced CEAP classification; for example, a patient with telangiectasias, varicose veins, edema, pigmentation, active ulcer and pain is classified as C6S in the basic (classical) CEAP but as C1,2,3,4a,6,S in the advanced (revised) CEAP. This approach carries much more information.

Etiology is reported by descriptor E:

- Ec: congenital (usually present at birth)
- Ep: primary (degenerative, typically varicose veins)
- Es: secondary (as in postthrombotic syndrome)
- En: no venous etiology identified

The anatomy of the venous network involvement is described by the A classification, with involved venous segments recorded with a number (see Table 5.1):

- As: superficial veins
- Ap: perforator veins

- Ad: deep veins
- An: no venous location identified.

Last, pathophysiology is reported with the P descriptor, again with involved venous segments recorded by numbers (see Table 5.1):

- Pr: reflux
- Po: obstruction
- Pr,o: reflux and obstruction
- Pn: no venous pathophysiology recognized

When performing vascular testing, the data must include the date of the patient's evaluation. Classification of the level of examination performed is as follows: L1 (level 1) is clinical examination plus continuous wave Doppler, L2 is noninvasive (duplex ultrasound, plethysmography) and L3 includes complex imaging such as computed tomography (CT) and magnetic resonance imaging and invasive investigations such as venograms, intravenous ultrasound and blood pressure measurement.

DIAGNOSTIC APPROACH

The first step in evaluating a patient with venous disease is to establish his or her clinical class, which progresses from cosmetic concerns to chronic venous insufficiency. The next step is to correlate any symptoms, which place the limb being examined into one of the classes shown in Table 5.1. The patient's clinical class will dictate the need for further evaluation. In patients with telangiectasias (class 1 or 2), the evaluation can be limited to a physical examination and evaluation of the superficial venous system with a handheld continuous-wave Doppler. Imaging of 83 limbs with clinical evidence of only telangiectatic vessels demonstrated that nearly 25% had insufficiency of the great saphenous vein (GSV) or small saphenous veins (SSVs), which was not apparent on physical examination.[11] Patients with symptomatic class 2 varicosities and classes 4, 5 and 6 skin changes require a duplex venous reflux examination because surgical intervention may be indicated.[12–16] Recalcitrant cases may require more extensive imaging studies to detect venous occlusive disease. Physiologic testing is relegated to documentation rather than to diagnosis, and phlebography should be performed only when venous reconstruction is considered.

PRIOR TREATMENT

The physician should discuss a patient's prior treatment for venous disease. However, he or she must realize that although proper ligation, with or without stripping of the main saphenous trunks, implies that reflux through the saphenofemoral junction (SFJ) and saphenopopliteal junction (SPJ) has been prevented, this is not always the case. Joshi et al[17] found that reflux in the residual GSV was the most common cause of recurrent varicose veins in 419 legs among 298 patients who underwent ligation of the SFJ and stripping of the GSV. Up to 27% of patients have a duplication of the GSV,[18–20] indicating that the removal of the GSV may be followed by the development of varicosity in the remaining GSV.

In 20% to 40% of patients, the SSV has a variable termination[21–24] that is not in the popliteal vein at or above the popliteal fossa. Therefore, the actual SPJ must be correctly located, or it will lead to an apparent rapid recurrence with varicose changes occurring in the remaining segment of the SSV and its tributaries. In a number of patients, a recurrence of varicose veins in the upper thigh may be a result of incomplete ligation and division of the other tributaries arising at the level of the SFJ or of failure to accomplish the ligation flush with the femoral vein. In fact, in a review of 341 extremities that underwent repeat operations for varicose veins, Lofgren et al[24] found that 61% had inadequate ligation. Thus, it is imperative that, even in a patient with a history of ligation, division and stripping, an examination for reflux through the SFJ and SPJ be performed.

The physician should consider responses to and complications due to all treatment modalities (e.g., sclerotherapy, laser). Certain complications, such as ischemic ulceration caused by inadvertent injection into an arteriovenous malformation, can be avoided more easily if a diagnosis is made before treatment. Given the predilection for these to occur in a particular anatomic distribution(s), the physician might avoid treating that area or use greater caution in the previously affected region. A history of prior hyperpigmentation, blushing or poor response to a particular sclerosing agent may support a variety of changes in treatment protocol, such as altering the sclerosant concentration, increasing the strength or duration of compression and paying greater attention to posttreatment thrombectomy.

SYMPTOMS

The presence and severity of symptoms does not necessarily correlate with the size or severity of varicose veins present. Symptoms usually attributable to varicose veins include feelings of heaviness, tiredness, aching, burning, throbbing, itching and cramping in the legs (Box 5.1). These symptoms are generally worse with prolonged sitting or standing and are improved with leg elevation or walking. A premenstrual exacerbation of symptoms is also common. Patients typically find relief with the use of compression in the form of either graduated support hose or an elastic bandage, but compliance can be a challenge. Weight loss or the commencement of a regular program of lower extremity exercise may also lead to alleviation of the severity of varicose vein symptoms. Clearly, these symptoms are not specific, as they may also be indicative of a variety of rheumatologic or orthopedic problems. However, their relationship to lower extremity movement and compression is usually helpful in establishing a

Box 5.1 Symptoms Attributable to Varicose Veins

- Aching
- Heaviness, tiredness
- Pain (throbbing, burning, sharp, tingling)
- Itching
- Cramping
- Tightness

venous origin for the symptoms. Significant symptoms suggestive of chronic venous disease should prompt further evaluation for valvular insufficiency and calf muscle pump dysfunction. If a venous etiology is suspected but all examinations are negative, repeat examination during a symptomatic period is warranted and often fruitful.

The recent development of an extremely painful area on the lower leg associated with an overlying area of erythema and warmth may be indicative of lipodermatosclerosis, which may be associated with insufficiency of underlying perforator veins or reflux from a proximal point; thus, examination for underlying perforator vein reflux should be performed. Lipodermatosclerosis may precede ulceration and has been shown to be improved by stiff compression and certain pharmacologic interventions.[25]

Rarely, patients with a history of iliofemoral thrombophlebitis who describe 'bursting' pain with walking may have 'venous claudication'. In these patients, an evaluation for persistent hemodynamically significant obstruction, possibly treatable with venous bypass surgery, is appropriate.[26]

COMPLICATIONS OF VARICOSE VEIN DISEASE

Complications such as ulceration and hemorrhage should be discussed with the patient, because this provides additional insight into both the severity and the probable locations of abnormality within the venous system. A history of ulceration of the medial aspect of the lower leg should prompt further examination of the GSV trunk,[12] whereas involvement of the lateral aspect of the lower leg suggests an abnormality in the SSV in addition to the deep and perforating vein systems. A history of hemorrhage from telangiectasias in a particular area suggests further examination for underlying incompetent perforators and is an indication to treat all suspicious telangiectasias.[27]

PURPOSE OF VENOUS EVALUATION

More extensive evaluation can provide essential information regarding both venous anatomy and function. Abnormalities of the superficial, perforating or deep systems can be diagnosed, and the exact sites of valvular insufficiency within the various systems (and therefore the sites where treatment must be directed) can be determined. The hemodynamic significance of each of these abnormalities may be defined, and the effect of correcting each site of reflux may be assessed. Insufficiency at a particular site within the venous system may be found to have no importance in the patient's pathologic venous hypertension or symptoms. This site may or may not be incorporated into the treatment plan to minimize the number of treatments. With the examination techniques discussed in the following sections, the result of sclerotherapy may be documented in a more accurate and sensitive manner than with simple observation and palpation. Treatment success may be enhanced significantly, with the goal being restoration of normal venous flow. If the presence of deep venous thrombosis (DVT) and/or deep venous valvular insufficiency is detected, these are absolute and relative contraindications to sclerotherapy. If diagnosed, serious complications in these noncandidates for sclerotherapy can be avoided.

PHYSICAL EXAMINATION

The best way to approach examination of the venous system before sclerotherapy is to be methodical. Although the exact method of examination is a matter of personal preference, a systematic approach is advisable.

Using skills of clinical practice, the practitioner can obtain a degree of information regarding overall venous outflow from the leg, the sites of valvular insufficiency, the presence of primary versus secondary varicose veins and the presence of DVT.

The screening physical examination consists of careful observation of the legs. Any patient with the following conditions should be examined more fully: large varicose veins; bulges in the thigh, calf or the inguinal region, representative of incompetent perforating veins (IPVs) or a saphena varix[28]; signs of superficial venous hypertension, such as an accumulation of telangiectasias in the ankle region (corona phlebectatica); or any finding suggestive of venous dermatitis (pigmentation, induration, eczema). This includes patients with obvious cutaneous signs of venous disease, such as venous ulceration, atrophie blanche or lipodermatosclerosis. An obvious but often forgotten point is the necessity of observing the entire leg and not confining the examination simply to the area that the patient feels is abnormal. The importance of this is demonstrated in the patient shown in Figure 5.1. This patient came for treatment of an obviously dilated anterior thigh vein, but further inspection revealed a saphena varix with incompetence at the level of the SFJ, thus defining the first step in her treatment. Similarly, patients often seek treatment of specific clusters of telangiectasia and do not notice the underlying reticular veins that should be treated initially or at the same time (see Chapter 12).

Because the veins of the leg empty into the pelvic and abdominal veins, inspection of the abdomen is very important. Dilation of veins on the abdominal wall or across the pubic region suggests an old iliofemoral thrombus[29] or, rarely, a developmental anomaly of the venous system.[30] Dilated veins along the medial or posterior aspect of the proximal thigh or buttocks most often arise from varicosities involving the pudendal or other pelvic vessels. These can be associated with vulvar varices that may remain symptomatic after the completion of the pregnancy during which they formed. Enlarged veins in the thigh or buttocks may also be quite symptomatic and respond well to treatment.

CLINICAL TESTING

Historically, tests of venous function have been part of the physical examination of venous insufficiency. These tests have been slowly abandoned due to lack of specificity and sensitivity. As the 'stethoscope' of the venous examination, the continuous-wave Doppler examination has replaced most of these tests, while confirmatory duplex testing has supplanted all. An educated physician who treats venous insufficiency must have knowledge of these tests and their physiologic background. Also, knowledge of the Trendelenburg test (or Brodie-Trendelenburg test) is important

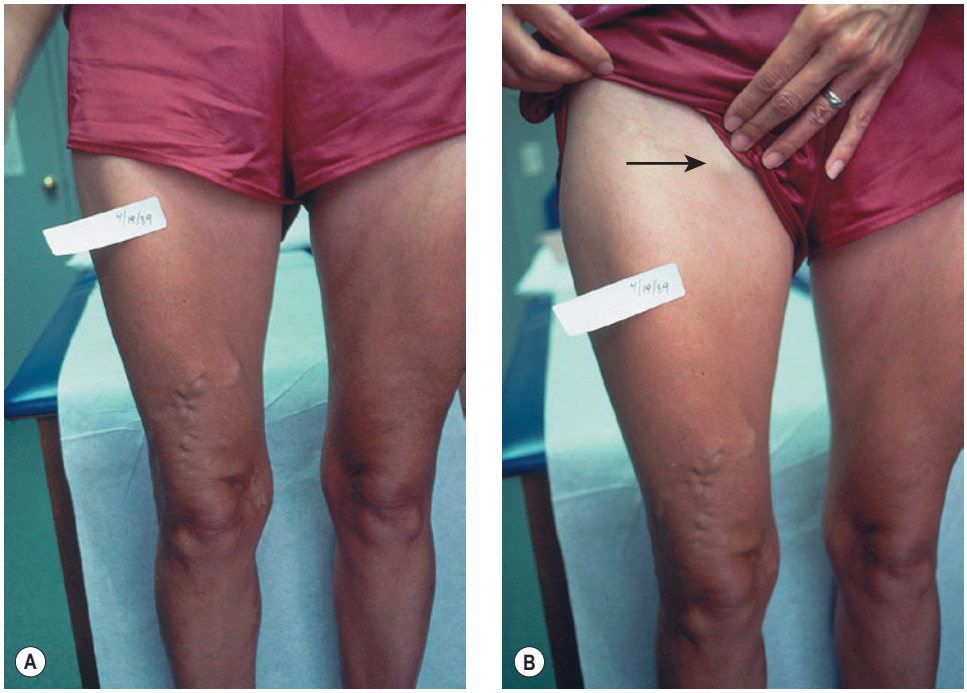


Figure 5.1 **A,** This patient sought treatment for an obviously enlarged vein in her thigh. **B,** Further inspection revealed a saphena varix *(arrow)* indicative of saphenofemoral junction insufficiency. (Courtesy Anton Butie, MD.)

for understanding venous physiology and is of historical significance.

TRENDELENBURG TEST

For the Trendelenburg test, a tourniquet may be placed around the patient's proximal thigh while the patient is standing. The patient then assumes the supine position with the affected leg elevated 45 degrees. The tourniquet is removed, and the time required for the leg veins to empty, which is indicative of the adequacy of venous drainage, is recorded.

When the affected leg is compared with the contralateral leg, the method just described may demonstrate a degree of venous obstructive disease. Another approach is to elevate the leg while the patient is supine and observe the height of the heel in relation to the level of the heart that is required for the prominent veins to collapse (Fig. 5.2). Unfortunately, neither procedure is sufficiently sensitive or accurate or able to differentiate acute from chronic obstruction, which means neither of them is of much assistance in current medical practice. This emphasizes the important role of duplex ultrasound in modern evaluation of the superficial venous system. One study found that pneumatic tourniquets occluded only 27% of saphenous trunks.[31] Several other physical examination maneuvers, described below, can provide information on the competence of the venous valves.

COUGH TEST

With the cough test, one hand is placed gently, without exerting pressure, over the GSV or SFJ, and the patient is asked to cough or perform a Valsalva maneuver (Fig. 5.3). Simply palpating an impulse over the vein being examined

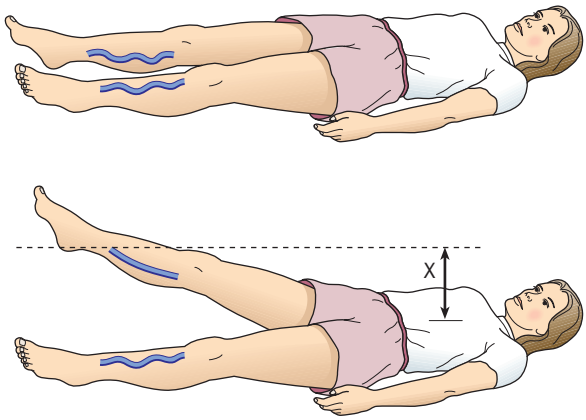


Figure 5.2 Venous outflow may also be assessed by elevating the leg until the superficial veins collapse and then measuring the distance *(X)* from the heart to the heel and comparing this measurement with the other leg.

may be indicative of insufficiency of the valve at the SFJ and below to the level of the palpating hand. This test, however, is not applicable to the examination of the SSV and SPJ (see following section).[21] Palpation of a thrill during this maneuver is generally more diagnostic. One study found a low sensitivity of 0.59 and low specificity of 0.67 with this test.[32]

PERCUSSION/SCHWARTZ TEST

With the percussion/Schwartz test, one hand is placed over the SFJ or SPJ while the other hand is used to tap very lightly on a distal segment of the GSV or SSV (Fig. 5.4). The production of an impulse in this manner implies insufficiency of the valves in the segment between the two hands. Confirmation of valvular insufficiency can be achieved by tapping

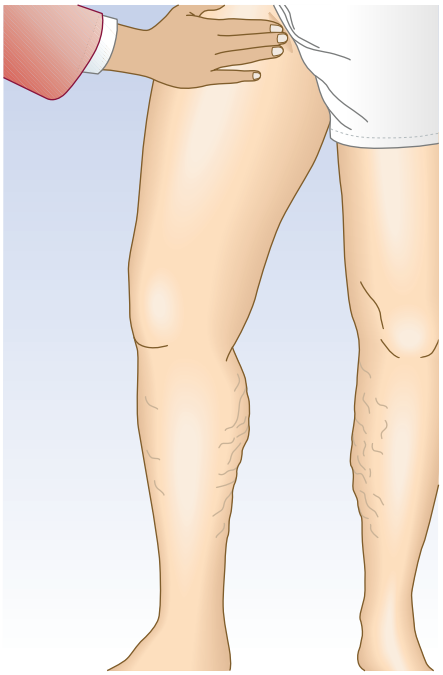


Figure 5.3 Cough test. The saphenofemoral junction (SFJ) is palpated while the patient coughs. Palpation of an impulse is indicative of SFJ insufficiency.

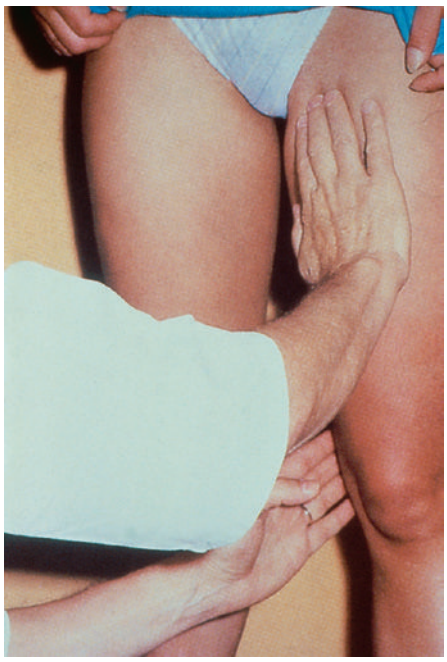


Figure 5.4 Percussion test. The saphenopopliteal junction (SPJ) is palpated while the small saphenous vein is gently percussed. Palpation of an impulse is indicative of SPJ insufficiency.

proximally while palpating distally. This test can also be used to detect whether an enlarged tributary is in direct connection with the GSV or SSV by palpating over the main trunk and tapping lightly on the dilated tributary, or vice versa. The presence of a direct connection results in a palpable impulse being transmitted from the percussing hand to the palpating hand. As might be expected, these tests are far from infallible. In a study of 105 limbs, Chan et al[33] found that these clinical examination techniques correctly identified SFJ incompetence in only 82% of limbs. False negatives were believed to be caused primarily by obesity and previous groin surgery with resultant scarring. However, false positives were the result of variations in venous anatomy, such as a dilated tributary emptying into the common femoral vein (CFV) adjacent to the GSV or the absence of valves in an otherwise normal CFV and external iliac vein (seen in 5–30% of patients) (M. Schadeck, personal communication, September 1989).[34] Researchers in another study found that this test had a low sensitivity of 0.59 and a high specificity of 0.92.[32] A further source of error with the cough and/or percussion test is simply a misinterpretation of the muscle contraction that occurs with coughing as a reflux impulse.

BRODIE-TRENDELENBURG TEST

The Brodie-Trendelenburg test traditionally involves the manual obstruction of the proximal end of the GSV (or SSV) while the patient lies supine with the leg elevated, after the vein is stroked in a cephalad direction to empty it of blood.[29,35–38] The patient then assumes the standing position, and the leg is observed for 30 seconds (Fig. 5.5). In a 'nil' test, the veins fill slowly from below and release of the compression does not result in rapid filling from above, indicating competence of valves in deep and perforating veins and at the SFJ (Fig. 5.6A). Rapid filling of the GSV or more distal tributaries that occurs only after release of the compression constitutes a 'positive' test, indicating the presence of an insufficient valve at the SFJ (Fig. 5.6B). In the 'double-positive' test, some distention of the veins occurs within the initial 30 seconds while the compression is maintained, as well as additional filling once the compression is released (Fig. 5.6C). This is taken as evidence of incompetent deep and perforating veins as well as reflux through the SFJ. A 'negative' test occurs when the veins fill within the initial 30 seconds with no increased filling after the compression is released, implying only deep and perforating valvular insufficiency (Fig. 5.6D). The reverse may not be true; that is, filling in longer than 30 seconds does not imply competence of perforating veins. In a study of 901 extremities, Sherman[39] found that 95% had a nil Trendelenburg test, but surgical exploration later showed incompetent perforators in 90% of these patients. Another study showed a high sensitivity of 0.91 with a low specificity of 0.15.[32]

The Brodie-Trendelenburg test thus can be an important method of localizing the most proximal site of reflux in most dilated superficial veins by obstructing the GSV, SSV or whichever vein is suspected of refluxing into a more distal vein. The physician can also place the examining finger over palpable fascial defects in the leg while the patient is supine and then release the obstructions one by one after the patient is standing. This allows the sites of insufficient perforators, or 'points of control' (considered so crucial in Fegan's technique of sclerotherapy), to be defined, because the superficial veins distal to the insufficient perforator fill rapidly once the obstructing fingers are removed (see Chapter 9).[40,41]

With this technique, described well in many papers,[28,40–43] the practitioner first marks on the leg the sites of all dilated

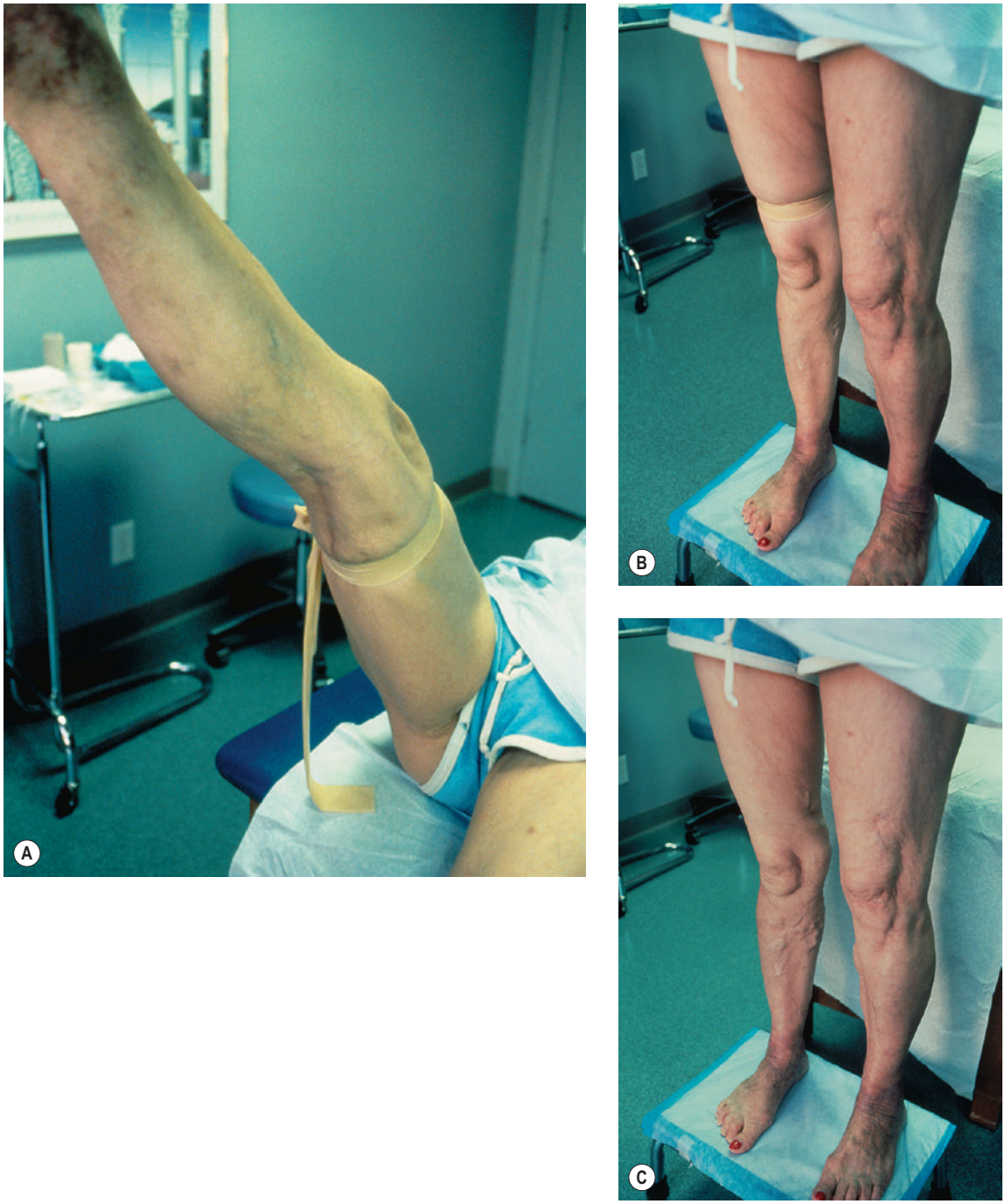


Figure 5.5 Brodie-Trendelenburg test. **A,** The proximal portion of the great saphenous vein is obstructed after the veins have emptied with the leg elevated. **B,** The distal veins are then observed after the patient stands. **C,** The veins are further inspected after the tourniquet is released. In this case, filling of the veins on standing and additional filling after tourniquet removal constitutes a double-positive test.

varicosities. The patient then assumes the supine position with the leg elevated to approximately 60 degrees to empty the veins. After at least 20 seconds, or when the distended veins are flattened, the leg is gently and rapidly palpated to detect any defects in the fascia. With experience, these can be detected easily as locations that allow the entrance of the examining finger without the use of any pressure. Fascial defects can be caused by many abnormalities other than perforating veins; thus, the practitioner continues the examination by compressing the individual fascial defects with his or her fingers and then having the patient stand. The fingers are then released one by one, starting with the most distal defect, and rapid filling of more distal varicosities is noted (Fig. 5.7). Those defects that cause distal filling when released are assumed to correspond to sites of IPVs. In the presence of a dilated GSV or SSV, these points of reflux first must be controlled with either digital compression or a tourniquet to evaluate the lower volume reflux through the perforators. For the evaluation to be helpful, compression of the defects must first cause sustained flattening of the varicosities when the patient initially stands. If the veins fill before any of the fingers are released, the test must be

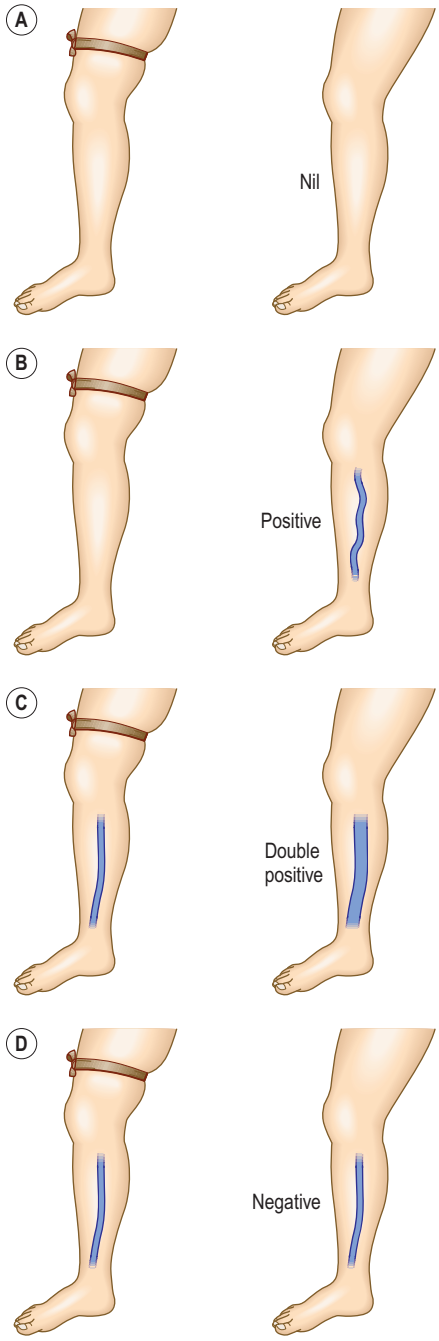


Figure 5.6 Interpreting the Brodie-Trendelenburg test. **A,** Nil: no distention of the veins for 30 seconds both while the tourniquet remains on and after it is removed implies a lack of reflux. **B,** Positive: distention of the veins only after the tourniquet is released implies reflux only through the saphenofemoral junction (SFJ). **C,** Double positive: distention of the veins while the tourniquet remains on and further distention after it is removed imply reflux through perforating veins and the SFJ. **D,** Negative: distention of the veins while the tourniquet remains on and no additional distention once it is removed imply reflux only through perforating veins.

restarted and other sites compressed until the sites responsible for the reflux are located. This examination is associated with 50% to 70% accuracy[42–45] compared with findings at surgical exploration. Repeated examination at different times and improvement of edema allow the detection of increased numbers of perforators.

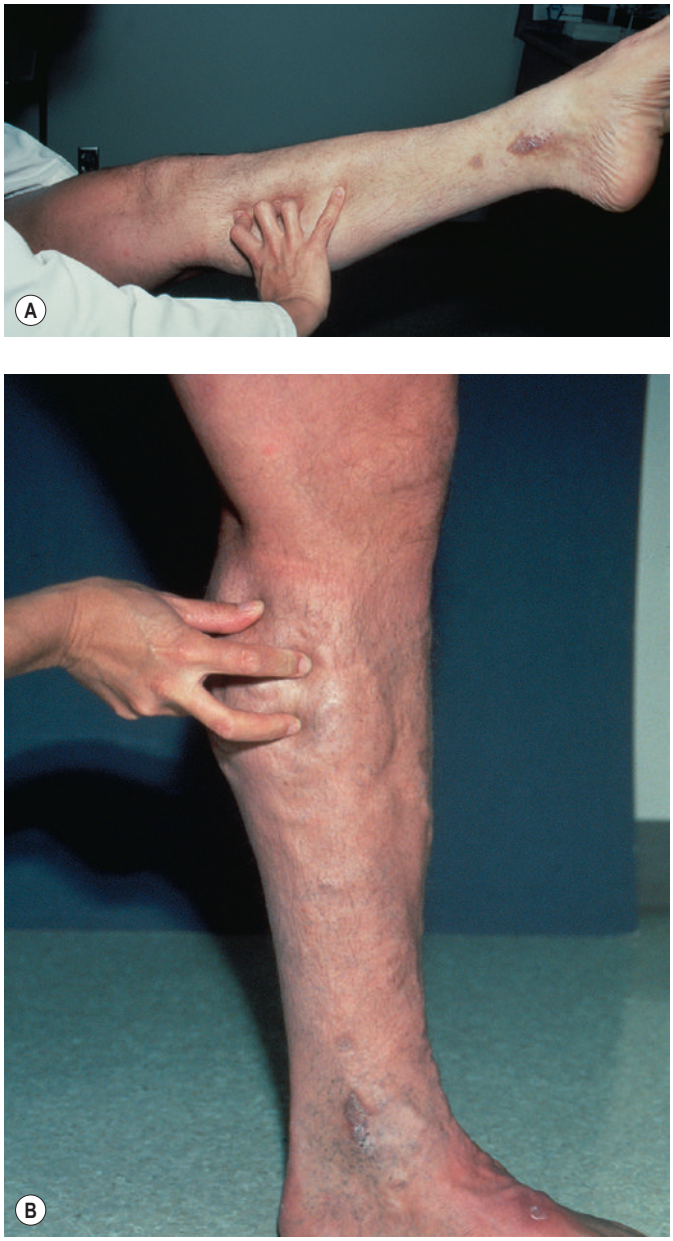


Figure 5.7 **A,** Compression of fascial defects indicating 'points of control' of an incompetent perforating vein with the leg elevated. **B,** When the patient stands, the varicose vein remains collapsed while pressure is maintained over control points and distends when the control point is released.

BRACEY VARIATION

A clever variation of the Brodie-Trendelenburg technique was proposed by Bracey[46] in 1958 (Fig. 5.8). He used a flat, 3.8-cm-wide rubber tourniquet and two rubber rings covered with latex, with inside diameters of 7 cm and 8.2 cm. The smaller ring is used between the ankle and knee and may also be used for the thigh if the patient is thin. If not, the larger ring is used for the thigh. With the patient standing, the small ring is rolled over the foot to just above the ankle, and the rubber tourniquet is then placed below the ring to obstruct any upward flow of blood through the superficial veins. The small ring is then slowly rolled upward, emptying the superficial veins as it moves. As soon as it passes an

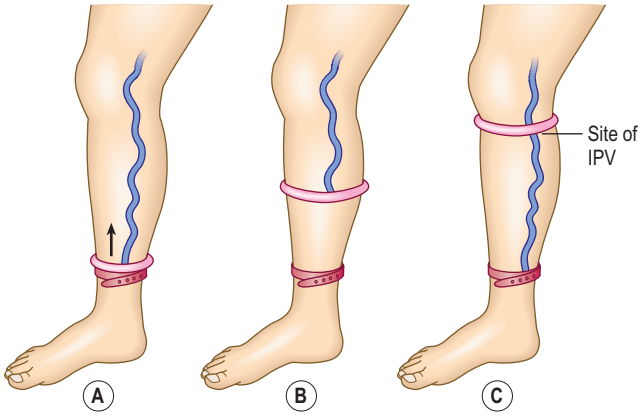


Figure 5.8 Device for the detection of incompetent perforating vein (IPV). **A,** Two rubber rings are placed around the ankle. **B,** The more proximally placed ring is slowly rolled upward. **C,** As it rolls above an IPV, the reflux of blood through the IPV causes an immediate distention of a superficial varix or the formation of a large bulge at the site of the IPV.

Table 5.2 Perthes Test

Finding	Interpretation
Decreased diameter of varicose veins	Primary varicose veins
No change in diameter of varicose veins	Secondary varicose veins
Deep venous patency	Impairment of calf muscle pump
Increased diameter of varicose veins	Deep venous obstruction

IPV, the blood enters the superficial vein that connects with it, causing a dilation of the vein. The exit site of the perforating vein may then be marked. This reflux of blood can be accentuated by asking the patient to repetitively dorsiflex the foot. When the ring reaches the knee, the tourniquet is moved up to the knee, just below the ring. Either the smaller or larger ring is then used similarly to examine the thigh.

PERTHES TEST

The Perthes test[29,38,47] has several uses, including distinguishing between venous valvular insufficiency in the deep, perforator and superficial systems and screening for DVT (Table 5.2). To localize the site of valvular disease, the physician places a tourniquet around the proximal thigh with the patient standing. When the patient ambulates, a decrease in the distention of varicose veins suggests a primary process without underlying deep venous disease because the calf muscle pump effectively removes blood from the leg and empties the varicose veins. Secondary varicose veins do not change caliber (if there is patency of the deep venous system) because of the inability to empty blood out of the veins as a result of impairment of the calf muscle pump. In the setting of a concurrent DVT, these veins may increase in size. If there is significant chronic or acute obstructive disease in the iliofemoral segment, the patient may note pain (venous claudication)[48–50] as a result of the obstruction to outflow through both the deep and superficial systems.

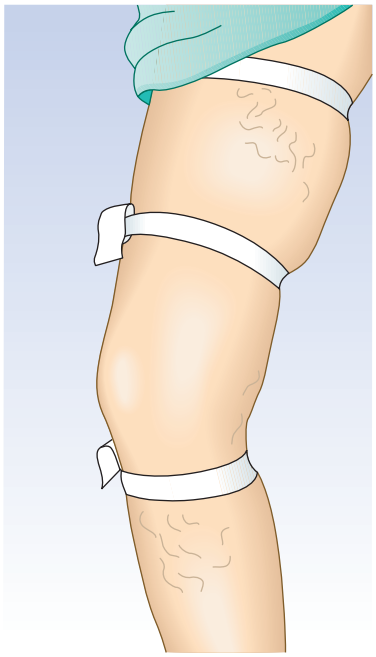


Figure 5.9 Comparative tourniquet test. Distention of the varices in each segment of the leg when the patient ambulates implies the presence of incompetent perforating veins in each segment.

Information regarding the presence of deep venous valvular insufficiency and thrombosis is important to note to aid in patient selection. This avoids causing catastrophic complications, such as pulmonary embolism resulting from an undiagnosed and worsened DVT or venous claudication caused by further impairment of venous return. Indeed, these two complications are serious enough to warrant the use of a much more sensitive and accurate method; therefore, the Perthes test is now of more historical than actual clinical importance.

To test for perforator valvular defects, the physician may embellish the traditional Perthes test by placing a tourniquet around the calf just below the popliteal fossa.[39] If the dilated superficial veins in the calf and ankle become less prominent as the patient ambulates, this implies that the blood is being drawn into the deep system through competent perforating veins. However, if the veins become increasingly dilated, the perforating veins must be incompetent. A more involved test, the Mahorner-Ochsner comparative tourniquet test, similarly localizes the site(s) of reflux by observing the leg while the patient walks with the tourniquet placed at various levels on the leg (upper, middle and lower thigh) (Fig. 5.9).[38]

NONINVASIVE DIAGNOSTIC TECHNIQUES

The preceding decades have provided a wealth of noninvasive technology that has revolutionized vascular diagnosis. A thorough description of all these techniques is beyond the scope of this book, but those not presented here may be found in several excellent texts.[11,20,51] Some of the new technologies have real utility in the everyday performance of sclerotherapy, and the following discussion attempts to acquaint the reader with their uses and limitations.

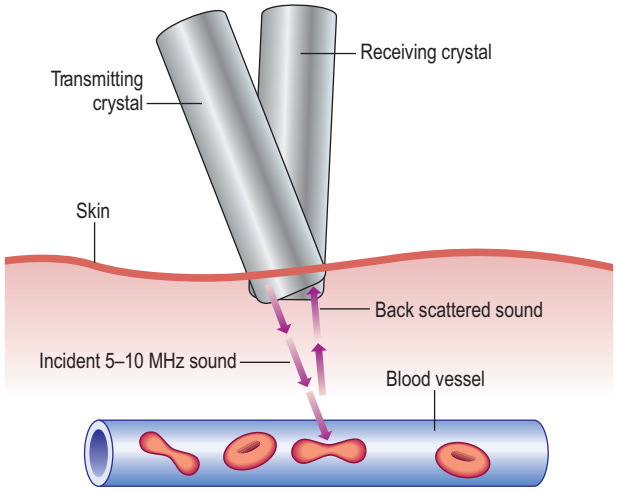


Figure 5.10 Doppler ultrasound. Sound waves are emitted from the transmitting crystal, reflected by moving particles (blood cells) within the vessel being examined and picked up by the sensing crystal.

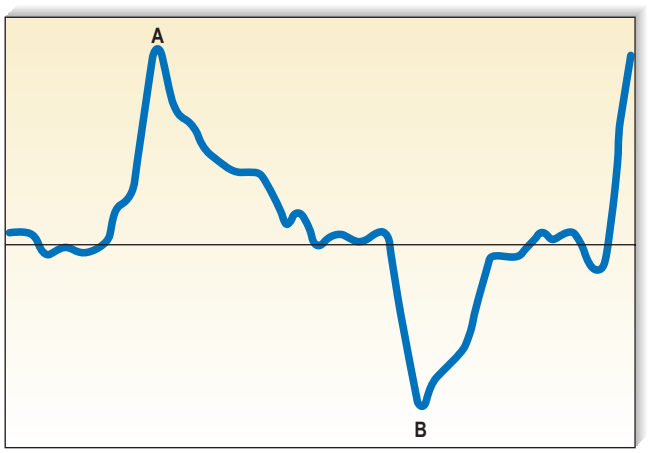


Figure 5.11 Bidirectional Doppler tracing. **A,** Positive deflection indicates flow toward the probe. **B,** Negative deflection indicates flow away from the probe.

DOPPLER ULTRASOUND

Although rapidly being replaced by duplex ultrasound, the most practical instrument for evaluating patients with venous disease is Doppler ultrasound. Its first vascular application came in 1960, when Satomura and Kaneko[52] described a method of studying changes in blood flow in peripheral arteries using an ultrasonic blood rheograph. Its use in the field of venous disease was promoted by many groups, including Sumner et al,[53] Strandness et al,[54] Felix and Sigel,[55] Sigel et al[56–60] and Pourcelot et al.[61] and it has again been recently confirmed as an accurate and reproducible method for venous assessment of the legs.[62] The instrument is based on the principle of the Doppler effect and consists of an emitting crystal and a receiving crystal. Sound waves are directed into the limb and reflected off the blood cells traveling through the vessel being examined (Fig. 5.10). The input picked up by the receiving crystal may be connected to a variety of audio or graphic recording systems. Dopplers come with either continuous or pulsed-wave ultrasound beams; the continuous-wave Doppler is adequate for venous examination, even though the signal represents a composite of the flow in all vessels in the path of the ultrasound beam. Thus, selective examination of one particular vessel may not always be possible. Pulsed Dopplers are used in sonar systems and medical ultrasound imaging and are required when the intent is to focus the beam at a particular depth. Dopplers are also available in either directional or nondirectional forms. The directional type is capable of determining the direction of blood flow and depicts the direction on the tracing as either a positive (toward the probe) or negative (away from the probe) deflection (Fig. 5.11). Although the directionality greatly simplifies the interpretation of the tracing, experience with a nondirectional Doppler allows the examiner to make this determination easily, based on certain augmentation maneuvers.

The transmission frequency of the ultrasound beam may range from 2 to 10 MHz; the depth of penetration varies inversely with the frequency. Therefore, a frequency of 4 MHz produces a broad beam with deep penetration, which is especially useful for examining the deep veins in the pelvis and abdomen. A frequency of 8 MHz is much better suited for the examination of more superficial veins, including superficial segments of the deep veins of the legs, because it produces a narrower beam with relatively less penetration. Dopplers used for evaluation of the venous system generally permit detection of flow rates as low as 6 cm/second.[57]

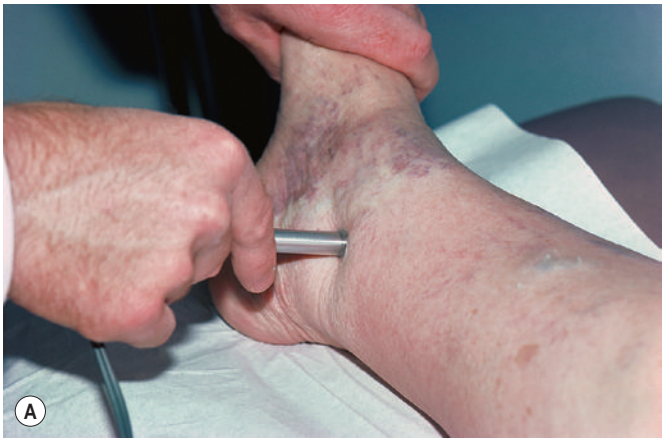
Box 5.2 Venous Doppler Characteristics

- Spontaneous
- Unidirectional
- Phasic with respiratory cycle
- Nonpulsatile
- Augmented

CHARACTERISTICS OF DOPPLER WAVEFORM

Venous Doppler signals display five characteristics (Box 5.2). In a normal patient, there should be a spontaneous signal over any vessel not otherwise vasoconstricted, and the flow should be only unidirectional. This signal diminishes in intensity with inspiration as descent of the diaphragm causes a rise in intra-abdominal pressure, thus decreasing venous outflow from the leg. It will be augmented similarly with exhalation. This waxing and waning of the intensity of the signal with the respiratory cycle is a phenomenon known as phasicity. Venous signals are continuous, except for their respiratory variation, and are not pulsatile, except in the setting of elevated right heart pressure such as congestive heart failure or tricuspid insufficiency[63] or in the normal CFV.[64] Finally, and most important to their usefulness in the evaluation of patients with varicose veins, venous signals may be augmented with certain compression maneuvers. It is the response to these maneuvers that provides information regarding the sites of valvular insufficiency and obstruction of the venous system.

By compressing the limb distal to the Doppler probe (Fig. 5.12), the examiner increases the flow through the vein; an immediate increase in the signal intensity should be heard



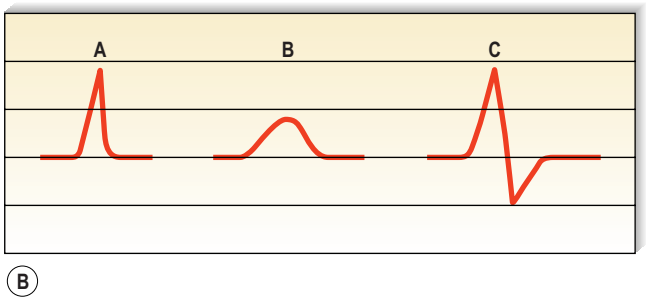
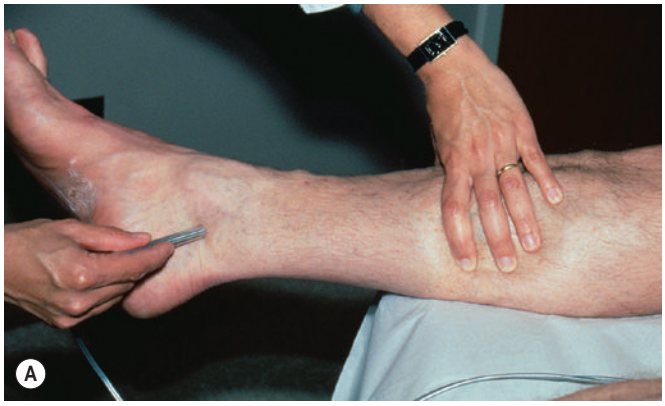


Figure 5.12 **A,** Method of producing augmentation of flow in the posterior tibial vein by distal (foot) compression. **B,** Normal flow *(A)*, venous obstruction *(B)*, and valvular insufficiency *(C)*.



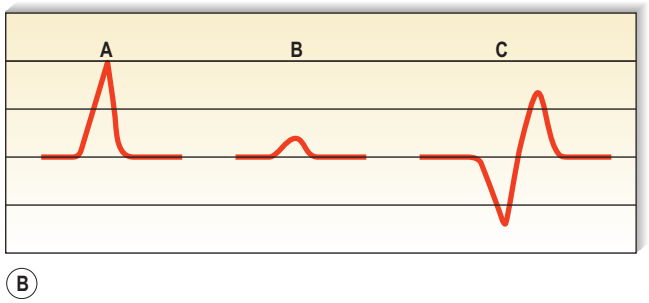


Figure 5.13 **A,** Method of producing augmentation of flow in the posterior tibial vein by release of proximal (calf) compression. **B,** Normal flow *(A)*, venous obstruction *(B)*, and valvular insufficiency *(C)*.

if there is no proximal obstruction. In the presence of a hemodynamically significant DVT, the augmented response is weaker and delayed compared with the contralateral side. With the patient in the upright position, release of distal compression should be followed by silence as the valves close in response to the downward pressure of the blood being pulled by gravity. With the patient in the supine position, release of the compression should normally be followed by the return of the lower intensity spontaneous signal or by silence in the smaller veins. In the setting of valvular insufficiency at the level of the Doppler probe, a loud reflux flow signal can be heard on release of distal compression as blood is pulled in a caudal direction by gravity. To quantify this reflux flow, the compression used may be standardized by using a pneumatic cuff inflated to a standard pressure (e.g., 80–120 mmHg), and the amplitude and duration of reflux may be read from the tracing obtained. To be considered true reflux and not merely delayed valve closure, the duration of reflux must be at least 0.5 seconds.[14,65]

The other method of augmentation is proximal compression and release (Fig. 5.13). Proximal compression produces a transient obstruction to outflow and thus causes an accumulation of blood distally, with an associated interruption of the Doppler signal. On its release, the large bolus of blood flowing past the Doppler probe creates a loud signal. This has also been found to be the more sensitive maneuver in diagnosing DVT, even that limited to calf veins, with a diminished or delayed signal indicative of a significant thrombosis.[66,67] Using this method, valvular insufficiency is discovered easily because proximal compression yields a loud reflux flow instead of silence.

Table 5.3 Interpretation of 'A' Sounds

Type of 'A' Sound	Condition if Present	Condition if Absent
Distal positive	Normal	Venous obstruction
Distal negative	Valvular insufficiency	Normal
Proximal positive	Valvular insufficiency	Normal
Proximal negative	Normal	Venous obstruction or marked valvular insufficiency

In early descriptions of the use of Doppler ultrasound for detection of venous disease, Sigel et al[57] named the various sounds 'S' for spontaneous and 'A' for augmented. They further specified 'A' sounds as distal (if the compression was distal to the probe) or proximal (if the compression was proximal to the probe) and as positive if the 'A' sound was heard directly with compression or negative if heard on release of the compression. This notation thus makes it possible for four 'A' sounds to be generated at each site being examined. Table 5.3 summarizes these sounds and their significance. This schema provides a useful method of categorizing these sounds; however, the 'S' and 'A' nomenclature has not found general acceptance. Instead, sounds are referred to as manifesting flux or reflux, antegrade or retrograde flow, patency or incompetence, and so forth.

Augmentation of the most proximal portion of the GSV and of the more proximal deep veins is accomplished either

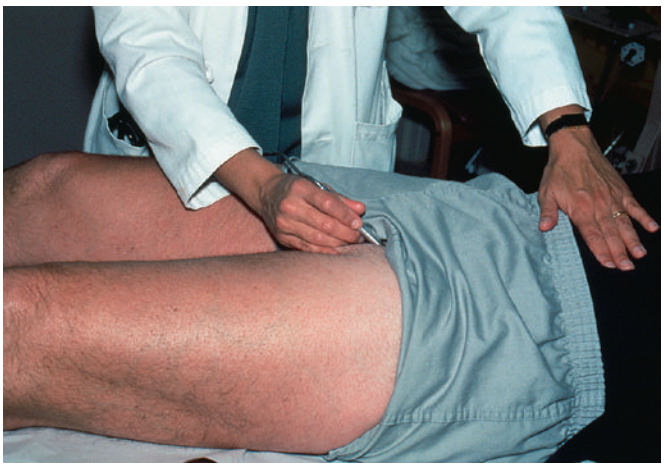


Figure 5.14 Augmentation of flow in the common femoral vein or through the saphenofemoral junction with intermittent compression of the abdomen, or with a Valsalva maneuver and release (not shown).

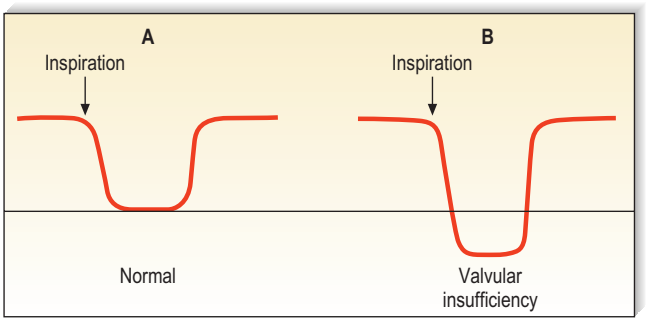


Figure 5.15 Venous Doppler tracings. **A,** Normal phasic flow. **B,** Reflux with deep inspiration in the setting of valvular insufficiency.

by compressing the abdomen or by using a variation of the proximal compression and release, and the Valsalva maneuver (Fig. 5.14). The rise in intra-abdominal pressure caused by descent of the diaphragm is accentuated by contraction of the intercostal muscles. In the normal patient, an abrupt closure of the valves results in silence. However, more than 38% of healthy persons have a brief period of reflux at the commencement of the Valsalva maneuver.[68] Also, with a weak effort by the patient, a slow retrograde flow may pass through the valve and produce a Doppler flow signal because sufficient force to cause valve closure has not been generated. Visualization of the valves using ultrasound demonstrates that these valves do close eventually and that they are not actually insufficient (C. Bishop, personal communication, September 1989). Therefore, the continuation of reflux through at least half of the period of compression, or at least 0.5 seconds (usually 1–4 seconds), is important in diagnosing pathologic valvular incompetence.[14,65] A less sensitive, but perhaps more specific, response may be elicited simply with deep breathing. With valvular insufficiency, instead of hearing the cessation of flow as the patient takes a deep breath, flow is reversed and a continuous signal is heard, which shows a reverse deflection on a directional Doppler tracing (Fig. 5.15). The Valsalva maneuver is sometimes hard to explain to patients and difficult to standardize; to facilitate, several tricks have been proposed, such as blowing into a surgical latex glove.[69] When using the

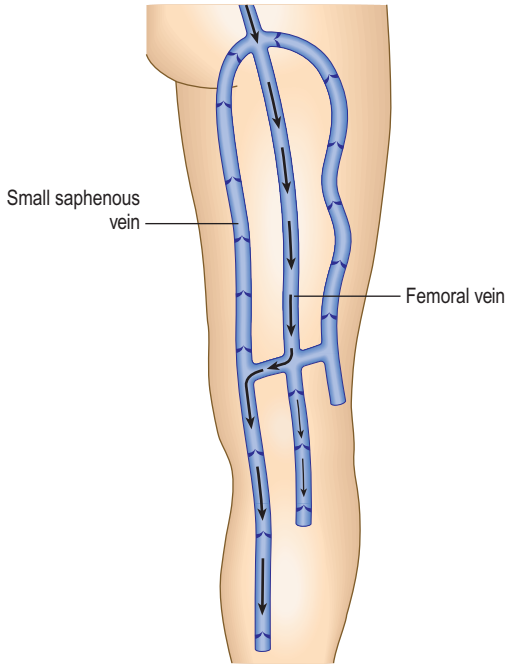


Figure 5.16 Pathways of reflux are typically through the saphenofemoral junction but may also be through atypical channels, such as through a deep vein via a perforating vein into a superficial vein (shown). Reflux may also travel through a superficial vein via a perforating vein into another superficial vein (not shown). (Redrawn from Schultz-Ehrenburg U, Hübner HJ. Findings in angiology and phlebology. Vol. 35: Reflux diagnosis with Doppler ultrasound: significance for diagnosis, indication, and objective followup in phlebology. New York: Schattauer; 1989.)

Valsalva maneuver to produce reflux while listening over more distal veins, the examiner must realize that the path of the reflux may be either straight down the superficial vein or through the deep vein to the perforating vein and into the superficial vein (Fig. 5.16).[70] Therefore, additional testing is necessary to clearly delineate the exact site of abnormality. This is easily accomplished by manually obstructing the superficial vein; if reflux is still heard, the retrograde flow is assumed to be traveling through the deep and perforating systems.

DOPPLER EXAMINATION TECHNIQUE

The Doppler examination of the patient is begun with the deep veins, several of which are easily accessible.

FEMORAL VEIN

With the patient supine and the hips slightly flexed and externally rotated, the physician first locates the pulsatile signal of the femoral artery in the groin. If desired, the examination can also be performed with the patient standing, which may provide a more physiologic evaluation because most symptoms occur when the patient is upright and reflux is more easily elicited. The Doppler probe is then gradually angled medially until the spontaneous, continuous sound of the femoral vein, reminiscent of a windstorm, is heard. Clear phasicity with respiration should be detected easily. Patency can be further tested by manually compressing the thigh or calf and listening for a strongly augmented signal. Valvular competence may be assessed by listening

first for the phasic waxing and waning of the signal that, in severe cases of insufficiency, shows a decrease in intensity of the signal followed by a reversal of flow direction as inspiration progresses, rather than the expected silence. The patient is then asked to perform a Valsalva maneuver; alternatively, the physician can press on the abdomen. These latter maneuvers should cause an abrupt closure of the valve and silence, followed by a more intense antegrade flow on release, if the valves are competent. A loud reflux flow heard through the Valsalva maneuver is pathognomonic of valvular insufficiency, which may also be present in 5% to 30% of normal patients and, in one study, was found in 100% of patients with bilateral GSV varicosities.[71] The effort invested in the Valsalva maneuver may be standardized to ensure the proper force and reproducibility by asking the patient to blow into a tube connected to a mercury manometer until the mercury column rises to 30 mm.

Differentiation of Femoral from Saphenous Veins

Because the SFJ is located close to the femoral artery pulsation, valvular incompetence at the junction can sometimes be mistaken for CFV insufficiency. Several techniques can be used to aid in making this important differentiation. The saphenous vein is much easier to compress than the femoral vein, so manual compression using the Doppler probe may occlude the saphenous vein and allow the physician to listen selectively to the femoral vein. A separate occlusive device, such as the physician's other hand or a tourniquet, may be used to compress the GSV distal to the Doppler probe and thus prevent reflux through it. Any reflux still heard is assumed to be through the femoral vein. Finally, moving or angling the Doppler probe in a cephalad direction may enable the physician to direct the ultrasound beam away from the saphenous vein to a more proximal segment of the femoral vein. Still, there are a small number of patients in whom differentiation of femoral from junctional signals may be impossible to determine by use of only the continuous-wave Doppler; an imaging procedure such as duplex scanning, which uses a pulsed ultrasound beam, may be necessary in such cases.[72,73]

To achieve uniform testing of venous reflux between institutions, comparable methods of testing by duplex and Doppler ultrasound scanning are desirable. In one study, the Valsalva maneuver was compared with rapid cuff deflation performed in the 15-degree reverse Trendelenburg position and with patients standing. Duplex technology allowed estimation of duration of retrograde flow and peak velocity. The general conclusions of the study were that the Valsalva method is best performed in the reverse Trendelenburg position as opposed to standing, but that the cuff technique is more effective in the standing position.[74]

POPLITEAL VEIN

For the next site of examination, the popliteal vein, the patient may be in the supine, prone or standing position. The most physiologic position is standing, and it is advisable to perform all presclerotherapy Doppler examinations in this position. It is important to have the knee slightly flexed, however, because full extension of the knee joint may cause a functional obstruction of the popliteal vein. Also, if the examination is performed while the patient is standing, the weight should be borne on the opposite foot (Fig. 5.17).

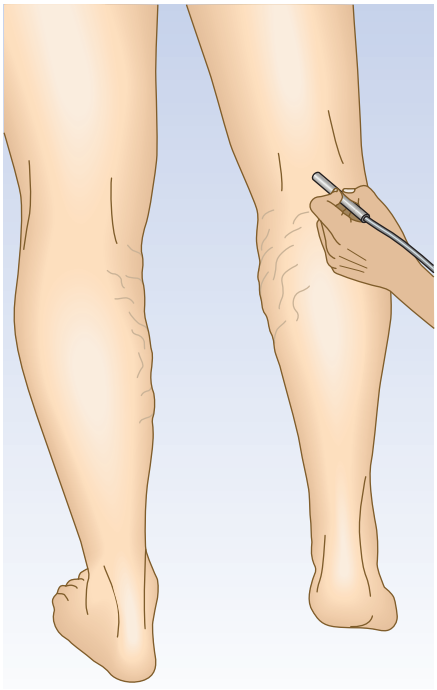


Figure 5.17 The popliteal vein is examined with the knee flexed and the weight borne on the opposite foot.

The pulsatile arterial signal is located generally in the popliteal crease just lateral to the midline; the Doppler probe may be angled medially to find a softer, although spontaneous, venous signal, or it may be left over the popliteal artery. Augmentation with either calf compression or thigh compression and release, as described previously, discloses both obstruction and valvular insufficiency. The Valsalva maneuver discloses reflux only if the more proximal deep veins (CFV) are also incompetent. As with reflux heard at the femoral level, reflux at the popliteal level may actually be caused by reflux through the SPJ. Therefore, in any patient who appears to have reflux through the popliteal vein, the test should be repeated while firm manual compression is applied to the SSV. Obliteration of the reflux in this manner localizes the site of reflux to the SPJ and not to the popliteal vein itself. Another method consists of slightly compressing an uninvolved portion of the calf with one finger, which causes flow through the popliteal vein and not the SSV.[70] Popliteal vein reflux can be detected in this way with a sensitivity of 100% and a specificity of 92%, with most false positive examinations being the result of variations in the anatomy of the SSV (see Chapter 1).[14,22,75] The presence of popliteal valvular insufficiency is an important finding because it is associated with diminished calf muscle pump function and may be the most important prognostic factor in the development of venous ulceration.[14,76,77] This relationship is not absolute, however; one study showed that popliteal incompetence was found in only 20% of patients with ulceration and 31.2% of postphlebitic legs.[68]

Although the continuous-wave Doppler is adequate for testing GSV incompetence, all reflux detected in the popliteal fossa should be checked by duplex examination. The continuous-wave Doppler examination has a sensitivity of 95% and a specificity of 100% for SFJ examinations, and a sensitivity of 90% and a specificity of 93% at the SPJ.[78]

POSTERIOR TIBIAL VEIN

The final deep vein that should be examined is the posterior tibial vein, located just posterior to the medial malleolus and beside the posterior tibial artery, which has an easily located pulsatile signal. This vein is frequently vasoconstricted, except if the patient is examined in a warm room, in which a spontaneous signal may be noticeable. Augmentation maneuvers are the same as described for the other deep veins. Again, although the Doppler is generally not felt to be sufficiently sensitive in the diagnosis of DVT below the knee, the response of posterior tibial venous flow to the release of calf compression has been found to allow 87% accuracy in this diagnosis.[66,67]

Scanning veins below the knees by ultrasound presents unique difficulties because of the small size of the veins and their deep position. The addition of color to the Doppler examination has improved this situation immeasurably, and the rates for detection of the posterior tibial, anterior tibial and peroneal veins have been raised to 98%, 96% and 96%, respectively.[79]

SUPERFICIAL VEINS

After the deep veins mentioned previously have been examined, attention is turned to the superficial and perforating systems. The major saphenous trunks and their junctions with the deep veins should be examined with the patient in the standing position. Because of the lower flow rate in these vessels, a spontaneous signal may only rarely be audible. The presence of a saphena varix, or a visible bulge over the SFJ, is nearly pathognomonic of valvular incompetence. The junction is easily located with the Doppler approximately two fingerbreadths in the femoral triangle below the inguinal ligament. Alternatively, the physician may first locate the SSV in the thigh and then gradually move the Doppler probe superiorly and laterally while repetitively compressing the GSV until its location is reached. A positive cough or percussion test may also help to localize the site of the SFJ. The presence of reflux on release of more distal compression is indicative of SFJ insufficiency. Again, the magnitude of the compression can be standardized for serial comparisons by using a pneumatic cuff inflated to a specific level. Also, the Valsalva maneuver may be used to elicit reflux, although manual compression of the SFJ by the inguinal ligament may occur during a forceful Valsalva, and more proximal competent valves may impede the retrograde flow,[80] thus creating the false impression of a competent valve.

If no reflux is heard over the SFJ, the physician should not assume that the entire GSV is competent.[81–83] The perforator(s) in Hunter's canal may frequently be the first abnormality to develop, leading to dilation and incompetence beginning just below the level of the middle thigh (see Chapters 1 and 3).[45,84] Reflux frequently originates in branches of the GSV[85]; the 'atypical refluxes' described by Schultz-Ehrenburg and Hubner[70] may be the most common. Incompetence of the GSV that is limited to the calf suggests insufficiency of the geniculate or lower leg perforators. Therefore, it is important to test the GSV for reflux in the groin, at the level of the knee, and in the lower leg and not to assume that it is normal until all sites fail to demonstrate reflux. In addition, there is a growing consensus that dilation may occur because of biochemical abnormalities in the muscle of the varicose vein wall. Thus, valvular insufficiency may not necessarily be a descending process, as was once assumed. This underscores the need to evaluate the entire length of the GSV when determining which portions of the vein to treat.[81]

Examination of the SSV and SPJ is best carried out with the patient standing and the knee slightly flexed, as previously described. The SSV is felt more easily with the knee flexed and the popliteal fossa relaxed.[21] When enlarged, the SSV generally is still not visible, but it is easily palpable as a spongy tubular structure leading inferiorly from the popliteal crease. By listening over the popliteal vein and tapping the leg very gently 5 to 10 cm below the probe, the examiner selectively compresses and thus listens to the SSV and not the popliteal vein, which requires a much stronger force. Because the termination of the SSV is variable, the exact location of the probe cannot be known for certain; therefore, it is difficult to determine if any reflux heard is originating from the SPJ or is simply within a dilated SSV. The Valsalva maneuver or compression of the thigh aids in this differentiation because it results in reflux only if the SPJ is incompetent. Distinction between flow through the SPJ and that through the popliteal vein can also be difficult but is facilitated by manually compressing the SSV below the probe while pressing on the calf, as described previously. Abolition of the reflux is evidence that the source is the SPJ.[22] Another method is to listen over a more distal segment of the SSV, along the posterolateral calf, and to compress and release the SSV at the popliteal crease. Reflux or only augmentation after release is detected easily.

PERFORATING VEINS

The examination of perforating veins is, at best, only 80% accurate using the Doppler.[86–88] Many believe that physical examination—that is, palpation of fascial defects in which the incompetent perforator meets a dilated superficial vein at the depth of the superficial fascia—is perhaps even more helpful.[89] In fact, published studies document that palpation is accurate only 51%[43] to 69%[44] of the time (Fig. 5.18). This technique, which is discussed more fully in Chapter 9, yields a large number of false-positive results because a fascial defect may result merely from dilation of a superficial varicosity or even from a separate pathologic process, such as a muscle hernia. In these situations, the Doppler affords increased reliability. In fact, Doppler examination for IPVs is advised after preliminary clinical localization of suspected sites (by listening for the characteristic to-and-fro movement of blood over sites of palpable defects in the fascia). Some authors have advocated the placement of tourniquets at 10-cm (4-inch) increments along the course of the lower leg before listening for flux and reflux at the sites of fascial weakness while the calf or thigh is repetitively compressed.[86–88] A simpler approach is to place one tourniquet just below the level of the fascial defect and another just above it. While listening with the Doppler over each marked fascial defect, the physician compresses the foot (Fig. 5.19). Any audible signal thus represents flow proximally through the deep system and outward through an IPV. This provides greater specificity because it interrupts the flow through the superficial veins, thus allowing selective examination of the perforating veins. Figure 5.20 provides a rational method of recording the venous Doppler examination findings.

Table 5.4 Comparison of Doppler Ultrasound and Duplex Scanning in the Presclerotherapy Evaluation

	Doppler	Duplex
Portability	Portable	Portable
Ease of use	Requires short period of training and experience	Requires longer period of training
Information obtained	Patency, competence of venous valves DVT in thigh (?calf)	Patency, competence of venous valves DVT with greater accuracy Velocity of reflux Anatomy and anomalies of venous system Termination of SSV Thrombosis vs sclerosis
Reliability	Less reliable because of blind, nonpulsed sound beam	More reliable because of actual visualization of vein being examined

DVT, Deep venous thrombosis; SSV, small saphenous vein.

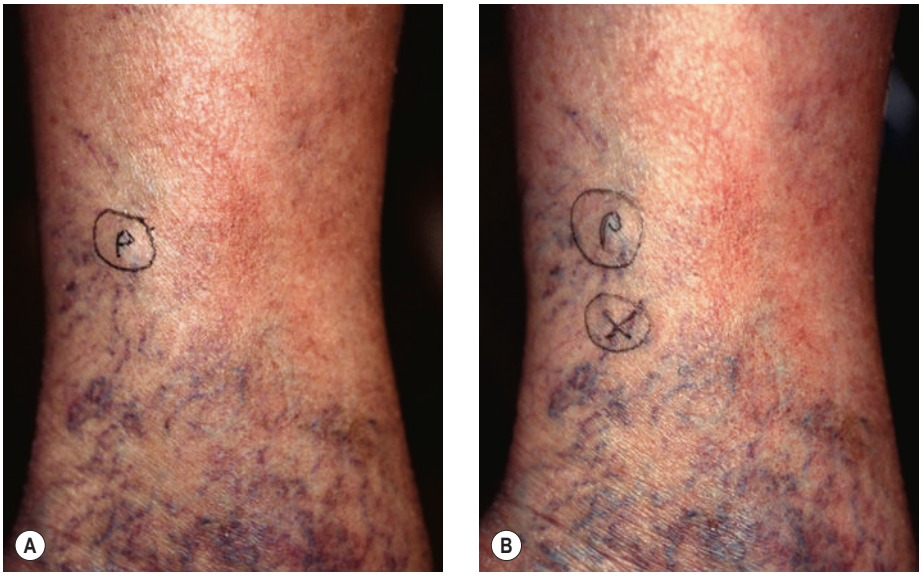


Figure 5.18 Palpation is often deceptive and clinical localization *(P)* of perforating veins is inaccurate. Duplex evaluation brings back the correct localization *(X)*.

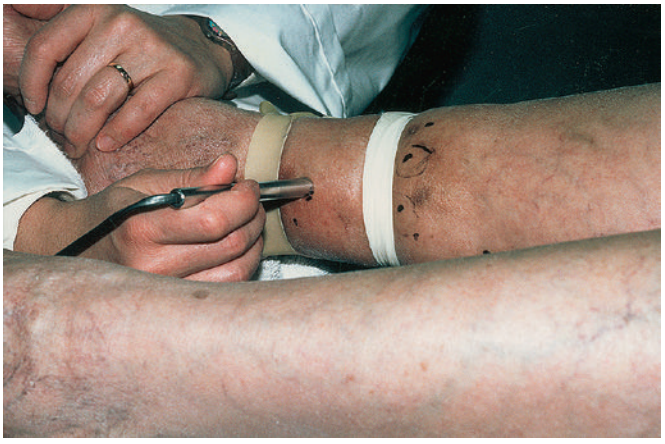


Figure 5.19 After making fascial defects palpable with the leg elevated, the Doppler is used to detect outward flow at each site. Tourniquets are placed just proximal and distal to each potential incompetent perforating vein, and the foot is compressed to produce flow upward through the deep veins.

POSTTREATMENT EVALUATION

Follow-up examinations of injected veins using the Doppler contribute more precise information regarding the response to treatment than physical examination does, because a vein that has been sclerosed loses both spontaneous and augmented flow signals. However, the Doppler detects flow through any vessel passing within the sound-wave beam and thus does not allow the examiner to be certain that the signal is from a particular vessel. Also, the Doppler does not differentiate a thrombus from fibrosis, because both lead to an absence of a flow signal. These limitations illustrate the advantages of the duplex scanner, another technologic advance that is revolutionizing the practice of phlebology (Table 5.4).[90–93]

DUPLEX ULTRASOUND SCANNING

Duplex scanners are accurate, reproducible, inexpensive ultrasound machines that generally use a 7.5- to 12-MHz

Deep veins		Right	Left
Common femoral	Phasicity		
	Reflux w/ inspiration		
	Reflux w/ Valsalva		
	Duration		
Popliteal	Reflux w/ Valsalva		
	Reflux w/ thigh compression		
	Reflux w/ calf release		
Posterior tibial	Reflux w/ calf compression		
	Reflux w/ foot release		
SFJ	Reflux w/ Valsalva		
	Reflux w/ calf release		
	Duration		
	Trendelenberg's test		
GSV distal thigh	Reflux		
	Diameter		
GSV calf	Reflux		
	Diameter		
SPJ	Reflux		
	Diameter		
SSV	Reflux		
	Diameter		

Tributary 1: Location		Diameter		GSV		SSV	
Tributary 1: Location		Diameter		GSV		SSV	
Tributary 1: Location		Diameter		GSV		SSV	
Tributary 1: Location		Diameter		GSV		SSV	

Figure 5.20 Chart for recording venous Doppler examination. *GSV,* Great saphenous vein; *SFJ,* saphenofemoral junction; *SPJ,* Saphenopopliteal junction; *SSV,* short saphenous vein.

imaging probe along with a 3- to 5-MHz pulsed Doppler to enable visualization of the superficial venous system and to determine the direction of blood flow within the examined veins. Anatomy, flow within the veins and the movement of the valves may also be studied (Fig. 5.21). Current scanners (sometimes termed *triplex* if displaying real-time color imaging and pulsed Doppler at the same time) use a computer-generated color system in which antegrade and retrograde flow may be coded to appear as different colors (red or blue) with varying intensities (brighter with lower velocities, paler with higher velocities), thus allowing immediate integration of this information by the examiner (Figs 5.22–5.24). Many new features have been introduced to

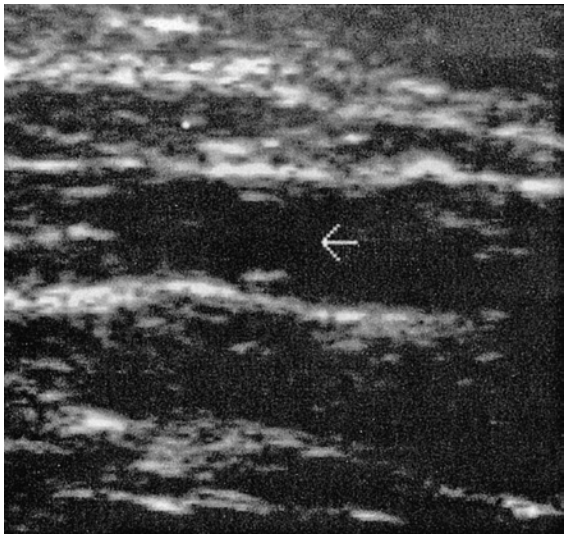


Figure 5.21 Duplex scanners may provide clear images of anatomic structures such as the saphenofemoral junction and venous valves *(arrow).*

enhance picture detail and contrast (e.g., B flow, power Doppler), which can be helpful in specific cases. Visual ultrasound images have one of their greatest uses within the field of venous disease in the diagnosis of DVT and now have all but replaced venography in centers where the instrumentation is available (Fig. 5.25).[94–99] Since the 1990s, alterations in the frequency range of the probes (higher frequencies of 10–20 MHz) have enabled clear resolution of superficial and deep veins, thus introducing an entirely new era in the diagnosis of varicose veins and their treatment by sclerotherapy.

While studies have demonstrated that the examination is best performed with the patient standing,[100] it is often difficult to perform this practically. Most examinations are not performed on a tilt table with patients at least 30 degrees in reverse Trendelenburg position. The cutoff value for reflux in the veins is greater than 500 milliseconds, except for the femoropopliteal vein, where it is 1 second (Fig. 5.26).

AID TO SCLEROTHERAPY

If the Doppler used to act as the 'ears' of the phlebologist, the duplex scanner must be considered both the ears and eyes as it allows the examiner to 'see' much more than is ascertainable otherwise. The duplex scanner allows for determination of the exact anatomy, including the important SFJs and SPJs. The anatomy of the SFJ is generally believed to be similar in all persons; however, there is actually significant variation. Duplication of the GSV has been reported to be found in up to 27% of persons[18–20] and is easily demonstrable with this technology (Fig. 5.27). Because the termination of the SSV is so variable, the exact location of the SPJ or the termination of the SSV in the GSV or its tributaries (the superficial or common femoral veins) or in tributaries of the internal iliac veins[98] can be seen on the duplex scan (Fig. 5.28). In the past, selective venography was advised to determine the exact site of termination of the SSV before the SSV was operated on.[101–103] Duplex ultrasound provides this piece of information noninvasively.[104,105]

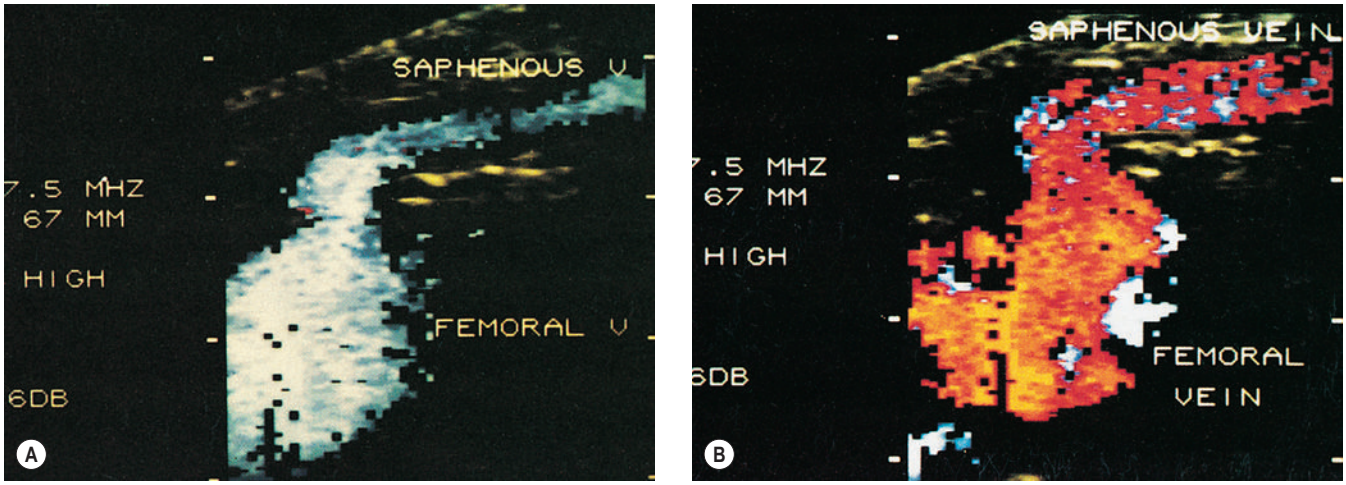


Figure 5.22 Color scanners display flow in the normal direction in *blue* **(A)** and reflux flow in *red* **(B).**

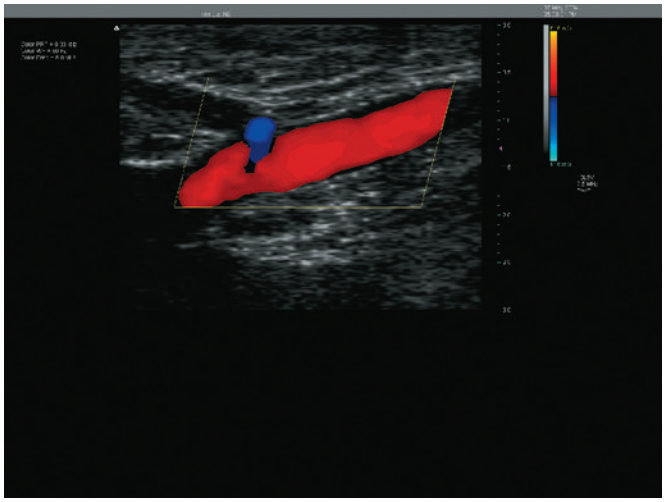


Figure 5.23 Color Doppler image of the confluence of the epigastric and great saphenous vein (GSV) showing reflux into the GSV. (Taken with Terason 2000 system; Terason, Burlington, MA).)

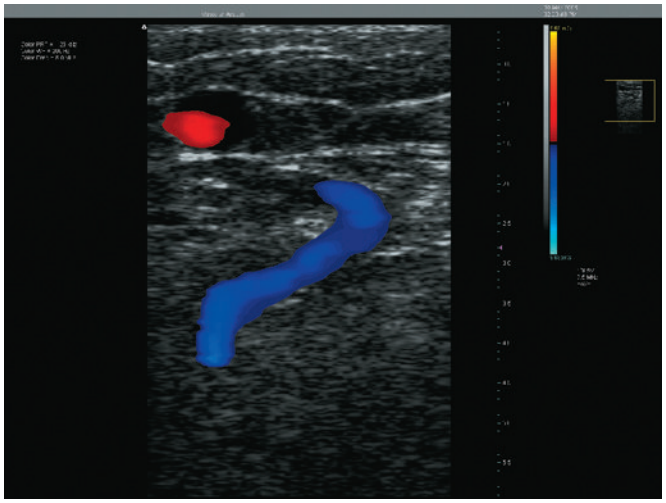


Figure 5.24 Color Doppler image of a perforator in the calf. (Taken with Terason 2000 system.)

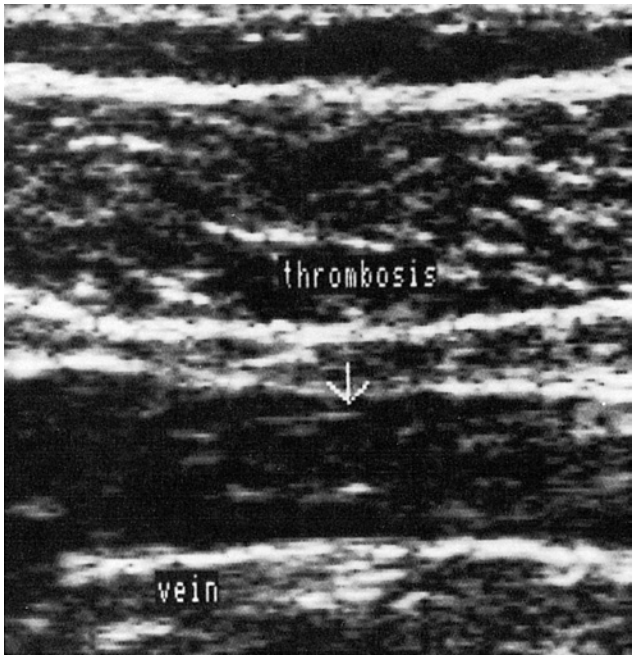


Figure 5.25 Ultrasound provides clear images of deep venous thrombosis *(arrow).* A thrombus may appear as an echogenic mass or simply result in the vein being noncompressible.

Injections into the SFJ or SPJ, if performed under ultrasonic guidance,[106,107] confer an added degree of accuracy and safety (Fig. 5.29). Injections into IPVs, particularly in areas of ulceration or lipodermatosclerosis, can be facilitated greatly by performing them under ultrasonic guidance.[108] Such areas may be particularly difficult to examine clinically or with a Doppler alone, and injections administered blindly into these areas can be quite risky because of the proximity of the posterior tibial vein and artery. The anatomic basis for proximal recurrences following GSV or SSV ligation may be found through duplex scanning. As 20% to 80% of patients who undergo varicose vein surgery will experience recurrence, duplex scanning allows for better classification of these recurrences so that future studies can be conducted in a rational and well-planned fashion.[109]

In addition, as McMullin and Appleberg[110] found, duplex measurement of antegrade flow rates through the CFV, superficial femoral vein, popliteal vein and GSV may be

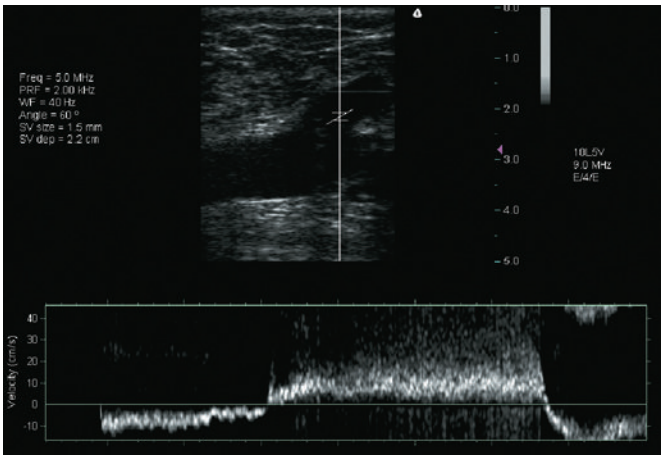


Figure 5.26 Duplex image showing reflux by pulsed-wave Doppler lasting more than 3 seconds. (Taken with Terason 2000 system.)

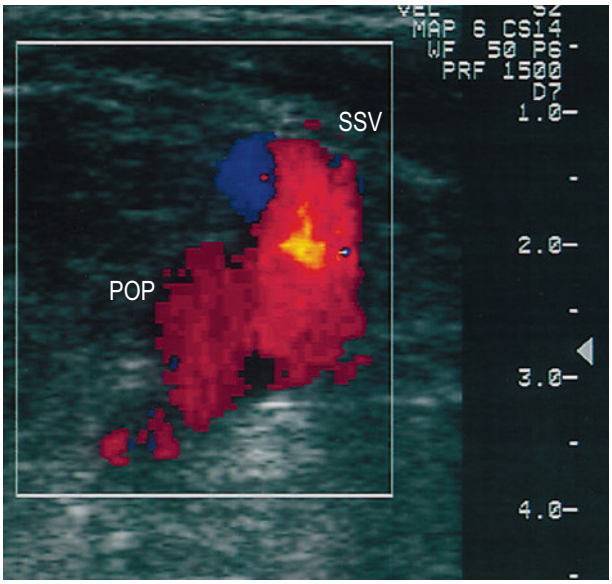


Figure 5.28 The termination of the small saphenous vein (SSV) can usually be visualized quite easily with duplex scanning. Image was taken after release of the calf compression, showing reflux. *POP,* Popliteal vein.

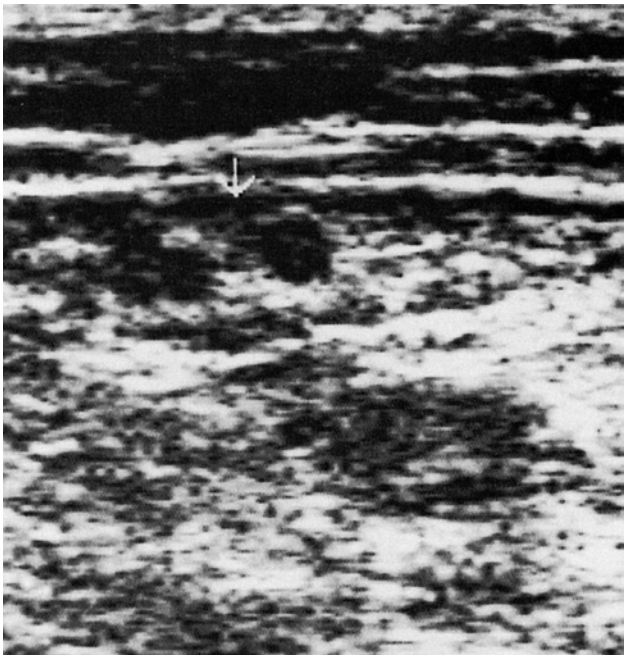


Figure 5.27 Anomalies such as this duplication of the great saphenous vein *(arrow)* may be visualized with a duplex scanner.

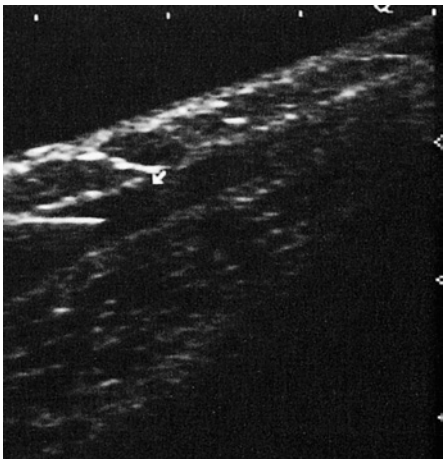


Figure 5.29 Injection into the saphenofemoral junction (SFJ) may be performed under ultrasonic guidance. The needle is seen inside the SFJ *(arrow).* (Courtesy Robert M. Knight, MD.)

used to determine the degree of resistance within the deep veins and thus the preferential flow up the superficial veins in patients with chronic venous insufficiency. If it is found that the flow rate upward through an incompetent GSV is quite high in a given patient with disease in more than one segment of his or her venous system, removal or closure of this vein might be contraindicated. The amount of flow generated by active dorsiflexion of the foot may also provide information on the efficacy of the musculovenous pump.

Duplex scanning has allowed for definition of the saphenous vein and its relationship to the superficial fascia and the deep or muscular fascia (Fig. 5.30). Throughout its length, duplex scanning has shown the GSV to lie on the muscular fascia. It is covered in its full length by the superficial or membranous fascia, a connective tissue lamina that descends from the inguinal ligament to the ankle. This lamina is formed by the interlacing of connective tissue sheets. After the superficial fascia arches over the GSV, it fuses with the muscular fascia to create a saphenous compartment. In duplex scanning, this compartment has been called the 'Egyptian eye'.[111] This identification is crucial for correct duplex scanning and separating varicose tributaries of the saphenous vein from the saphenous vein itself.

POSTTREATMENT EVALUATION

Another major use of duplex ultrasound in sclerotherapy is for follow-up of treatment. As mentioned previously, the Doppler does not allow differentiation between a thrombus and fibrosis, both of which yield abolition of flow through the involved vein segment. The duplex scanner can differentiate these two situations very clearly. Depending on its age, a thrombus may appear as a variably echogenic space associated with soft tissue swelling and inflammation, whereas fibrosis appears more often as a dense line with no associated inflammatory reaction (Fig. 5.31). Because

patient response to treatment is so variable, physicians now can more accurately determine if the treatment rendered has been completely effective, resulting in fibrosis, or if the vessel is occluded by a thrombus, thereby necessitating additional treatment. Many apparent treatment failures with early recurrence are likely to be found to be the result of inadequate treatment and not inadequate response.

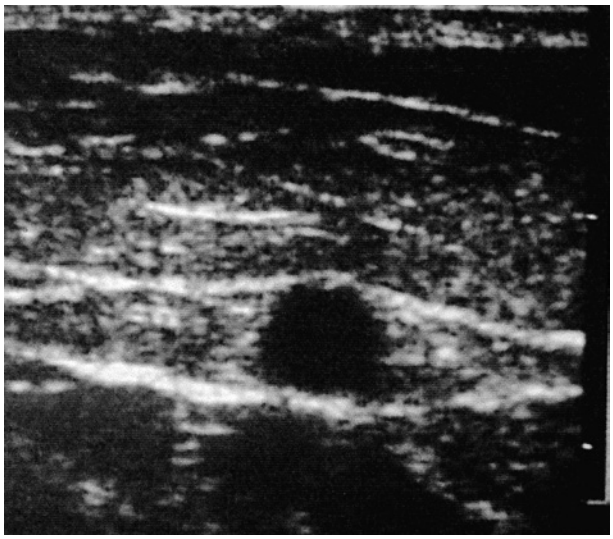


Figure 5.30 Duplex scanning defines the saphenous vein and its relationship to the superficial fascia and the deep or muscular fascia. The superficial fascia, after arching over the great saphenous vein, fuses with the muscular fascia to create a saphenous compartment. This compartment has been called the 'Egyptian eye' in duplex scanning, as shown in this scan.

Another important advantage of duplex ultrasound over the Doppler is its ability to quantify venous reflux. This parameter has been found to have some prognostic potential. The flow in milliliters per second at peak reflux was measured in 47 limbs of patients who had chronic venous problems. It was found that dermatitis or ulceration did not develop if the sum of the peak refluxes in the GSV, SSV and popliteal vein was less than 10 mL/second. A sum greater than 15 mL/second was associated with a high incidence of these sequelae.[14,112] In addition, superficial venous reflux alone may cause ulceration if the peak flow is greater than 7 mL/second.[113]

In summary, advantages provided by duplex scanning include evaluating the anatomy of the main saphenous trunks and recurrences, injecting difficult areas under ultrasonic guidance, determining the presence of fibrosis and quantifying both reflux and forward flow. Unfortunately, both the Doppler and duplex scanners are usually used to obtain only anatomic information, thus leaving the actual hemodynamic effect of various abnormalities unknown. Functional studies may therefore be necessary in certain situations.

PHOTOPLETHYSMOGRAPHY

The most widely used functional evaluation for presclerotherapy purposes is photoplethysmography (PPG).[114–117] Various forms of plethysmography have been used to

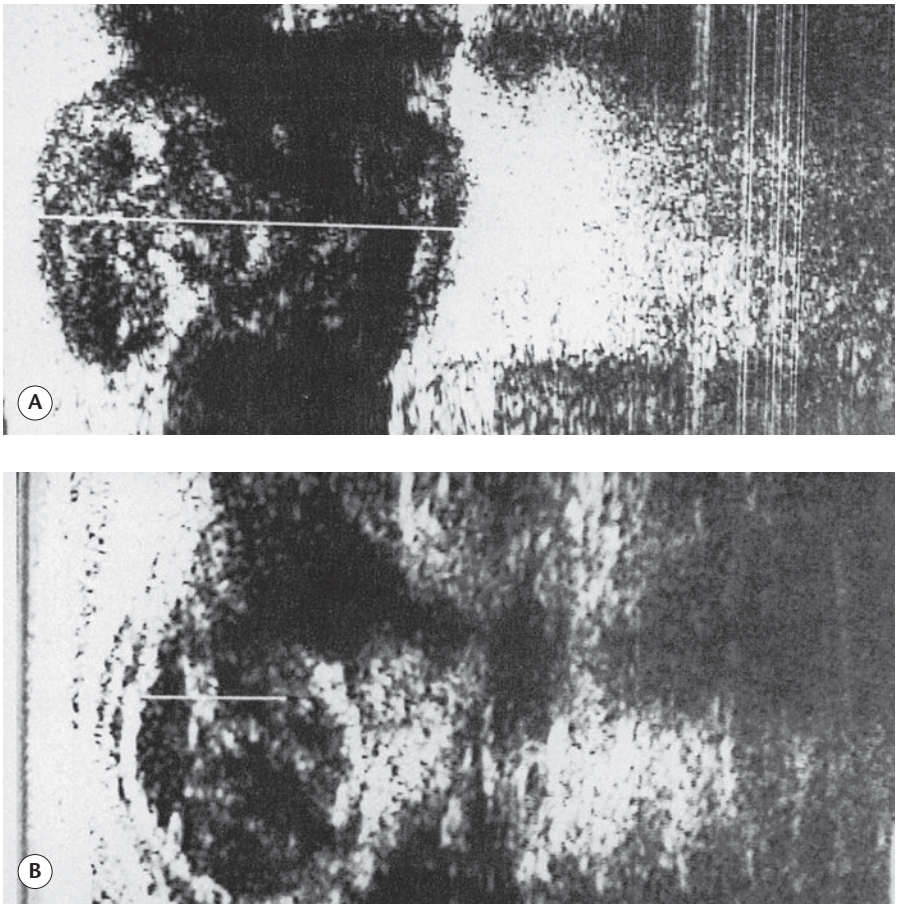


Figure 5.31 Ultrasound can be used to differentiate thrombosis **(A)** from sclerosis **(B).** *Horizontal white line* indicates the diameter of the vessel. (Courtesy P. Raymond-Martimbeau, MD.)

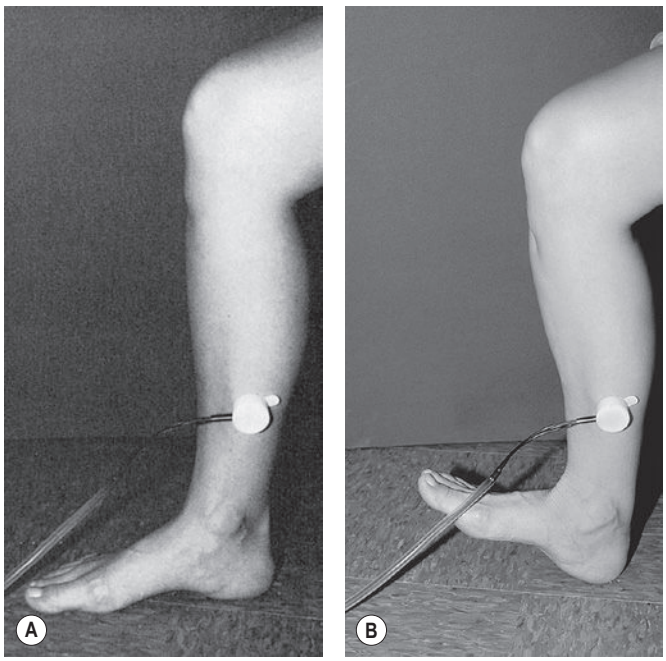


Figure 5.32 **A,** Photoplethysmography measures venous emptying during, and refilling after, exercise of the calf and foot muscles. **B,** Emptying is accomplished with 5 to 10 dorsiflexions of the foot.

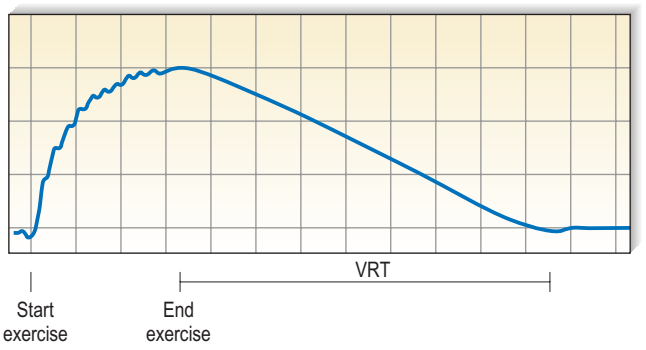


Figure 5.33 Photoplethysmography. Light reflection is enhanced as the calf muscle is exercised and blood is pumped out of the leg. A reduction in light reflection is seen once the leg is allowed to rest. The venous refilling time (VRT) indicates the degree of reflux, although it is not quantitative.

evaluate venous function since 1956,[118] and they have been shown to correlate well with venographic findings[119] and AVP measurements. In one study of 338 paired measurements of PPG and AVP, the correlation coefficient was 0.9.[114] The principle of PPG is quite simple, and the test is easy and quick to perform. An infrared light source and sensor are attached with adhesive to the medial aspect of the lower leg, approximately 10 cm proximal to the medial malleolus. The infrared light is transmitted into the leg to a depth of approximately 0.5 to 1.5 mm within the subdermal venous plexus, where it is absorbed by hemoglobin in red blood cells. Of the light that is not absorbed, a certain amount returns to the sensor. Therefore, the amount of infrared light reflected is inversely proportional to the volume of blood in the skin. Once a baseline level is reached, the patient is asked to actively dorsiflex the foot 5 to 10 times, which activates the calf muscle pump and produces venous outflow (Fig. 5.32). With a reduced volume of blood in the calf and the subdermal plexus, more light is reflected and the tracing shows a gradual deflection; the direction of the deflection depends on the electronics of the particular instrument. At the conclusion of exercise, the patient is asked to relax and the tracing then either returns to the original baseline value or levels off at a new value of light transmission. The time required for this value to be reached, the venous refilling time (VRT), provides information on the presence and degree of reflux of blood through either superficial or deep veins (Fig. 5.33).

Normally, refilling of blood occurs only through the arterial circuit and takes at least 20 to 25 seconds. A value less than 20 seconds indicates the presence of an abnormal refilling channel, namely retrograde flow through incompetent superficial or deep veins. Repeating the test while firmly compressing a particular vein allows the physician to assess the degree of hemodynamic disturbance contributed by that vein. Specifically, if the VRT lengthens from 15 to 35 seconds when a vein is compressed, the examiner can be assured that this vein is contributing significantly to the patient's problem. Similarly, in the setting of both superficial and deep venous incompetence, by compressing the superficial veins, the examiner theoretically can prevent reflux of blood through these veins and observe the effect of the deep venous system alone. If the VRT lengthens significantly when a tourniquet is placed around the thigh to occlude the superficial veins, this implies the dominance of the superficial system in the patient's pathology. If the VRT remains essentially unchanged, the examiner can assume that the deep veins are the primary problem. A word of caution must be mentioned, however, relating to the method of compression of the vein(s). A simple tourniquet, such as that used in phlebotomy, is used frequently and has the advantage of compressing all of the superficial veins, even those that are not suspected of being enlarged and insufficient. However, it is important to be aware that this type of compression may not adequately compress all of the superficial veins, particularly large, thick-walled varicosities.

The need for the awareness just mentioned is especially important in obese patients, but it is also necessary in patients of normal weight. By using a duplex scanner to visualize the flow through the GSV, pressure within a 2.5-cm-wide tourniquet required to prevent reflux through the vein varied between 40 and 300 mmHg in 40 patients studied (G. McMullin, P. Coleridge-Smith, J. Scurr, personal communication, 1990). Therefore, manual compression applied directly to the vein being considered is the preferred method because it allows more reliable interruption of the flow and gives reproducibly accurate results.

VRT has been found to correlate well with AVP measurements, which have long been considered the gold standard in the functional evaluation of venous hemodynamics. VRT may vary between 20 and 65 seconds when AVP is below 40 mmHg, but a VRT less than 15 seconds is found only if the AVP is higher than 40 mmHg.[120] AVP measurements show a linear relationship between their value and the incidence of venous ulceration.[14,121]

PPG may be used to quantify the blood changes within the subdermal plexus, thus quantifying the degree of reflux. This involves performing an in vivo calibration maneuver that allows the examiner to assign a numeric value to the deflections on the tracing.[122,123] The transducer is placed on the leg in its usual location while the patient rests in the

supine position, and the tracing on the recorder is set to a zero baseline. The patient then stands, bearing weight on the opposite leg, and, after the tracing levels off, the gain is adjusted so that the deflection reflects the calculated hydrostatic pressure in the superficial veins, measured by the distance from the right atrium to the site of the transducer on the leg. This maneuver is repeated until the zero baseline and standing levels of subdermal plexus blood content reproducibly reflect the hydrostatic pressures. The decrement in the tracing is then proportional to the degree of fall in AVP, as measured by invasive venous pressure recordings.

Plethysmography has been vigorously defended and advocated by some.[124] However, others have questioned the use of this tool because of its lack of correlation with duplex scanning.[125] The authors of this study stated, 'These results do not warrant the continued use of PPG for surgical decision-making in patients with suspected venous insufficiency'.

Recent studies have demonstrated the efficacy of PPG in evaluating venous hemodynamics.[126,127] A PPG system can be calibrated to quantify the blood volume displacement with leg elevation and/or exercise. In a study of patients with isolated superficial venous disease, digital PPG generated reproducible results.[128] A determination of venomuscular pump efficiency has been demonstrated to quickly gauge the severity of venous disease. The use of PPG may also allow the practitioner to assess the effectiveness of superficial vein treatment.

LIGHT REFLECTION RHEOGRAPHY

Light reflection rheography (LRR), which is basically a form of PPG, was intended to improve on the original PPG system.[129,130] On account of its incorporating three light sources, the infrared light beam can be focused at a standardized depth of penetration (0.3–2.3 mm) to cover the subcutaneous venous plexus. Dermal pigment, such as that commonly found in patients with chronic venous insufficiency, is concentrated in the more superficial layers of the skin and interferes with light transmission, yielding inaccurate and variable values. It was hoped that by focusing its light beam on the deeper tissues, the LRR would not be as affected by the tissues containing the majority of the pigment. This did not prove to be the case, however, and it was felt that calibration of the system might neutralize the effect of variables such as skin thickness, skin pigment and local blood volume on light absorption. This improvement is now available as digital PPG (D-PPG) or calibratable PPG (C-PPG).[120]

The D-PPG contains a computer that permits changes in light intensity from the infrared light source according to the optical properties of the skin. The machine emits a standard light intensity and awaits reflection of the unabsorbed light. If it is below a certain level, the intensity of the emitted light is automatically increased until the intensity of reflected light reaches a level at which the machine can function accurately. This was demonstrated nicely by Kerner et al,[131,132] who recorded essentially the same response to dorsiflexion even after the leg was covered with a dark paint.

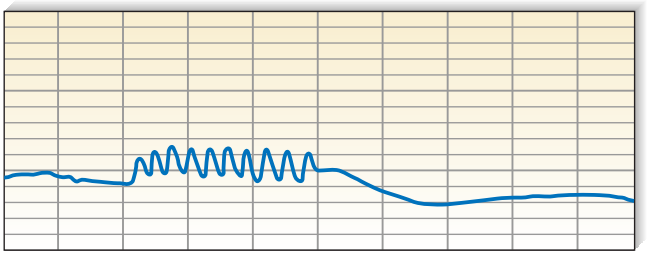


Figure 5.34 A 'picket fence' pattern may indicate deep venous thrombosis but may also be seen with chronic venous insufficiency without thrombosis.

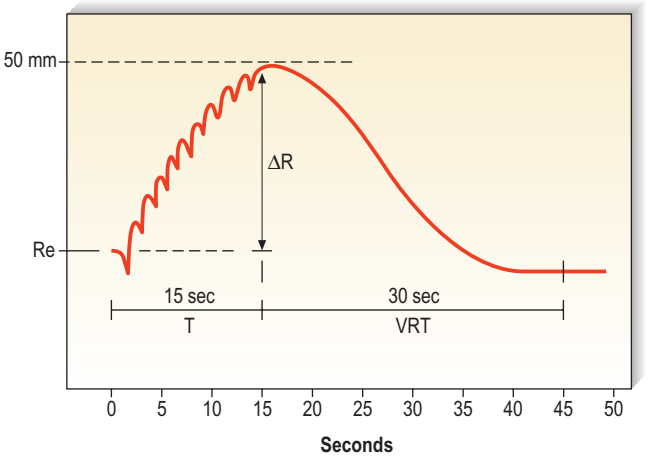


Figure 5.35 Usefulness of photoplethysmography in the diagnosis of deep venous thrombosis (DVT) may be improved by examination of the slope *R/T*; less than 0.31 mm/s predicts the presence of DVT with 96% sensitivity. *R,* Refilling; *T,* time; *VRT,* venous refilling time.

The C-PPG is essentially the same as the D-PPG, except that the changes in light intensity are adjusted manually. This device was tested on healthy subjects and on patients with venous disease. By comparing the time with 90% refilling, or by combining the results obtained during postural changes and dorsiflexion to obtain exercise drainage volume, it was possible to significantly differentiate patients with venous ulcers from those with varicose veins and from the healthy controls.[120] Other parameters that can be calculated include venous filling volume and pump efficiency.

The usefulness of PPG in the assessment of venous valvular insufficiency is undisputed; however, claims that it is accurate in diagnosing DVT are controversial. The general statement that a 'picket fence' pattern (Fig. 5.34) produced by 10 dorsiflexions with essentially no vertical movement off the baseline is diagnostic of DVT is certainly incorrect, because many false positive results are obtained using this criterion. In a study of 30 limbs, the correlation coefficient between venous emptying and AVP was only 0.73.[129] However, in a study performed at the University of Miami (Hemodynamics Inc., personal communication, 1989), the slope of the deflection correlated well with the presence of acute DVT as documented by venography. As shown in Figure 5.35, the finding of a slope (R/T) less than 0.31 mm/second predicts the presence of DVT with 96% sensitivity. Still, LRR alone currently is not considered sufficient to make the diagnosis of DVT, and at least one other noninvasive test is required to confirm the diagnosis.

AIR PLETHYSMOGRAPHY

Air plethysmography (APG) is a technology that is simple to use and potentially supplies a great deal of additional information compared with the conventional PPG.[133] This device consists of a 14-inch-long, tubular, polyvinyl chloride air chamber that surrounds the leg from knee to ankle. This is inflated to 6 mmHg and connected to a pressure transducer, an amplifier and a recorder. A smaller bag placed between the air chamber and the leg is used for calibration by injecting a certain volume of air or water and measuring the change in the recording that is associated with that volume (Fig. 5.36). Parameters assessed include (1) functional venous volume (VV), or the volume in the leg while the patient stands; (2) venous filling time 90 (VFT90), or the time required to achieve 90% of the VV; (3) venous filling index (VFI), or 90% VV/VFT90; (4) ejection volume (EV), or the volume expelled from the leg with one tiptoe motion; (5) residual volume (RV), or the volume at the end of 10 tiptoe motions; and (6) residual volume fraction (RVF), or RV/VV100 (Fig. 5.37).

In a study of 22 patients with superficial venous insufficiency and 9 patients with deep venous disease, VV was found to be elevated in 80% of patients.[134] VFT90 was greater than 70 seconds in normal limbs, 8 to 82 seconds in limbs with superficial venous insufficiency, and 9 to 19 seconds in limbs with deep venous disease. In normal limbs, the VFI was less than 1.7 mL/second, in limbs with superficial venous insufficiency it was 2 to 30 mL/second, and in limbs with deep venous disease the value was 7 to 28 mL/second. Ejection fraction (EF) appeared to show better discrimination than EV. The RVF was 20% in normal legs, 45% in legs with superficial venous insufficiency and 60% in legs with deep venous disease (Fig. 5.38). A linear correlation with $r = 0.83$ was present between RVF and AVP. In a study of 104 patients,[113,135] VFI was found to correlate with the incidence of sequelae of venous disease, such as chronic swelling, skin changes and ulceration (Table 5.5). In a third study of 205 limbs,[133] the same authors found an increasing incidence of ulceration in patients with diminished EF and elevated VFI (Table 5.6) and found that the RVF showed a good correlation ($r = 0.81$) with the incidence of ulceration and AVP measurements. A small study of 92 patients used elevated VFI to predict late recurrence after varicose vein surgery.[137]

The real advantages of this method are its ability to quantify reflux with the VFI and thus determine prognosis and its ability to measure calf muscle pump function through the determination of the EF.[113,134–138] Still, APG measurements should not be used alone. They should be combined with Doppler or duplex findings and clinical evaluation, because a great deal of overlap in values between normal and abnormal occur, decreasing the predictive value of abnormal APG measurements.[139] Neglen and Raju[140] demonstrated quite well in their evaluation of 118 limbs that VFI alone had a positive predictive value of 66% in separating clinical severity class 0 or 1 from class 2 or 3. VFI combined with information gleaned from duplex scanning had a positive predictive value of 83%.

Some have validated the use of APG in clinical practice.[140,141] However, in clinical practice, the use of APG appears to be limited. Part of the problem is the difficulty in testing a large number of patients in a busy clinical setting. Another is the fact that the skin changes of severe

Table 5.5 Venous Filling Index (VFI) and Sequelae of Venous Disease

VFI (mL/s)	Chronic Swelling (%)	Ulceration (%)	Skin Change (with or without Ulcer)
<3	—	—	—
3–5	12	—	19
5–10	46	46	61
>10	76	58	76

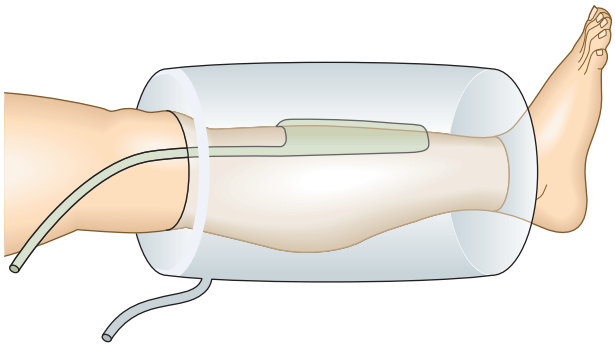


Figure 5.36 The air plethysmograph consists of a long tubular polyvinyl chloride chamber that surrounds the entire leg. This chamber is inflated to 6 mmHg and is connected to a pressure transducer, an amplifier and a recorder. A smaller bag is placed between the air chamber and the leg for calibration. (From Christopoulos DG, Nicolaides AN, Szendro G, et al. J Vasc Surg 1987;5:148.)

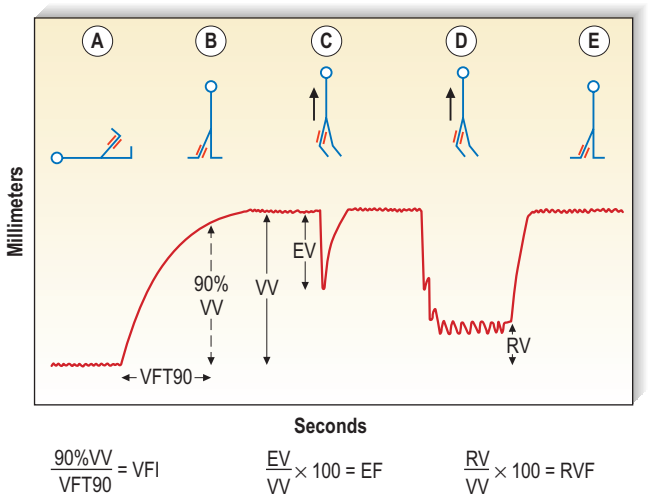


Figure 5.37 Diagrammatic representation of a typical recording of volume changes during a standard sequence of postural changes and exercise using the air plethysmograph. **A,** Patient in supine position with leg elevated 45 degrees. **B,** Patient standing with weight on nonexamined leg. **C,** Single tiptoe movement. **D,** Ten tiptoe movements. **E,** Patient standing with weight on nonexamined leg. *EF,* Ejection fraction; *EV,* ejected volume; *RV,* residual volume; *RVF,* residual volume fraction; *VFI,* venous filling index; *VFT,* venous filling time; *VV,* functional venous volume. (From Christopoulos DG, Nicolaides AN, Szendro G, et al. 1987;5:148.)

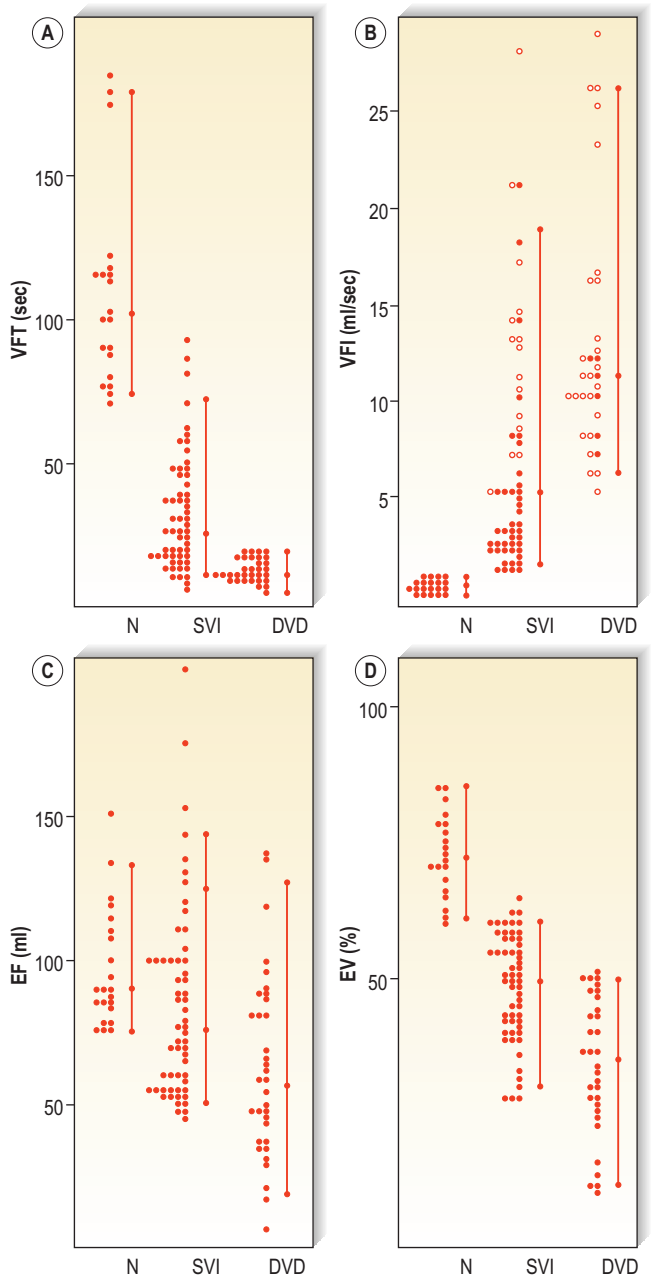


Figure 5.38 Air plethysmography. **A,** Venous filling time 90 (VFT90). **B,** Venous filling index (VFI). **C,** Ejected volume (EV). **D,** Ejection fraction (EF). *DVD,* Limbs with deep venous disease; *N,* normal limbs; *SVI,* limbs with superficial venous incompetence. (From Christopoulos DG, Nicolaides AN, Szendro G, et al. J Vasc Surg 1987;5:148.)

chronic venous insufficiency are caused by many factors, and the data obtained by APG can represent only the hemodynamic factor and not the effects of leukocyte infiltration and activation and leukocyte–endothelium interactions that produce the inflammatory response.[142]

Perhaps the most carefully performed evaluation of the use of APG was accomplished under David Sumner's direction in Springfield, Illinois.[143] In his report, he stated, 'We conclude that plethysmographic measurements of functional venous parameters do not discriminate well between limbs with uncomplicated varicose veins and limbs with ulcers or stasis dermatitis and that the VFI correlates poorly with the presence of incompetent veins and their diameters'. Both duplex scanning and plethysmography seem to be necessary for a complete evaluation of limbs with chronic venous insufficiency.

FOOT VOLUMETRY

Yet another method for evaluation of the functional state of the venous system is foot volumetry.[144–149] Introduced in the early 1970s, this technique has not earned a prominent place in phlebology, probably because of certain logistics of performing the test. However, it is necessary to have an accurate way to measure leg swelling either for evaluation of chronic venous disorders (day-to-day edema measurement) or for calf pump function assessment.[150] The patient stands with the feet in an open, water-filled plethysmograph (Fig. 5.39). The water level is monitored by a photoelectric sensor, and changes in foot volume are continuously measured, first while the patient is standing still, then during the performance of 20 knee bends and again while standing still. The parameters measured include the volume of blood expelled from the foot during exercise, the flow rate after exercise and the time required for half and then full refilling to occur. Norgren et al[147] have shown good correlation between foot volumetry and invasive venous pressure measurements in control subjects ($r = 0.662$) and in patients with varicose veins ($r = 0.760$) but poor correlation in patients with deep venous valvular insufficiency ($r = 0.410$). In their study, venous pressure measurements differed significantly in patients with varicose veins and controls but were similar in patients with primary varicose veins and those with deep venous valvular insufficiency. However, with the use of foot volumetry, there were significant differences between all three groups. Thus, although it is possible that foot volumetry is inaccurate in this important categorization, it is

Table 5.6 Effect of Venous Filling Index (VFI) and Ejection Fraction (EF) on Incidence of Venous Ulceration

	EF >40%			EF <40%			
	Limbs with Ulcers			Limbs with Ulcers			
	Total Limbs	Number	%	Total Limbs	Number	%	*P* Value
VFI <5	41	1	2	19	6	32	<0.01
VFI <10	37	11	30	19	12	63	<0.02
VFI >10	32	13	41	27	19	70	<0.05

From Christopoulos DG, Nicolaides AN, Cook A, et al. Surgery 1989;106:829.
EF, Ejection fraction; VFI, venous filling index.

Table 5.7 Functional Venous Studies

	Photoplethysmography	Foot Volumetry	Air Plethysmography
Ease of use	Easy Hygienic 5-min test	Easy Communal bath 5- to 10-min test	Requires practice by patient Hygienic 5- to 10-min test
Information obtained	Presence of reflux Superficial vs deep Deep venous thrombosis*	Presence and degree of reflux Calf muscle pump function	Presence and degree of reflux Superficial vs deep Calf muscle pump function

*Limited sensitivity and specificity.

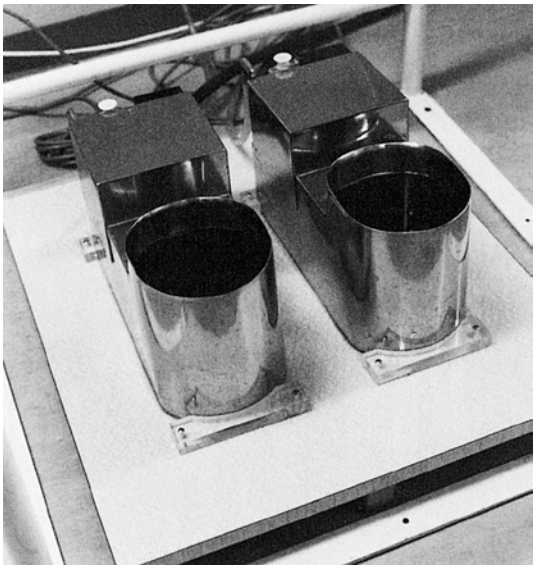


Figure 5.39 The apparatus for foot volumetry consists of an open water-filled plethysmograph that allows continuous measurement of foot volume at rest and during exercise through monitoring of the water level by a photoelectric float sensor. (Courtesy Lars Norgren, MD.)

likely that this technique is more sensitive in distinguishing these groups than are venous pressure measurements.[148] It has been shown that both the volume expelled with exercise and the refilling time increase after treatment of varicose veins.[149] Therefore, this test could be used to evaluate the success of a particular treatment, to follow the effect of different stages in treatment and to monitor the severity of chronic venous insufficiency. It does not, however, allow localization of a particular site of reflux, thus limiting its usefulness for presclerotherapy evaluation compared with other methods (Tables 5.7–5.10, Fig. 5.40).

USE OF NONINVASIVE TECHNIQUES

Each of the previously described techniques has advantages, limitations and uses in specific situations. Prohibitive cost or limited access may preclude the use of the most sensitive and accurate method. The following section discusses a reasonable use of various noninvasive techniques for a variety of situations commonly encountered in the everyday practice of sclerotherapy (Table 5.11).

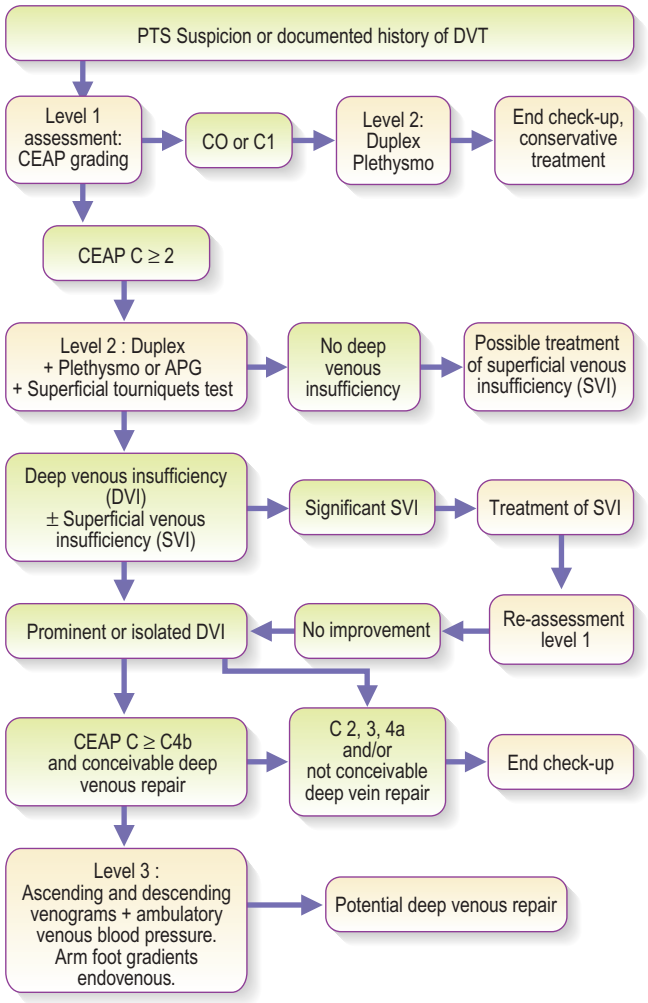


Figure 5.40 Organization chart of venous investigation workup in case of suspicion of postthrombotic syndrome (PTS). (From Perrin M, Gillet JL, Guex JJ. Encycl Méd Chir (Elsevier SAS, Paris, tous droits réservés), Angéiologie 2003;19-2040 [12p].)

Many practitioners have noted changes in the findings of flow and reflux depending on timing within the menstrual cycle, time of day, recent use of compression hosiery and psychological stress of the patient. Clearly, there are enough experimental data to support a physiologic cause for these fluctuations.[151] Therefore, an effort to examine patients in the most physiologic circumstances (e.g., premenstrually, late in the day) may be rewarded by a more revealing study.

Table 5.8 Instrumental Evaluation of Postthrombotic Syndrome—Relevance of Investigations According to Considered Abnormalities

	Venous Anatomy	Venous Reflux	Calf Muscle Pump	Venous Obstruction	Venous Wall Lesions	Drawbacks
Noninvasive						
Continuous-wave Doppler	Nil	Identification errors	Nil	Nil	Nil	Obsolete
Color duplex scan	Excellent	Excellent, indicates duration and situation	Not applicable	Excellent, except iliac veins	Excellent	Nil
Photoplethysmography	Nil	Good but not discriminating	Good	Doubtful	Nil	Nil
Air plethysmography	Nil	Excellent but global	Good	Doubtful	Nil	Not available everywhere
Strain gauge plethysmography and rheoplethysmography	Nil	Nil	Nil	Modest correlation	Nil	Obsolete
Volumetry	Nil	Excellent but global	Good, global	Doubtful	Nil	Not very handy
Invasive						
Ambulatory blood pressure	Nil	Excellent, global	Excellent	Doubtful	Nil	Invasive
Arm–foot pressure gradient	Nil	Nil	Nil	Excellent at femoroiliac level	Nil	Invasive
Ascending venogram	Good, false negatives	Nil	Nil	Good	Good	Invasive
Descending venogram	Good	Excellent	Nil	Good	Good	Invasive, requires femoral venous access
Endovenous ultrasound	Nil	Nil	Nil	Excellent	Excellent	Invasive, not easily available

Table 5.9 Relevance of Investigations According to Considered Abnormalities—Associated Investigations

	Basic	Optional
Level 1	Interrogation, medical history Physical examination, CEAP grading	Continuous-wave Doppler
Level 2	Color duplex scan Photoplethysmography or air plethysmography	Superficial tourniquets test
Level 3	Ascending venogram Descending venogram Ambulatory venous blood pressure Arm–foot pressure gradient	Endovenous ultrasound

CEAP, Clinical manifestations (C), etiology (E), anatomy (A) and underlying pathophysiology.

Ultrasound duplex scanning has gained definitive popularity and is now widely available nearly everywhere. Therefore, duplex scanning is now the preferred tool for initial and most complete assessment of chronic venous disorders. Continuous wave Doppler has been relegated to clinical assessment (like a stethoscope).

EXAMINATION OF DEEP VEINS

Duplex ultrasound is the standard for examination of deep veins of the leg. A reflux duration of at least 0.5 seconds after the release of calf compression identifies valvular insufficiency.[65] Descending venography provides accurate information on the state of the deep venous valves. Although its invasiveness, associated risks and pain make it a much less attractive option for routine use, occasionally descending venography provides information unobtainable with other studies (Fig. 5.41). PPG detects the presence of valvular insufficiency, and compression of the superficial veins (either manually or with a tourniquet) allows differentiation between superficial and deep venous reflux; however, PPG cannot localize reflux to the level within the deep system (e.g., femoral vs popliteal). When both superficial and deep venous reflux are present, PPG will allow determination of the relative importance of each segment. Although ascending venography was once considered the gold standard for the diagnosis of acute or chronic deep venous obstructive disease, most institutions now use B-mode ultrasound or color duplex scanning in everyday clinical practice. Magnetic resonance venography may find a place in the diagnostic armamentarium as well, because it has been found to be as accurate as duplex scanning in the diagnosis of DVT.[152]

Descending venography detects deep venous valvular reflux, but, again, the duplex scanner offers the additional

Table 5.10 Relevance of Investigations According to Considered Abnormalities—Critical Values

	Measure	Critical Value	Significance
Color duplex scan	Reflux duration	Less than 0.5–1 s	Normal valve closure time
	Psathakis venous reflux index	Less than 0.40	No reflux
Photoplethysmography	Venous refilling time after exercise (VRT)	More than 20 s	Normal venous function
Air plethysmography	Venous filling index	?	
	90% VRT	More than 20 s	Normal venous function
Ambulatory venous blood pressure	Maximum	More than 40 mmHg	Associated with grades C5 and C6
	VRT	More than 20 s	Normal venous function
Arm–foot pressure gradient	At rest	Less than 4 mmHg	No obstruction
	Hyperemia	Less than 6 mmHg	No obstruction

Table 5.11 Preferred Methods of Evaluation

	Preferred Method	Pitfalls	Additional Methods
Deep veins	Doppler ultrasound	Differentiation SFJ vs CFV, SPJ vs popliteal vein	PPG/LRR Venography Duplex
Saphenous trunks	Doppler ultrasound	Same as above	Percussion Trendelenburg Venography Duplex
Tributaries of saphenous trunks	Doppler ultrasound		Percussion Duplex
Perforating veins	Clinical examination + Doppler	50–80% accurate	Venography Duplex Thermography Fluorescein
Contribution of superficial vs deep reflux	PPG/LRR		AVP Duplex velocities
Functional evaluation	PPG/LRR		AVP Foot volumetry
Vulvar varices	Clinical examination for SSV reflux		Varicography

AVP, Ambulatory venous pressure; CFV, common femoral vein; LRR, light reflection rheography; PPG, photoplethysmography; SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; SSV, small saphenous vein.

advantage of quantifying the reflux by determining flow velocities. The finding of deep venous valvular insufficiency is worrisome because it may be associated with chronic venous obstructive disease, which may give rise to venous claudication[48–50] in a small number of patients who rely on their dilated superficial channels for venous return. This has been determined using strain gauge plethysmography[153,154] and most likely may be assessed with PPG as well. Impairment of VRT with the tourniquet might caution the examiner to avoid treatment. Alternatively, the simplest and most practical test is to place a 30- to 40-mmHg compression stocking on the patient for 24 hours. The development of pain while walking contraindicates sclerotherapy and suggests the need for a venous bypass procedure. Using APG, Spence et al[155] found that compression therapy in patients with venous claudication caused a deterioration in the EF and/or AVP as measured by RVF. Noninvasive tests do not provide sufficient sensitivity if there is genuine concern about venous claudication. The examiner must proceed with invasive pressure measurements, such as the arm–foot vein pressure differential or the foot vein pressure elevation after reactive hyperemia, as described by Shami et al.[16] Deep venous valvular insufficiency has also been found to reduce the likelihood of successful long-term sclerosis of the main saphenous trunk.[70]

EXAMINATION OF SAPHENOUS VEIN TRUNKS

Duplex ultrasound is now the standard for examination of saphenous vein trunks. Historically, Thomas and Bowles[156] found that Doppler ultrasound grossly overdiagnosed incompetence compared with venography, and they recommended that all GSVs be examined with venography before ligation and stripping. One reason for this is the fact that Doppler examination is 'blind'; thus, dilated tributaries of the saphenous vein or pelvic varicosities may be mistaken easily for the GSV. This was addressed in two early studies that compared the results of continuous-wave Doppler examination with those obtained with duplex scanning.[72,73] The researchers found that in the examination of the GSV, Doppler was no better than 77% sensitive and 83% specific compared with the duplex scan. In a later study using

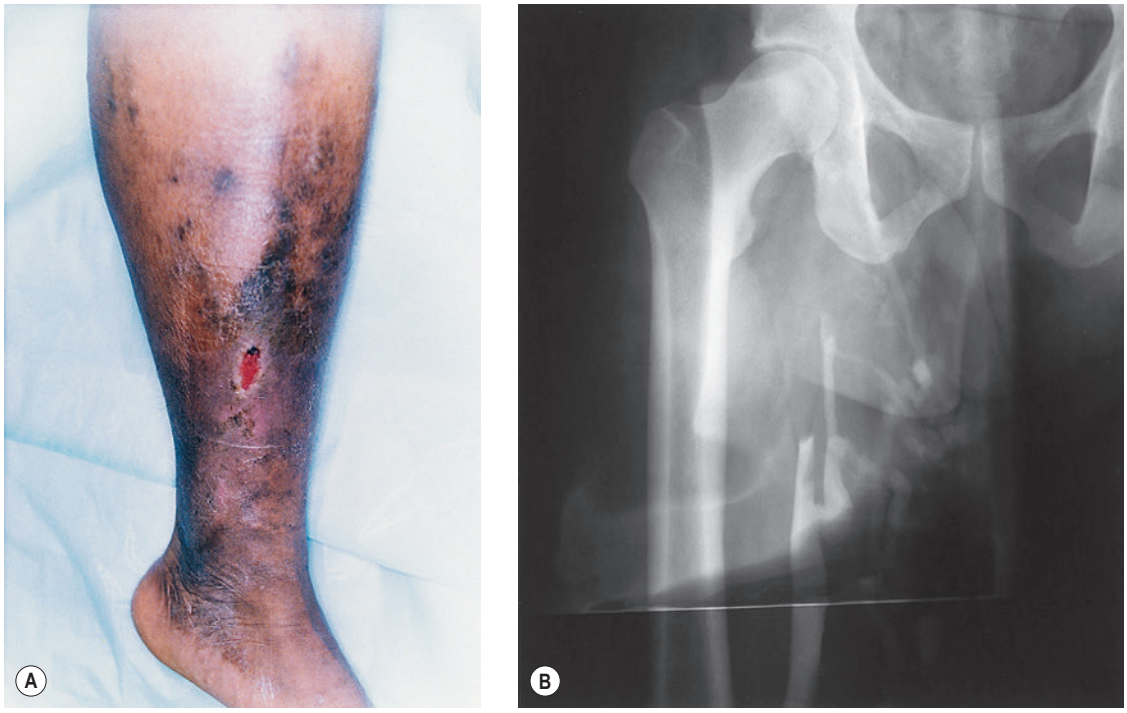


Figure 5.41 **A,** This 36-year-old man with recurrent venous ulcers was noted to have numerous large varices in the anteromedial thigh. A duplex scan was complicated because of the large number of veins. **B,** Descending venography successfully shows an absent or occluded segment of the common femoral and superficial femoral veins with a large number of collateral veins around the obstruction.

duplex scanners with even greater sensitivities, DePalma et al[157] found a sensitivity of 48%, specificity of 83%, positive predictive value of 83% and negative predictive value of 44% in the determination of GSV reflux. By obtaining duplex scans preoperatively, 10 of 80 limbs were spared GSV stripping.

Doppler examination of the junction of the saphenous trunks with the deep veins (SFJ and SPJ), and the distinction between reflux through these junctions versus reflux through the deep veins themselves, is often difficult and a common source of error. In fact, in studies using Doppler ultrasound, researchers have quoted an incidence of deep venous valvular reflux from 5% to 30% (M. Schadeck, personal communication, September 1989),[34,70] a range that is most likely partially determined by the difficulty of the examination and not solely by differences between the populations examined.

The distinction between junctional and actual deep venous reflux is important for several reasons. First, Schultz-Ehrenburg[34,70] found that patients with deep venous valvular incompetence fared far better with a surgical approach to their disease than with treatment that was limited to sclerotherapy. Thus, the accuracy of this portion of the examination has important implications for treatment. In addition, patients with deep venous valvular insufficiency should be questioned regarding a history of iliofemoral thrombosis and possible chronic venous obstructive disease, which might contraindicate treatment of their GSV. Finally, it is possible to have only deep venous valvular insufficiency with a normally functioning saphenous vein. Thus, without this differentiation, a patient may be sent for treatment of a normal superficial vein.

The technique of examination is quite simple. The Doppler probe may be placed over the site of the SFJ or over the femoral vein with the patient standing or supine, and the patient is asked to perform the Valsalva maneuver. The procedure is then repeated with the GSV firmly compressed below the Doppler probe. If reflux still can be heard after compression is applied, the examiner assumes that the reflux is in the femoral vein. In contrast, if the reflux is obliterated with this maneuver, the retrograde flow is only through the SFJ and not through the femoral vein itself.

EXAMINATION OF TRIBUTARIES OF THE SAPHENOUS TRUNKS

Duplex ultrasound is now the standard for examination of tributaries of saphenous vein trunks. The examination of the tributaries of the saphenous trunks focuses on two major questions: (1) To which saphenous trunk does the tributary belong? and (2) Is there reflux of blood from the deep vein directly into the tributary? Both answers may be obtained by either physical examination maneuvers with the Doppler or, most definitively, with duplex ultrasound. The origin of any tributary may be assessed with the percussion test, in which the palpating hand is placed gently over the tributary while the GSV or SSV is percussed with the other hand (or vice versa). The palpation of an impulse with percussion of a particular trunk localizes the origin of the tributary to that trunk. Alternatively, a modified Trendelenburg test supplies this information. The patient is asked to lie down with the leg elevated to nearly 90 degrees. The proximal GSV or SSV is then firmly compressed, and the patient is asked to stand. If the varicose tributary remains empty and fills only when the compression is released from the GSV, the origin of the tributary is localized to that system. The presence of reflux from the deep system may then be discovered by using the

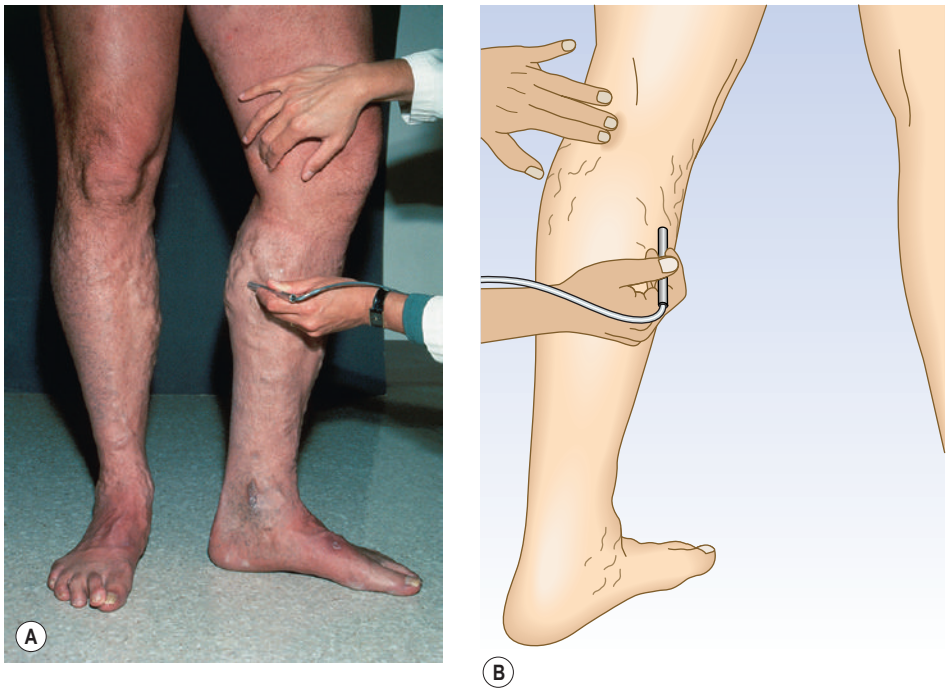


Figure 5.42 The origin of a particular varicosity may be defined by listening over the dilated vein while alternately compressing the great saphenous vein **(A)** and small saphenous vein trunks **(B)**.

cough test, in which the palpation of an impulse over the tributary when the patient coughs implies reflux of blood from the deep system through incompetent valves into the tributary.

As mentioned previously, although the Trendelenburg test is reasonably accurate, the cough and percussion tests are now considered confirmatory because the Doppler provides a more accurate answer to these questions. Placement of the Doppler probe over the tributary while intermittently compressing or percussing either the GSV or SSV allows determination of the origin of the tributary (Fig. 5.42). Listening for reflux while the patient coughs or performs the Valsalva maneuver uncovers connections to the deep system (because there should be no reflux unless there is a pathway directly to the deep vein that is unobstructed by incompetent valves). The applicability of the first piece of information is obvious. Careful evaluation must then be directed to that particular incompetent saphenous trunk to achieve sclerosis of the tributary as well. However, the connection of the tributary to the deep system must be explored further because the exact route that the blood has taken from the deep to the superficial system must be defined. On one hand, if the connection is simply through the SFJ or SPJ, again the treatment directive is apparent. On the other hand, if the connection is actually through a perforating vein or another tributary,[70] treatment must be aimed at that particular vein and, perhaps, treatment of the saphenous trunk may be unnecessary. Manual occlusion of the involved saphenous trunk at its proximal end, followed by repeat examination, offers this important differentiation. If, on one hand, this occlusion causes the obliteration of reflux with the cough or Valsalva maneuver, then the blood must have flowed through the SFJ or SPJ. If, on the other hand, this maneuver does not change the result of the test, then the saphenous trunk is an important conduit and the perforating vein must be the important route.

The importance of duplex scanning in patients with varicose disease has been verified by studies in which clinical examination, duplex ultrasound and plethysmography have been compared.[158] These studies have revealed that quantitative plethysmography was not particularly helpful, owing to its nonspecificity. The duplex scan, however, was able to identify patients without SFJ reflux and could ascribe varicosities to tributary incompetence. Such incompetence would be the target for sclerotherapy or isolated ambulatory phlebectomy.

EXAMINATION OF PERFORATING VEINS

The perforator segment of the venous system is probably the most mysterious because of its variability, the difficulty of locating perforators even under direct visualization in the operating room, and the overwhelming importance ascribed to perforating veins in the development of varicose veins and the skin changes associated with chronic venous insufficiency.[159] It is no wonder, therefore, that no consensus exists about what constitutes the best method for examination of perforating veins and their valvular competence. Nearly every technique, including venography, Doppler, duplex, thermography, fluorescein injection and physical examination of fascial defects, has been used, with varying degrees of success. Complicating the evaluation of each method is the fact that all are compared with subsequent surgical findings, which likely also miss many IPVs and are impossible to standardize. Underscoring the current difficulties in this aspect of venous diagnosis are data that show that the number of IPVs detected per limb in studies of the various diagnostic methods ranges from 1 to 4, whereas anatomic studies have shown a range of 1 to 14, with an average of 7.[38] Thus, it is still impossible to test the exact sensitivity and accuracy of each method. At best, the

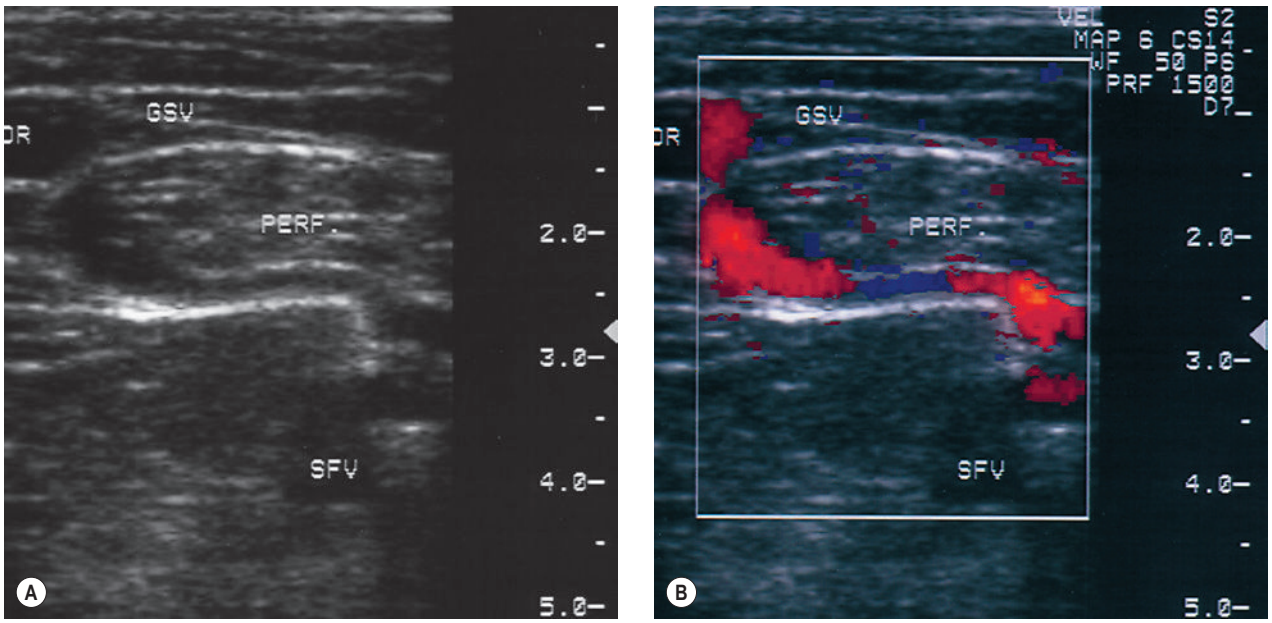


Figure 5.43 Incompetent perforating veins can usually be discerned with duplex scanning. **A,** Grayscale longitudinal scan. **B,** Color image showing reflux. *GSV,* Great saphenous vein; *PERF,* perforating vein; *SFV,* superficial femoral vein.

examiner may miss a great deal of important pathology. In spite of the pitfalls and limitations of current diagnostic methods, examination for IPVs is crucial and usually productive. As mentioned previously, in a study of 901 limbs with varicose veins, 90% were found to have incompetent perforators.[38] Of interest, only 9% of the perforators were found in the thigh. Thigh perforators may be single or multiple and may occur anywhere from just proximal to the patella to just below the SFJ, with most being single and located in the middle third of the thigh.[160] In evaluating patients with IPVs in the lower leg, Dodd[161] found that 45% were associated with incompetence of the GSV, 15% with incompetence of the SSV and 2% with an IPV in Hunter's canal. Therefore, any patient with significant truncal varicosities, as well as those with signs of chronic venous insufficiency, should undergo evaluation for perforator valvular insufficiency.

Historically, the most important and probably the most commonly used technique for detection of outward flow through perforating veins was that of clinical examination. With its ability to detect 50% to 70% of IPVs, clinical examination should be the first step in the evaluation. Other techniques have been studied extensively, such as thermography,[42,45,162,163] fluorescein injection[164,165] and ascending[42,43,164] and intraosseus[45] venography, generally demonstrating accuracies between 60% and 90%. Unfortunately, the required instrumentation makes these techniques impractical for most practitioners. The techniques can be used, however, when perforator disease is strongly suspected but has escaped localization by other methods.

Ultrasound technology can be helpful and is associated with greater ease and lower risks than the other methods. Probably the most effective method of locating perforator veins is to inject a low concentration of foamed detergent sclerosant and follow its flow into perforating veins. Doppler evaluation of perforator incompetence provides a diagnostic accuracy of 60% to 90%[43,86,88,165] and significantly improves with experience. In one study of 39 legs,[43] its accuracy improved from 60% to 87% when it was paired with clinical examination, thus making this combination of techniques well suited for routine clinical practice. Duplex scans are extremely useful in visualizing the site(s) of IPVs (Fig. 5.43) and may be considered if the examiner is otherwise unable to localize a vein in a suspected area and has the necessary equipment.

The clinical significance of outward flow through perforating veins has long been debated, and the physiologic to-and-fro movement of blood through perforating veins in normal feet is well accepted. Thus, the finding by Sarin et al[166] that the direction of blood flow within medial calf perforators can be either inward or outward in legs without venous disease is quite interesting. They observed outward blood flow in 21% of medial calf perforators in normal limbs during compression of the foot with a cuff inflated to 60 mmHg. However, during the relaxation phase (distal cuff deflation), flow occurred in 33% to 44% of perforators in limbs with venous disease but in none of the perforators in limbs without venous disease. Thus, this criterion may allow the first true differentiation of pathologic flow within perforating veins.

DIFFERENTIATION OF THE RELATIVE CONTRIBUTION OF DEEP AND SUPERFICIAL REFLUX

PPG, with and without compression, is especially useful in the setting of both deep and superficial venous disease. It is also simple and inexpensive to use. If the Doppler examination has disclosed that both the superficial (GSV or SSV) and deep veins (CFV or popliteal) are incompetent, this test can help to determine the relative importance of each segment of the venous system and whether correction of the superficial problem offers the patient sufficient benefit

(given the persistent deep vein reflux) to be worth the potential risks of treatment. This is exemplified by the case of a 40-year-old woman with congenital absence of valves within her femoral veins and a history of bilateral leg edema, lymphedema and, more recently, progressive enlargement of varicosities of her main long saphenous trunks. Although it was believed that her main problem was a deep venous defect, the application of this relatively simple examination scheme allowed a more precise understanding of her condition. By manual compression of the patient's GSV, her initial refilling time of 8 seconds lengthened to 19 seconds, indicating a significant contribution by her superficial system to her pathologic hemodynamics. In further testing of these findings, a duplex scan was performed, showing that the peak velocity of reflux flow through the GSV was greater than 33 cm/second, whereas that through her CFV was only 9.5 cm/second. The patient underwent high ligation and division of her GSV as well as postoperative sclerotherapy. Marked improvement in the discomfort and edema in her legs resulted, and she was able to reduce the use of her Lympha Press (Lympha Press, Freehold, NJ) and periodically able to wear hose with less compression without the disabling aching in her legs that she had experienced previously. Other examples of the usefulness of the PPG are illustrated in Case Study 1.

CASE STUDY 1

J.S., a 59-year-old woman, sought treatment for dilated veins in her left calf. These connected with a minimally enlarged GSV in her thigh, and reflux was heard with the Doppler through her SFJ, whereas her deep veins all displayed valvular competence. The refilling time with PPG was found to be 15 seconds and lengthened to 25 seconds with obstruction of her GSV, thus indicating that obliteration of the flow through her SFJ would provide significantly improved hemodynamics.

R.S., on the other hand, a 72-year-old woman with a similar picture of dilated veins only in her right calf, had a different etiology. The Doppler examination revealed reflux through her SFJ and normal deep venous valvular function as well. However, her refilling time of 15 seconds did not improve with obstruction of her GSV, thus implicating her perforating veins as the origin of the problem. By further varying the location at which the GSV was obstructed, the exact location of the responsible perforator was found. If obstruction of the GSV just above the knee results in improvement in the refilling time, the mid-thigh (Hunterian) perforator must be involved. If the refilling time is not improved until the GSV is obstructed just below the knee, the geniculate perforator must be responsible. If this fails to improve the refilling time, the Boyd or Cockett perforators may be implicated.

As mentioned previously, the method of compression of the superficial vein(s) is of extreme importance because the examiner must ensure that adequate pressure is achieved to prevent flow through the vein. When the examiner attempts to compress a particular vein, manual pressure directly over the vein is probably most effective. On the other hand, when there are multiple veins, placement of a tourniquet might be a more appropriate method.

EVALUATION OF THE ORIGIN OF RECURRENCES AFTER LIGATION AND STRIPPING

Duplex ultrasound is considered to be the best method to evaluate recurrences after ligation and stripping. There are several noninvasive or minimally invasive methods that provide information helpful to understanding the remaining connections and therefore the necessary sites of treatment. Lofgren,[24] in his study of 510 operations performed on patients with recurrence after ligation and stripping, found most of the recurrences to be the result of inadequate surgery; the most common findings were either treatment of a dilated tributary with the actual saphenous trunk left untouched or ligation distal to the SFJ/SPJ.

Lofgren felt strongly that all patients with recurrence should be explored surgically, thus obviating the need for an imaging procedure. Because many of these patients will be found to have problems amenable to sclerotherapy alone, this is not a very satisfactory approach, and the physician first should attempt to define the anatomy of the recurrence before proceeding with treatment decisions.

The approach to the kind of patient just mentioned begins in the same way as the approach to any patient with involvement of the saphenous trunk. The palpation of the GSV or SSV is attempted, followed by the Doppler examination for reflux. It is always possible that the dilated vein noticed by the patient may simply be, in fact, a collateral vein that is functioning normally and does not need to be treated. Once reflux through the vein has been documented, a Valsalva maneuver will demonstrate whether this vein is still in connection with the deep venous system. If not, sclerotherapy generally may be used successfully. If reflux is heard with a Valsalva maneuver, the patient may then be approached as if he or she were presenting de novo with SFJ or SPJ reflux. Historically, venography has been used in this situation and provides a good image of the exact connection of the recurrent varix. However, duplex scanning provides excellent images without the associated risks of the contrast media and radiation, and it has been recognized as the gold standard for evaluation of recurrences.[167]

EVALUATION OF VULVAR VARICES

Vulvar varices generally arise from the pudendal or iliac veins and require treatment only of the varices themselves. In some cases, however, they connect directly with the long saphenous system. Therefore, before treatment, the presence of an incompetent SFJ should be sought because long-term control of these varices requires control of the SFJ if blood is refluxing through it into the vulvar veins. The technique for this determination has been described previously. The exact connection may also be determined by varicography (Fig. 5.44). Because the association between pelvic varices (often complicated by pelvic congestion syndrome) and inguinal varices is common, a retrograde selective catheterism and venogram of pelvic veins will frequently help to solve both problems at the same time by means of specific endovenous treatment (association of coils and foam sclerotherapy).[168–170]

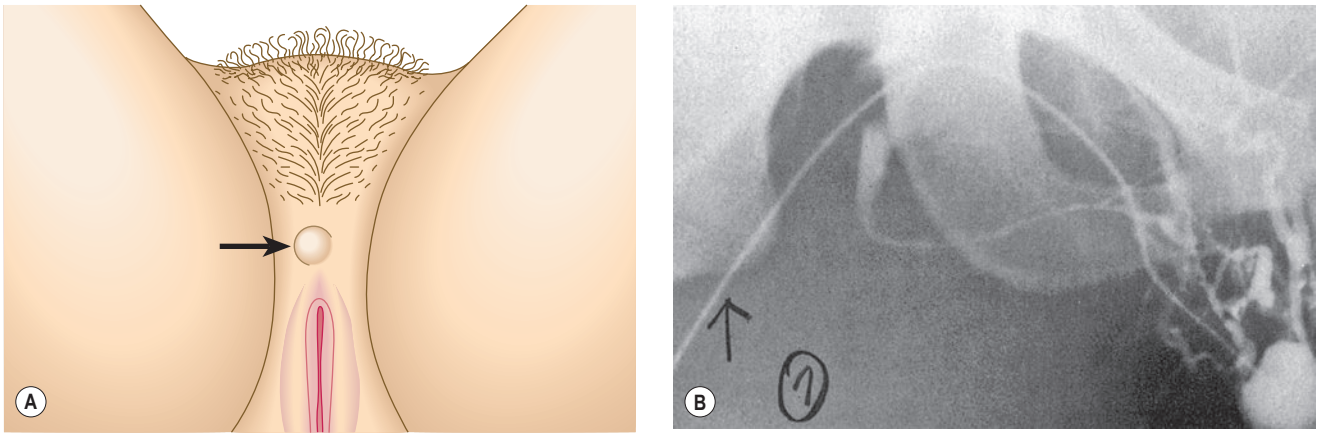


Figure 5.44 **A,** Vulvar varix *(arrow).* **B,** Varicography may be used to define its origin. (Courtesy Jeffrey Weisfeld, DO.)

INVASIVE DIAGNOSTIC TECHNIQUES

VENOGRAPHY

The most significant disadvantages of venography are its invasiveness, the frequent development of superficial phlebitis as a result of the procedure, and a 5% to 10% incidence of allergy to the contrast medium. The latter complications have been significantly reduced through the introduction of newer nonionic contrast media,[20] and venography continues to find some use in the diagnosis and treatment planning of venous disease. It also has great use in the evaluation of groin and pelvic recurrences, including vulvar varicosities.[171] Four techniques have been described: ascending venography, descending venography, intraosseous venography and varicography.

A variation of venography involving the injection of fluorescein into a vein on the dorsum of the foot has been used for the localization of incompetent ankle perforating veins.[172] This test is performed by placing a 2.5-cm cuff, inflated to 80 mmHg, just above the malleoli. The leg is elevated to 90 degrees, and the patient is asked to plantarflex the foot 10 times. A second 13-cm cuff is then inflated to 120 mmHg just above the knee, and the leg is lowered. Five milliliters of aqueous fluorescein is then injected into the distal portion of the foot, and an ultraviolet light is directed toward the leg in the darkened room. A second set of 10 plantar flexions is performed, drawing the solution into the deep veins and outward through any incompetent perforators. This is reflected on the skin surface as a circle of yellow–green fluorescence, 1 to 2 cm in diameter, within 30 seconds to 2 minutes. In 37 legs studied, this method had a 96% accuracy, identifying 50 of the 52 perforating veins later found to be incompetent at surgery, with 2 false negatives and 4 false positives.

ASCENDING VENOGRAPHY

Ascending venography[20] is performed by injecting the contrast medium into a superficial vein on the dorsum of the foot after a 2.5-cm tourniquet has been placed around the ankle to prevent flow through the superficial venous system. This forces the contrast to enter only the deep veins and allows clearer visualization of the deep system. Fluoroscopic imaging with the patient in various positions allows the deep veins, from the foot to the lower segment of the inferior vena cava, to be examined for the presence of thrombi (Fig. 5.45A). Passage of the contrast into the perforating veins is abnormal and diagnostic of valvular insufficiency (Fig. 5.45B).[44] The addition of a Valsalva maneuver shows competent venous valves and defines bicuspid structures with a concentration of contrast media in their sinuses, and it might obviate the need for descending venography if this procedure were to be considered later. Ascending functional venography requires the patient to plantarflex the foot, thus forcing the contrast into the superficial veins through any IPVs during muscle relaxation.[13]

DESCENDING VENOGRAPHY

Descending venography involves injection of the contrast into the femoral or the popliteal vein with the patient lying supine or in head-up tilt and performing a Valsalva maneuver. Valvular insufficiency is readily demonstrated because the contrast flows rapidly in a retrograde direction. Five grades of reflux have been described (Fig. 5.46).[68,173] One of the disadvantages of this technique is that the demonstration of reflux at a given level relies on the presence of reflux at the higher levels. Therefore, using descending venography alone, the examiner might miss isolated incompetence of tibial veins or gastrocnemius veins, both of which have been shown to be responsible for the production of significant symptoms (see Chapters 3 and 4).[174,175]

Dynamic popliteal phlebography[176] had been the latest and a successful attempt to improve phlebography, especially for analyzing deep venous function and structure. It has been rendered obsolete, however, by ultrasound duplex scanning.

INTRAOSSEOUS VENOGRAPHY

Intraosseus venography is simply a variation of ascending venography in which the contrast is injected into bone rather than directly into a vein, with rapid distribution throughout the deep venous system. This technique may be significantly easier to perform in patients with edema[177] and may be especially helpful in diagnosing IPVs[44]; yet, it has not been found to have significant use recently.

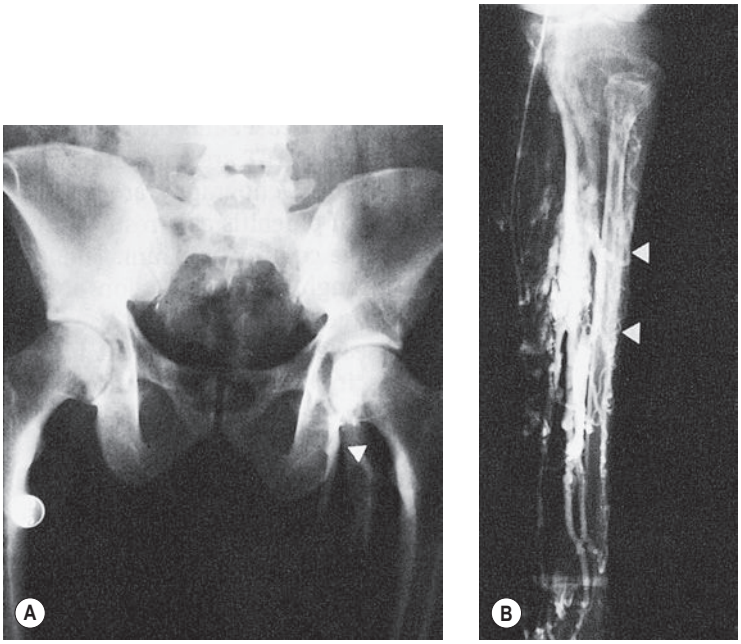


Figure 5.45 Ascending venography. **A,** A thrombus as a space-filling defect *(arrowhead).* **B,** Incompetent perforating vein *(arrowheads).*

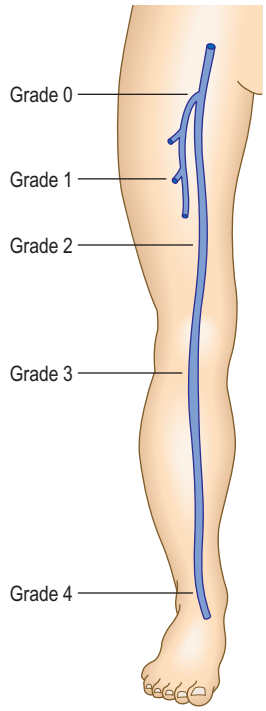


Figure 5.46 Descending venography may demonstrate five grades of reflux: grade 0, no reflux below the confluence of the superficial and profunda femoris veins; grade 1, reflux into the superficial femoral vein but not below the middle of the thigh; grade 2, reflux into the superficial femoral vein but not through the popliteal vein; grade 3, reflux to just below the knee; grade 4, reflux to the ankle level.

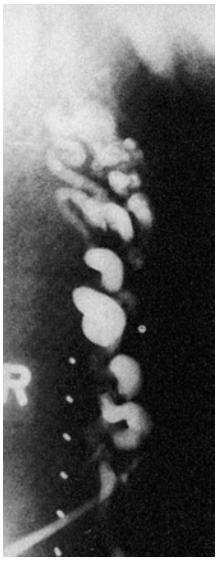


Figure 5.47 Varicography. Injection directly into the varix may demonstrate the origin of a recurrence in the groin after vein stripping. (From Lea Thomas M, Mahraj RPM. Phlebology 1988;3:155.)

VARICOGRAPHY

Varicography (Fig. 5.47) is a very helpful technique in which the contrast agent is injected directly into the dilated varix, showing the extent of the varicosities and their connection with other superficial, perforating and deep veins.[20,171,178,179] The direction of blood flow, and therefore the competence of valves, is not discernible, although other criteria have been found to correlate with valvular insufficiency. For instance, if a perforator is greater than 3 mm in diameter and is seen to be tortuous, it is assumed to be incompetent.[20] When other methods, such as duplex scanning, fail to demonstrate the proximal connections of a varicosity (because of obesity of the patient, masses of varicosities in the area, and so forth), varicography provides a relatively simple way of showing this anatomy clearly (Fig. 5.48).

THERMOGRAPHY

Infrared thermography is based on the fact that infrared waves radiate from the skin surface in proportion to the

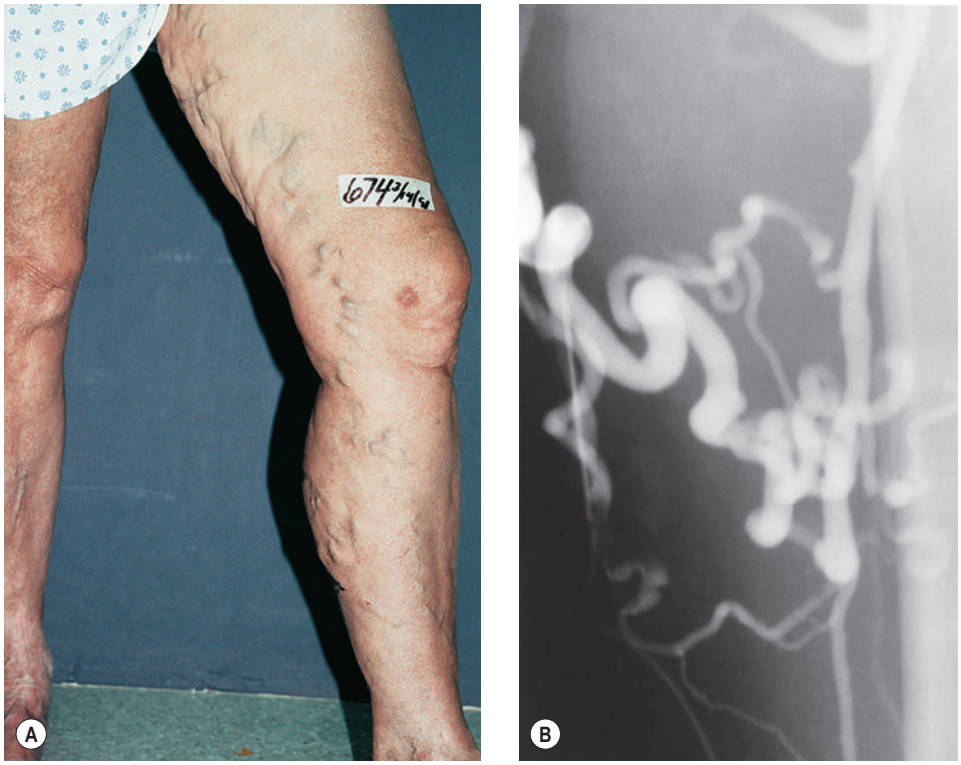


Figure 5.48 **A,** This patient presented with a recurrent varicosity 25 years after great saphenous vein (GSV) stripping. Duplex ultrasound showed no reflux at the level of the saphenofemoral junction and no evidence of a GSV but was unable to demonstrate the connection of the varicosity to the deep venous system. **B,** Varicography clearly showed the proximal site of connection as well as sites of additional incompetent perforating veins.

temperature of that surface.[180,181] It is possible to scan the surface with an infrared detector and create an image in which gradations of white and black or color reflect degrees of heat. Two identical symmetric skin areas of the body should be at the same temperature unless certain factors are present. These factors include structural abnormalities of vessels (dilation and incompetence), abnormalities of vascular control, local effects on vessels, changes in thermal conductivity of the tissues and increased heat production of the tissues. If veins are dilated, as with varicose veins or an underlying arteriovenous communication, the overlying skin is warmer because of the accumulation of the extra blood volume in the dilated vein. Similarly, when venous valves are incompetent, the reflux of blood from the more central CFV down the GSV (when the limb is lowered), or outward from the warmer deep veins through a perforating vein when the calf muscle is activated, produces a rise in skin temperature; this may be visualized on the thermograph as a white, or 'hot', spot (Fig. 5.49). In fact, this technique may be used to localize the site of an IPV (see Chapter 3).[45] After the general distribution of thermal patterns is recorded in the standing position, the leg is elevated for 1 minute to drain the veins and the leg temperature is lowered with a cold, wet towel or a fan for 5 minutes. A tourniquet is placed around the proximal thigh to occlude the superficial veins, and the patient is asked to stand. Areas of rapid rewarming suggest possible sites of IPVs. These areas are re-examined after tourniquets are placed above and below each site. The segment in question is again cooled, and the appearance of a hot area within 60 seconds of standing (in the case of a thigh perforator) or of calf muscle action (in the case of a lower leg perforator) identifies the site of an incompetent perforator. Of 84 IPVs later found at operation, thermography correctly identified 79 (94%). The five that were missed by thermography were found at surgery to be very small in diameter or in close

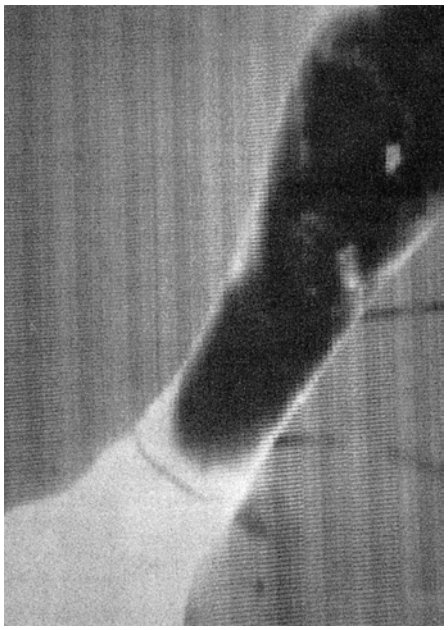


Figure 5.49 Positive thermograph. The presence of an incompetent perforating vein may be indicated by a 'hot' spot. (Courtesy K. Lloyd Williams, MD, CHIR, FRCS.)

proximity to a larger incompetent perforator that was correctly identified. Of the 12 false positives, 4 were caused by inadequate surgical exploration of the area and the others were the result of heat changes from communicating sites of superficial veins or from the penetration of the GSV into the deep fascia of the thigh. The relationship of arteriovenous fistulas to varicose veins remains controversial, and thermography has been validated as a technique for identifying arteriovenous fistulas when they are present.[182]

FUTURE EVALUATION TECHNIQUES

Studies continue for objective noninvasive quantification of superficial varicose veins using infrared photography. Photographs taken through a 700-nm lens filter allow visualization of blood-containing vessels 2.5 mm below the skin.[183] When analyzed in a computer grid, this technique may allow for a reproducible evaluation of veins before and after treatment, as well as validate C1 and C2 classification.

Infrared imaging of subcutaneous veins as an aid in performing surgical or injection therapy is also being investigated. An infrared device comprising a head-mounted infrared light-emitting diode array (880 nm) has been developed.[184] This device provides good contrast of subcutaneous veins 0.5 to 2 mm in diameter at a depth of 1 to 3 mm.

NEAR-INFRARED IMAGING

Infrared imaging can be used to visualize superficial reticular veins. Bustos et al[185] showed that this could be performed with the use of either a red light source close to 700 nm or an infrared night-day vision camera system (Vision Viewer Gen3; Night Vision Experts, Buffalo, NY). Both of these systems allow the operator to visualize veins 2 to 3 mm in depth. A more elaborate infrared imaging device, the Luminetx VeinViewer (Luminetx Corp., Memphis, TN), was used by Miyake et al[186] and found to be useful in treating reticular veins. A study of 23 subjects with varicose veins and telangiectasia demonstrated that 100% had feeder veins that could be detected using the VeinViewer. These visualization techniques may be useful in allowing more efficient treatment of superficial veins. Near-infrared fluorescence venography using indocyanine green has also been demonstrated to be helpful in visualizing superficial veins before ambulatory phlebectomy.[187] Ishikawa et al[188] described the use of a near-infrared fluorescence camera device (Photodynamic Eye; Hamamatsu Phototonics K.K.; Shizuoka, Japan) to visualize real-time spread of sclerosant in venous malformations of the lower extremity, upper extremity and face during percutaneous sclerotherapy.

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6 Use of Compression Therapy

Hugo Partsch

HISTORICAL DEVELOPMENT

The oldest known illustration of compression bandages dates back to the Neolithic Age (5000–2500 BC) (Fig. 6.1).[1] The ancient Hebrews, Egyptians, Greeks and Romans used compression therapy for treatment of wounds and ulcers, as described in the Smith Papyrus (1650–1552 BC) and in the Book of Isaiah (Isaiah 1:6), eighth century BC.[2] Hippocrates wrote about compression treatment in the fourth century BC, and this was followed by further refinements from Celsus and Virgo. Roman soldiers who marched for days at a time quickly learned that applying tight strappings to the legs reduced leg fatigue. The knowledge concerning the beneficial effects of compression was rediscovered by physicians during the Middle Ages, including Guy de Chauliac (1363), Giovanni Michele Savonarola (1440) and Fabrizio d'Aquapendente (1537–1619). They used compression bandages, plaster dressings and laced stockings made from dog leather.[3]

Ambroise Paré (1510–1590), Richard Wiseman (1622–1676), Christian Anton Theden (1714–1787) and Thomas Baynton (1797) were pioneers, especially in the treatment of leg ulcers, who recommended different kinds of compression material that were mainly inelastic. In 1885, the dermatologist Paul Unna introduced his zinc paste boot for the treatment of venous dermatitis, and in 1910 his pupil, Heinrich Fischer, recommended firmly applied 'Unna boots' for treating venous thrombosis.[3,4]

The use of elastic compression occurred with the development of elastic stockings in the mid 1800s and the discovery by Charles Goodyear in 1839 of a vulcanizing process for rubber that would increase its elasticity and durability. In 1839, John Watson, MD, reported on the usefulness of an elastic stocking in treating varicose veins in a 23-year-old woman with Klippel–Trenaunay syndrome.[5] However, these stockings, made exclusively from rubber threads, were uncomfortable. It was not until Jonathan Sparks patented a method for winding cotton and silk around the rubber threads that elastic stockings became comfortable and popular.[3]

During the late 1800s and early 1900s, technical advances in the manufacturing process led from the development of the frame-knitting to the flat-knitting method, which increased production efficiency in addition to providing a proper fit. Stockings became even more comfortable and better looking when ultra-fine rounded latex yarns became available, which permitted the construction of seamless stockings. Two-way stretch stockings were developed next, which led to easier application of the stocking. Finally, the development of synthetic elastomers in the 1960s gave rise to latex-free compression stockings. Synthetic (spandex, polyurethane and nylon) stockings are still the ideal form of material to use today because of the relative resistance to moisture from sweat and other environmental factors and also the very fine threads and stretch–contraction characteristics that lead to the production of fine stockings.

Today there are more than 200 different brands of graduated compression stockings. As a complete discussion comparing all of the available stockings is beyond the scope of this chapter, concepts are discussed that are central to all forms of compression stockings, and information is given on the more commonly used and available brands.

MECHANISM OF ACTION

EDEMA

By increasing the tissue pressure, compression works against filtration, which is the basis of both prevention and removal of edema. Occupational leg swelling in sitting and standing professions can be prevented by light compression stockings,[6] which are also able to reduce mild edema.[7,8] Reduction in intradermal edema has been measured with 20-MHz ultrasound in patients with chronic venous insufficiency (CVI) and lipodermatosclerosis.[9] Application of class I or II graduated compression stockings decreased dermal edema by 17% in 4 days with no statistical difference between the two classes of compression. It could be demonstrated that stockings with a pressure of about 20 mmHg are quite effective in reducing leg edema and that this effect can be maintained by donning a second stocking over the first.[10]

Compression may also exert beneficial effects in nonphlebologic causes of edema, such as inflammatory edema (arthritis, cellulitis), cardiac edema, dysproteinemic edema, renal edema, lymphedema and cyclic idiopathic edema.[11] A study by Arpaia et al[12] showed an improvement in the quality of life (QOL) in patients with chronic CVI who wore class I graduated compression stockings.

LYMPH DRAINAGE

Several beneficial mechanisms of compression therapy on the swollen extremity may be explained by its effects on the lymphatic system[13]:

- Reduction of capillary filtration
- Increase of capillary reabsorption
- Shift of fluid into noncompressed parts of the body

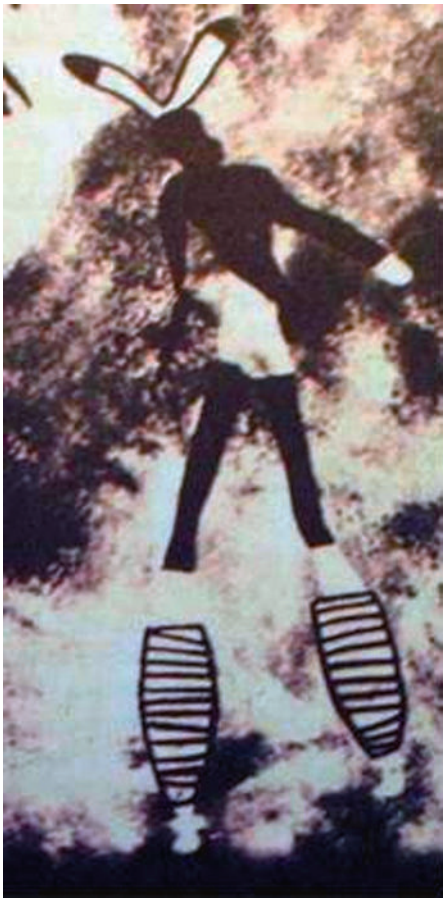

Figure 6.1 Mural paintings in the Tassili caves (Sahara), 5000–2500 BC. (From Partsch H, Rabe E, Stemmer R. Compression therapy of the extremities. Paris: Editions Phlébologiques Françaises; 1999.)

- Increase of lymphatic reabsorption and lymphatic transport
- Breakdown of fibrosclerotic tissue
- Down regulation of proinflammatory cytokines and receptors for growth factors[14]

One mechanism of central importance is the restriction of capillary filtration, which corresponds to the amount of the lymphatic load. With compression, the skin and dermal tissues are in closer contact with the superficial capillary network, which is otherwise separated by a pericapillary halo of protein-rich edema fluid.[15]

Compression removes more water than protein from the tissue, thereby increasing oncotic tissue pressure and reinforcing the need for sustained compression. Therefore, in chronic edema, success is dependent on continued compression.[16]

Compression together with movement enhances the contraction of the lymphatic system. Olszewski was able to demonstrate that both compression and exercise stimulated the movement of stagnating lymph through the lymph collector in lymphedema patients whose lymphatic trunks were filled.[17,18] This is probably one explanation for the reduction in intralymphatic hypertension obtained by complex decongestive therapy as demonstrated by Franzeck and co-workers by lymph capillary pressure measurements.[19]

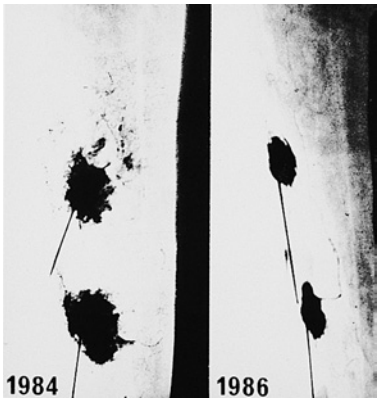

Figure 6.2 Indirect lymphography by subdermal infusion of water-soluble contrast into lipodermatosclerotic skin above the medial malleolus. Before treatment (1984), irregular lymphatics with dermal backflow and extravasation can be seen. After compression therapy, with removal of edema and normalization of the skin changes (1986), normal lymph drainage is obtained. (From Partsch H. J Dermatol Surg Oncol 1991;17:799.)

Intermittent pneumatic compression enhances prefascial lymph drainage.[15] Unna boots are able to increase subfascial lymph transport, which is reduced in postthrombotic syndrome.[20] Consequent compression leads to a morphologic improvement of pathologic initial lymphatics in patients with lipodermatosclerosis, which can be demonstrated by indirect x-ray lymphography (Fig. 6.2).[21]

VENOUS SYSTEM

Depending on the exerted pressure and the body position, external compression is able to narrow or occlude superficial and deep leg veins.[22] In the supine position an external pressure of 10 to 15 mmHg is enough to decrease the venous diameter. This results in an increase in blood flow velocity as shown by measuring the circulation time with isotopes,[23] and is the rationale for recommending light compression stockings for thromboprophylaxis in bedridden patients. A graduation in pressure (18 mmHg at the ankle, falling to 8 mmHg at the thigh) leads to a significantly increased velocity in the deep femoral vein flow.[24]

In the upright position, such low pressure will have only a minimal effect on decreasing the diameter of the leg veins.[25,26] However, a very small decrease of venous diameter will result in an over-proportional decrease of the local blood volume as demonstrated by several plethysmographic studies.[27–34] Stockings with an ankle pressure of around 20 mmHg have been shown to improve the venous pump.[27,32,33] Elastic compression stockings with low pressure have also been found to significantly reduce symptoms of CVI in patients during daily work activity.[35–38]

Bandages may provide much higher pressure in the upright position. Magnetic resonance imaging (MRI) is able to show that during standing deep veins will be narrowed by an external pressure of 42 mmHg and nearly occluded by a pressure of 82 mmHg[26] (Fig. 6.3). During ankle movements and walking with stiff bandages, pressure peaks of this magnitude will lead to an intermittent occlusion of the veins (Fig. 6.4). Such high pressure may be tolerated only with inelastic (not with elastic) material.

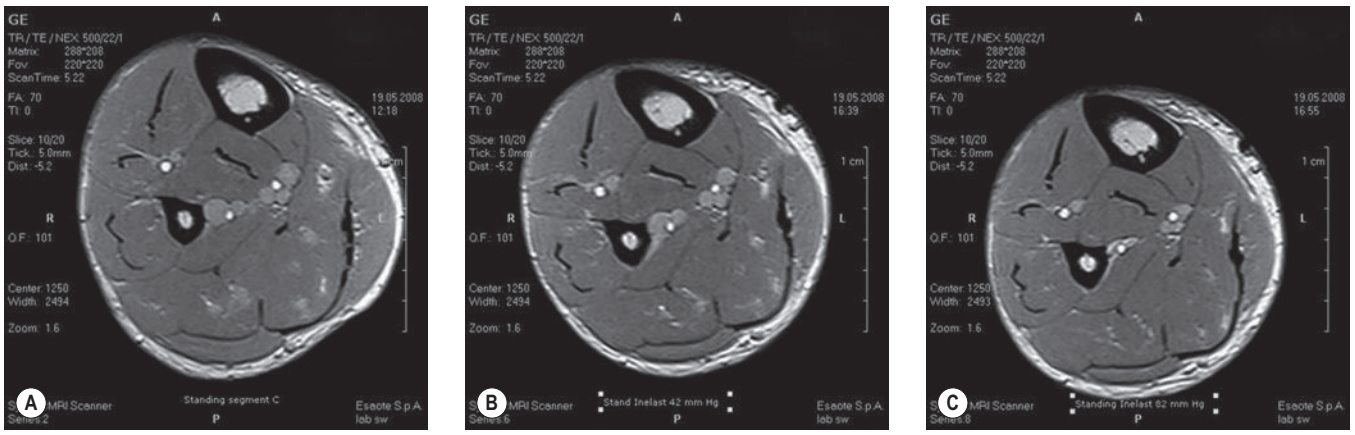

Figure 6.3 Magnetic resonance imaging of a crosssection through the largest calf segment in the standing position. **A,** Without compression; **B,** with a short-stretch bandage exerting a local pressure of 42 mmHg; **C,** with a pressure of 82 mmHg. A diameter reduction of the deep tibial posterior and peroneal veins can clearly be seen with increasing pressure. (Investigations together with G. Mosti at the laboratory of ESAOTE, Genova, Italy).

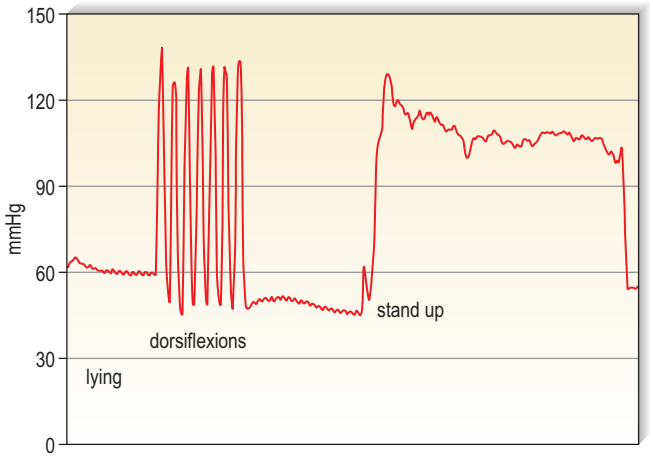

Figure 6.4 Interface pressure measured 12 cm above the inner ankle after application of a tight, zinc paste bandage aiming to produce a very strong bandage. The initial pressure in the lying position *(left)* is 60 mmHg. Ankle movements performing maximal dorsiflexions produce pressure peaks up to 120 mmHg. By standing up *(right)* the pressure rises to 100 mmHg. During the next 2 h there was a pressure drop to 25 mmHg in the supine and to 60 mmHg in the standing position.

The compression pressure when starting to walk counteracts the lateral expansion and dilation of leg veins during muscle contraction by encasing the veins in a semirigid envelope.[39,40]

The application of an external pressure with a blood pressure cuff blown up to 40 to 60 mmHg to various portions of the leg containing incompetent valves led to an abolishment of reflux.[41,42] This effect was directly associated with a decreased vein diameter. Reduction of venous refluxes and improvement of ambulatory venous hypertension by external compression could be demonstrated even in patients without any valves (avalvulia), indicating that this effect is not necessarily explained by coaptation of distended valve leaflets, but rather seems to be owing to increasing the resistance to retrograde flow.[43] Increasing external pressure in the upright position increases the ejection fraction of the calf muscle pump function.[44]

Conflicting results have been reported concerning an improvement in ambulatory venous hypertension by using compression stockings.[39,45] One study showed a significant decrease of such hypertension with short-stretch bandages applied with a resting pressure on the distal leg of more than 50 mmHg, but no decrease with elastic compression stockings exerting a pressure of 30 to 40 mmHg.[40] This may be explained by the fact that inelastic short-stretch bandages lead to an intermittent short venous occlusion during the muscle systole while walking. In patients with venous ulcers resulting from deep venous incompetence, short-stretch bandages are able to impede venous reflux more effectively than are elastic stockings exerting the same resting pressure.[46] Patients with severe stages of CVI benefit more from high compression pressure, whereas lower pressure is sufficient for milder stages such as varicose veins.[47]

The key mechanism of compression therapy to reduce ambulatory venous hypertension in patients with severe CVI is an intermittent occlusion of the veins during walking. In contrast, continuous obliteration of veins by external compression may be desirable after varicose vein surgery to stop bleeding and after sclerotherapy to prevent refilling of blood.

To achieve complete occlusion of superficial veins the external pressure should be higher than the intravenous pressure, and this depends on the body position. It was shown that occlusion of the leg veins can be obtained with an external pressure in the range of 20 mmHg in the supine position, but that in the sitting and standing positions the pressure has to be between 50 and 70 mmHg.[22,26] With compression stockings, such pressure ranges can only be achieved when rolls or pads are applied over the vein, thereby increasing the local pressure by reducing the local radius (law of Laplace, see later). Such rolls may be especially useful if local compression over treated veins on the thigh is intended.[48]

MICROCIRCULATION

Compression accelerates blood flow in the enlarged capillary loops and reduces capillary filtration because of enhanced tissue pressure. Improvements are seen in normalization of

venular flow, volume and velocity, improved distribution of microcirculation blood flow and normalization of leukocyte adhesion.[49–55] Different studies using electron microscopy were able to show a restoration of the structural changes in the media myocytes in stripped veins[56] and a tightening of intercellular junctions.[57] Laser Doppler flux measured a 29% increase in blood cell velocity in patients with CVI and lipodermatosclerosis.[52] Even in patients with mixed arterial–venous ulcers an increase of laser Doppler fluxmetry could be demonstrated up to a compression pressure of 40 mmHg.[58] Increasing flow velocity may reduce the likelihood of white blood cells interacting or sticking to endothelium with release of various factors. Effects on mediators involved in the local inflammatory response may explain both the immediate pain relief that occurs with good compression and ulcer healing.[59] Studies in patients wearing class II graduated compression stockings demonstrate an improvement in skin microcirculation in as little as 1 week, with near normalization of the functional state of microcirculation becoming apparent by day 30.[55] Model experiments with intermittent pneumatic compression were able to demonstrate that there is an increased release of the endothelial relaxing factor (EDRF) nitrogen oxide from the endothelial cells, depending on the amount of shear stress produced by the compression waves.[60] Compression tightens the junctions between the endothelial cells of capillaries[57,61] and reduces proinflammatory cytokines in venous leg ulcers.[62]

ARTERIAL FLOW

A reduction in arterial flow may be expected when the external compression pressure exceeds the intraarterial pressure. This may happen in patients with arterial occlusive disease with a reduced peripheral arterial pressure. To avoid ischemic skin lesions from external compression, it is essential to measure the peripheral arterial pressure using a Doppler probe before strong compression bandages or stockings are applied. It is generally accepted that a Doppler ankle–brachial index (ABPI) of less than 0.5 is a contraindication for sustained compression. However, external compression does not invariably mean reduction of arterial flow.[63] Mayrovitz reported on several experiments concerning arterial blood flow and compression,[64–66] and was able to demonstrate an increase of the pulsatile flow below the knee in healthy volunteers using nuclear magnetic resonance flowmetry.[64] He also demonstrated a reduction in toe blood perfusion, which was greater with increased compression, but not of sub-bandage skin perfusion.

Patients with edematous legs and with an ABPI of between 0.5 and 0.8 may benefit from inelastic or short-stretch bandages applied with a mild resting pressure, because of the edema-removing massage effect that will occur with every ankle movement (see later). Completely inelastic bandages together with walking have a similar effect as intermittent pneumatic compression. The rhythmic pressure peaks of an inelastic bandage during walking can be compared with those exerted by an intermittent pneumatic pressure pump. Several experiments with intermittent pneumatic compression have demonstrated an increase of arterial flow in patients with arterial occlusive disease.[67–72] The decisive mechanisms of action are the reduction of edema, an increase of the arteriovenous pressure gradient, myogenic mechanisms and the release of vasoactive substances from the endothelial cells. Especially during walking with inelastic bandages the increase of the ejection fraction of the venous calf pump may considerably contribute to an increase of arterial blood flow.[73]

BASIC PRINCIPLES OF COMPRESSION

TERMINOLOGY

A confusing variety of partly overlapping terms can be found in the literature.[1,74–84] Only terms of practical importance are listed here:

- **Elasticity:** Capability of a strained body to recover its size and shape after deformation.
- **Extensibility:** Maximum degree, expressed as a percentage of the unloaded size of the compression material to which it can be stretched in the circumferential or longitudinal direction.
- **Hysteresis:** A measure of the energy loss that occurs between loading (stretching) and unloading (relaxing) (see Fig. 6.10). Yarns with minimal hysteresis are best because they have maximum holding power with minimum stretch resistance.
- **Stiffness:** Increase in compression per centimeter increase in the circumference of the leg, expressed in hectopascals per centimeter and/or millimeters of mercury per centimeter.[74] Using in vitro testing, this definition applies also to the 'slope value'.[1]
- **Static stiffness index:** Difference between standing and lying interface pressure measured in vivo at the transition between the muscular and tendinous parts of the medial gastrocnemius muscle ('B1 point').[75,84] Figure 6.5 shows an example.
- **Dynamic stiffness index:** Difference between maximal peak pressure and resting pressure measured in vivo.[85]
- **Resting pressure:** Pressure from the compression device itself with the muscles at rest.

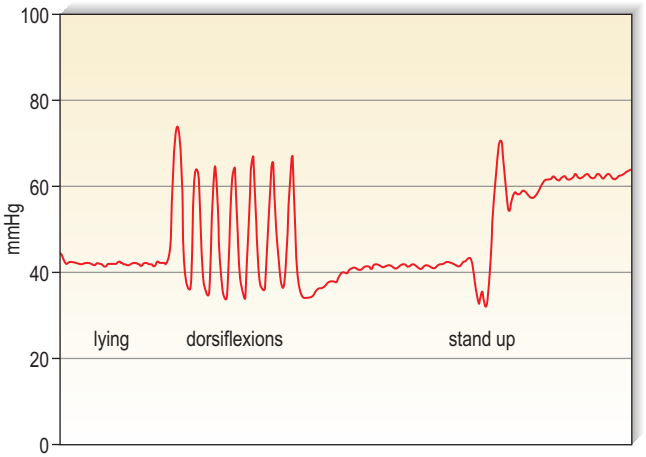

Figure 6.5 Typical pressure curve from the medial lower leg under an inelastic bandage in the supine position *(left),* with dorsiflexions and after standing up. The resting pressure of 40 mmHg rises to 60 mmHg by standing up. The difference between standing and lying pressure has been termed the static stiffness index (SSI).

- **Working pressure:** Pressure coming from inside the device, originating from contracting muscles.
- **Pressure amplitudes:** Difference between maximal and minimal pressure fluctuations during exercise, characterizing the 'massaging effect' of the compression device.
- **Pressure profile, pressure gradient:** Representation of the compression exerted by the device along the leg.
- **Residual pressure:** Compression at a certain point expressed as a percentage of the compression at the ankle.[74]

COMPRESSION PRESSURE AND LAPLACE'S LAW

The compression pressure (Pascal) is defined by the force (Newton) that is exerted to an area of 1 m^2 (Fig. 6.6). The tension in a bandage is determined by the force applied to the fabric during application.

The unit for pressure is 1 Pascal (Pa), which is 1 Newton (N) per square meter. In the medical field, for example measuring blood pressure, the usual unit for pressure is the weight of one cubic millimeter of mercury: 1 mmHg = 133,332 Pa = 1333 hPa

From Figure 6.6, it is clear that the curvature of the leg plays a deciding role for the exerted pressure. If the cylinder in the model was replaced by a cube, the pressure over the flat areas would be zero, whereas it would be very high along the sharp edges of the cube. This is described by Laplace's law stating that the pressure (P) is directly proportional to the tension (T) of the bandage, but inversely proportional to the radius (R) of the curvature to which it is applied (Fig. 6.7):

$$P \sim T/R$$

P decreases as R increases. When R is going to be indefinite such as over the flat areas of a cube, P will become zero.

PRACTICAL CONSEQUENCES OF LAPLACE'S LAW

In general, pressure is calculated for the circumference of the limb at a specific level. Because the leg has an irregular cross section that is not circular, the applied point pressures vary at different locations around the leg. Using Laplace's formula, it is evident that the effective pressure is greatest at the point of minimum radius and least at the point of maximum radius. Thus when a stocking is applied, the anterior aspect of the leg receives the greatest amount of pressure, and the lateral and medial sides of the leg receive the least compression pressure. This is especially important in the malleolar area, where the lowest degree of compression occurs, because the medial and lateral surfaces are flat or concave and the local radius is 'negative' (Fig. 6.8). If there is a venous ulcer situated in the dip behind the malleolus, the only way to bring compression to this region is to put a pad over that area (Fig. 6.9). The reduction of the local radius by pads or rolls in order to increase local pressure has been termed 'positive eccentric compression'.[1]

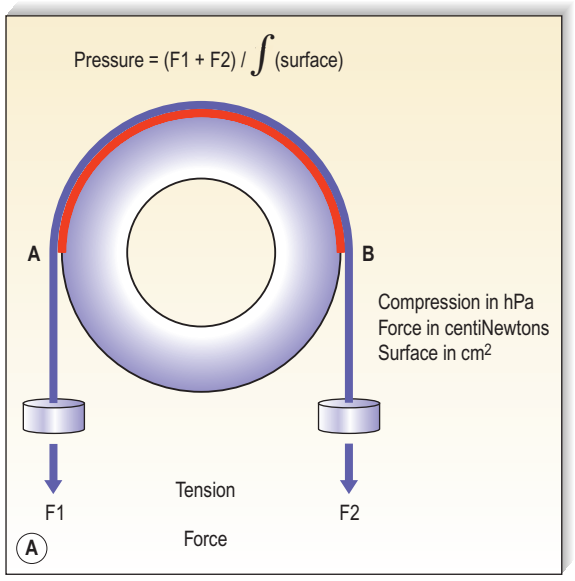

Figure 6.6 The pressure generated by an inelastic bandage is determined by the tension of the fabric. (Courtesy Bernard Lun, Ganzoni, St Just, France.)

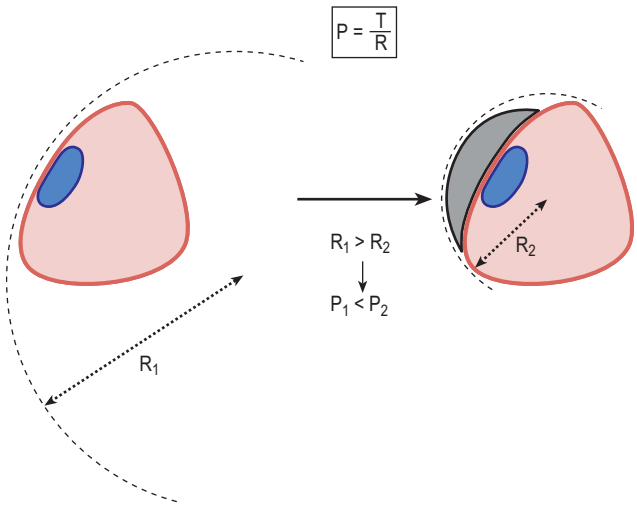

Figure 6.7 According to Laplace's law, the pressure exerted by a bandage is in direct proportional to the radius of the leg. To increase local pressure on flat parts of the lower leg circumference, rubber pads are attached over the area (*black sickle*) to decrease the radius. The *oval* represents a leg ulcer. (From Partsch H. J Dermatol Surg Oncol 1991;17:799.)

On the other hand, tendons and bony prominences are susceptible to a high compression pressure and should therefore be protected under a bandage by decreasing the radius using a cotton wool inlay. The enlargement of the local radius has been termed 'negative eccentric compression'.[1]

It is obvious from Laplace's law that a very thick leg requires more tension to achieve the optimum cutaneous and subcutaneous pressures, whereas a thin leg should be wrapped with a much lower tension.

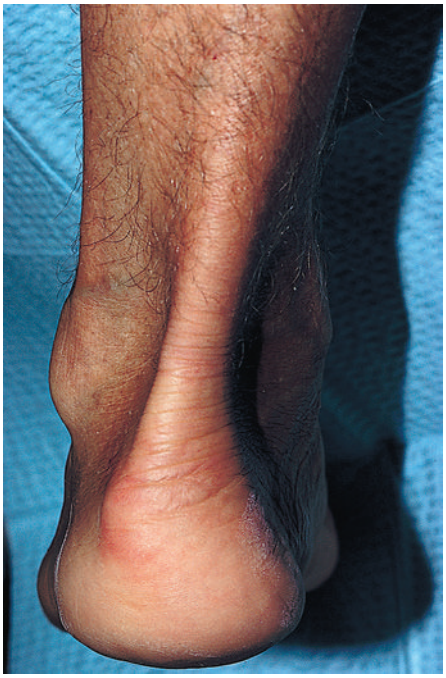

Figure 6.8 Typical appearance of an ankle in posterior orientation. Note the bulging malleoli and the resulting concavity produced on the lateral and medial aspects.

MEASUREMENT OF COMPRESSION PRESSURE

LABORATORY MEASUREMENTS OF COMPRESSION STOCKINGS

The effects of compression depend widely on the exerted pressure, which should be adapted to the underlying condition. Basically the pressure of a stocking is calculated from the force–extension diagram of the elastic fabric on a wooden leg model with defined circular cross sections using Laplace's formula (Fig. 6.10). The range of the compression

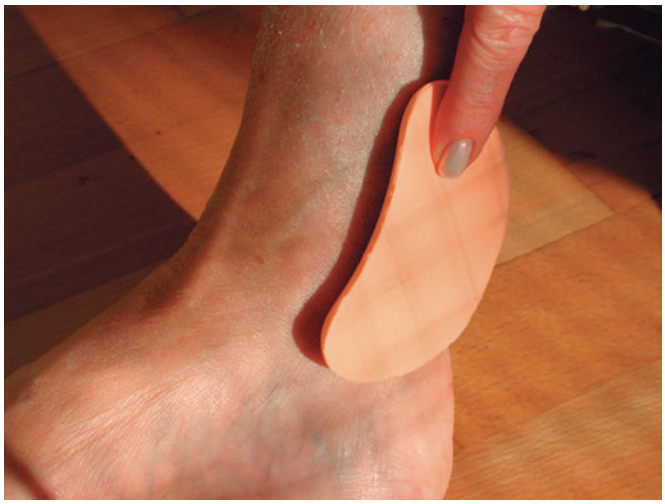

Figure 6.9 A rubber pad put behind the inner ankle increases local pressure. Note that the concave part of the pad is directed towards the skin.

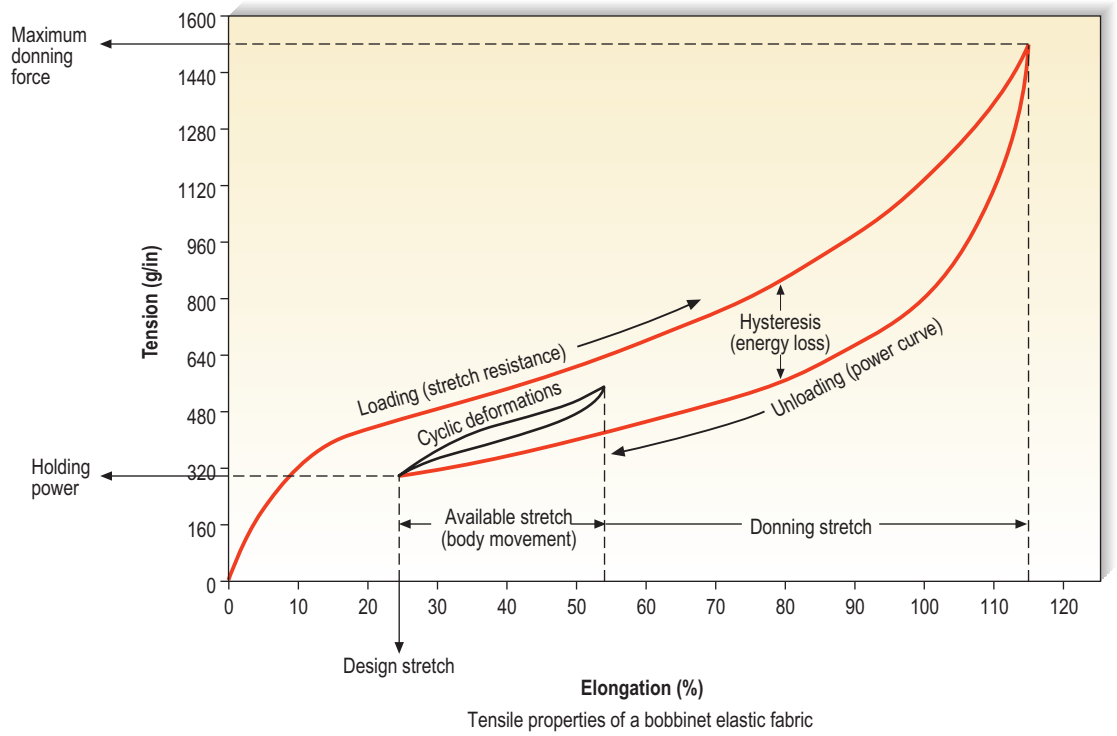

Figure 6.10 Hysteresis curve generated by a bobbinet elastic fabric. (Courtesy Beiersdorf-Jobst, Charlotte, NC.)

pressure indicated by the manufacturers is determined by the measurement of the force necessary to stretch the stocking at certain leg levels (B, B1, C, D, F, G) in a transverse direction. The proportion of stretch and force for each circumference level, which corresponds to the steepness of the so-called slope in the hysteresis curve, reflects the elasticity of the material of the stocking.

Several industrial measuring systems for obtaining hysteresis curves are used, such as the Hosy method, the Hatra tester, the Instron method, the French ITF method and others.

Measuring points, lengths and girths defined by the European standardization proposal (CEN, Centre Européen de Normalisation)[74] are shown in Figure 6.11.

Table 6.1 gives a comparison of compression classes for ready-to-wear and custom stockings used in several countries. The range of compression pressures and also the verbal description of these classes are amazingly variable from one country to another. Additionally, it is important to realize that the given ranges are measured by different methods and so comparisons are problematic. These facts underline the necessity of in vivo pressure measurements on the individual leg in future clinical studies. For a better universal understanding, it is recommended using the pressure range in mmHg rather than compression classes in general.

The pressure values in Table 6.1 refer to level B. The European prestandard[74] defines the ranges of pressure profiles in comparison with the pressure at the smallest leg circumference (position B) as follows: for level B1 70% to 100%, for C and D 50% to 80%, and for F and G 20% to 40% for compression classes III and IV; 20% to 60% for compression classes A and I, and 20% to 50% for compression class II (Fig. 6.12). The producers of compression stockings recommend adjusting the compression class according to the clinical severity.

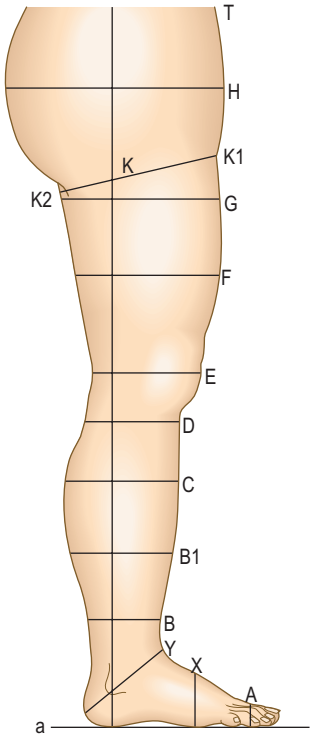

Figure 6.11 Measuring points, lengths and girths on the human leg. Note: measurements should be taken of the patient's leg in a standing position.[74]

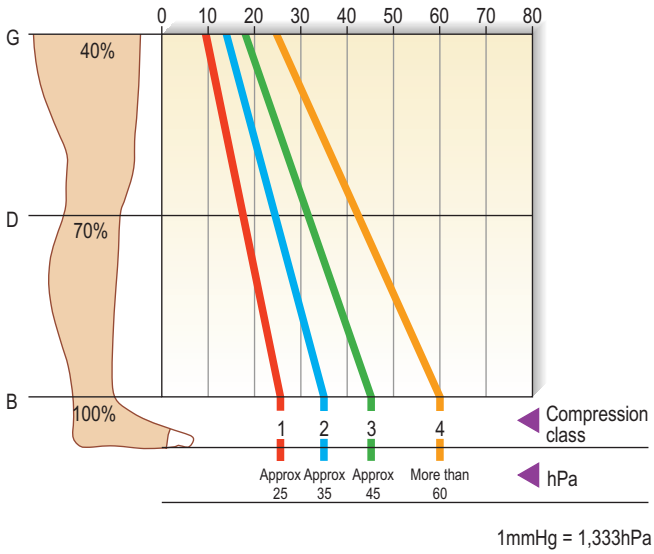

Figure 6.12 Diagram comparing the degree of compression exerted at various locations on the leg with different compression class stockings. *B* is the pressure generated at the ankle; *D* is the pressure generated at the knee; *G* is the pressure generated at the superior thigh. Note that there is a graduation of pressure with all classes of stockings, with the highest pressure exerted at the ankle. Also note that the most significant difference in pressure generated by the different classes of stockings is at the ankle. (Courtesy Juzo, OH.)

Table 6.1 Compression Classes Used in Several Countries*

Compression Class	EU (CEN)[74]	USA	UK (BS 6612)[77]	France	Germany[78]
A	10–14 (light)				
I	15–21 (mild)	15–20 (moderate)	14–17 (light)	10–15	18–21 (light)
II	23–32 (moderate)	20–30 (firm)	18–24 (medium)	15–20	23–32 (medium)
III	34–46 (strong)	30–40 (extra firm)	25–35 (strong)	20–36	34–46 (strong)
IV	>49 (very strong)	40+		>36	>49 (very strong)

*Values are mmHg (1 mmHg = 1333 hPa).
The values indicate the compression exerted by the hosiery at a hypothetical cylindrical ankle.

Table 6.2 Mean Compression Values for an Average Ankle Size

8–15 mmHg	15–20 mmHg	20–30 mmHg	30–40 mmHg	40+ mmHg
Tired, aching legs	Minor varicosities	Moderate to severe varicosities	Severe varicosities	Severe varicosities
Minor ankle, leg and foot swelling	Minor varicosities during pregnancy	Postsurgical	Severe edema	Severe edema
	Tired, aching legs	Moderate edema	Lymphatic edema	Lymphatic edema
	Minor ankle, leg and foot swelling	Postsclerotherapy	Management of active venous ulcerations	Management of active venous ulcerations
	Postsclerotherapy	Helps prevent recurrence of venous ulcerations	Helps prevent recurrence of venous ulcerations	Manage manifestations of PTS
	Helps prevent DVT	Moderate to severe varicosities during pregnancy	Manage manifestations of PTS	Orthostatic hypotension
		Superficial thrombophlebitis	Helps prevent PTS	Postphlebitic syndrome
		Helps prevent DVT	Orthostatic hypotension	CVI
			Postsurgical	
			Postsclerotherapy	
			Helps prevent DVT	
			CVI	

CVI, Chronic venous insufficiency; DVT, deep venous thrombosis; PTS, postthrombotic syndrome.

There is no American standard. Table 6.2 gives an example as recommended by one company (BSN-Jobst, Charlotte, NC).

MEASUREMENTS OF INTERFACE PRESSURE ON THE LEG

Compression therapy is a very effective treatment tool for which the 'dosage', that is the pressure on the individual leg, has been completely underestimated up to now. At least for clinical trials comparing different compression products, we need to measure the interface pressure on the individual leg and not just rely on the specifications of the producers. This is true not only for compression stockings whose pressure range is measured by different laboratory methods, making a comparison in treated patients problematic, but even more so for compression bandages. The pressure exerted by a compression bandage depends completely on the skill and experience of the bandager and only single standards are available that are far away from clinical practice.

Several instruments are available, which should be calibrated on the leg according to a recent consensus recommendation.[86] In this consensus paper, some prerequisites of an 'ideal' pressure sensor are summarized. One location that should always be included in future pressure measurements is B1. This is where the tendinous part of the gastrocnemius muscle changes into the muscular part, showing the most pronounced protrusion of the tendon and the most extensive enlargement of the leg circumference during dorsiflexion or by standing up from the supine position. Whenever in vivo measurements of interface pressure are performed, it is essential to indicate the exact measuring point, the main specifications of the instrument, including the dimensions of the probe, and the body position in which the measurements have been performed. Figure 6.13 shows a pressure measuring instrument that allows continuous pressure registration. The flat probe is inflated only when pressure is measured and can stay on the leg for several days.

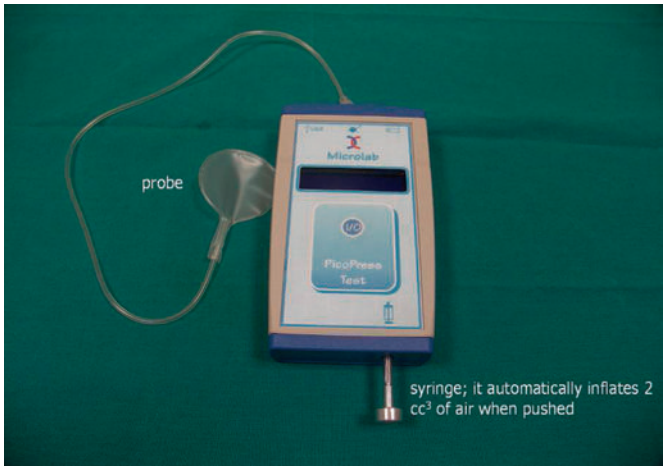

Figure 6.13 Instrument to measure interface pressure continuously. The flat probe is filled with 2 mL air and may be left deflated on the leg for several days. (Picopress, Micolab, Italy.)

Figures 6.4 and 6.5 show pressure curves obtained with this instrument.

RESTING AND WORKING PRESSURE

Some probes allow measurements of interface pressure not only at rest but also continuously during movement. Figure 6.14 shows an example where the interface pressure on the distal leg was measured continuously in different body positions, both for an inelastic and for an elastic bandage. Starting with comparable resting pressure for both bandages, the inelastic bandage has a higher working pressure than the elastic bandage. This difference has a major impact on the efficacy of the compression device concerning edema reduction and improvement of venous pump. Stockings with high stiffness or slope value, even at the same compression level, are better for patients with edema from CVI or other causes.[87] Inelastic bandages are more effective to reduce venous reflux and ambulatory venous hypertension.[40,46]

Measurements of intramuscular pressure have shown higher resting pressure with elastic than with inelastic material, suggesting that elastic compression applied over a long period in the recumbent posture may impede microcirculation and jeopardize tissue viability.[88]

MEASUREMENT OF STIFFNESS

Stiffness is defined as the increase in compression per centimeter increase in the circumference of the leg, expressed in millimeters of mercury per centimeter.[74] This parameter characterizes the distensibility of a textile in addition to the elastic property of a composite bandage, which plays an important role concerning the performance of a compression device during standing and walking. Stiffness may be measured in the laboratory, where it corresponds to the slope of the hysteresis curve. The fact that it can also be assessed by in vivo measurements on the individual leg will certainly achieve increasing practical importance in future trials.[85,86,89]

Measurement of dynamic stiffness during walking requires sophisticated instrumentation and can therefore not be used in routine clinical practice.[85] To obtain valuable information about the elastic property of a compression device, which may be quite complex when several materials are combined, the so-called 'static stiffness index (SSI)' may be a useful alternative.[84] A calibrated pressure sensor is fixed to the medial aspect of the leg at B1. This is the area that will show the most extensive changes in local curvature and leg circumference when the body position is changed between supine and standing. The difference between the interface pressure in the standing and in the lying position, called SSI, is a valuable parameter for the stiffness of the compression system that determines the relationship between resting and working pressure. As is shown in Figure 6.15, inelastic material produces a much higher pressure increase in the upright position than elastic material. It is important to note that different indices may be obtained with different sensors. Therefore reliable comparisons of different compression devices will only be possible by testing using the same sensor on the same site.

It has been shown that different padding materials may change the stiffness of the final bandage.[89]

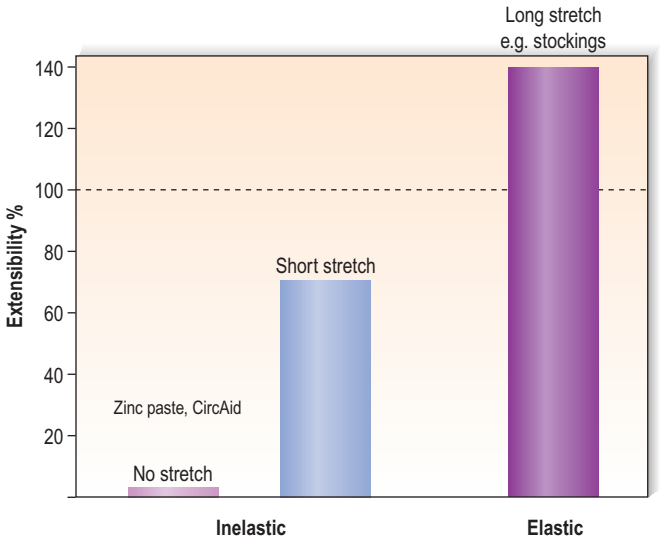

Figure 6.14 Differentiation between inelastic (<100% stretch) and elastic bandage material (>100% stretch) based on measurements in textile laboratories.

COMPRESSION MATERIAL

Different devices/materials are available for compression therapy (Box 6.1). The main categories of compression concerning the elastic properties of the materials are summarized in Table 6.3. Extensibility is the ability of a bandage to increase in length in response to an applied force.

COMPRESSION BANDAGES

There are three basic types of bandages: completely non-elastic bandages, virtually without any stretch, e.g., Unna boot or Velcro-band products; short-stretch bandages (<100% extensibility); and long stretch (>100% extensibility) (see Table 6.3).

No-stretch and short-stretch material is frequently called 'inelastic' and long-stretch material 'elastic' (see Fig. 6.14).

STANDARDS FOR COMPRESSION BANDAGES

There is currently only the British standard (BS) 7505:1995, for compression bandages. It contains four categories

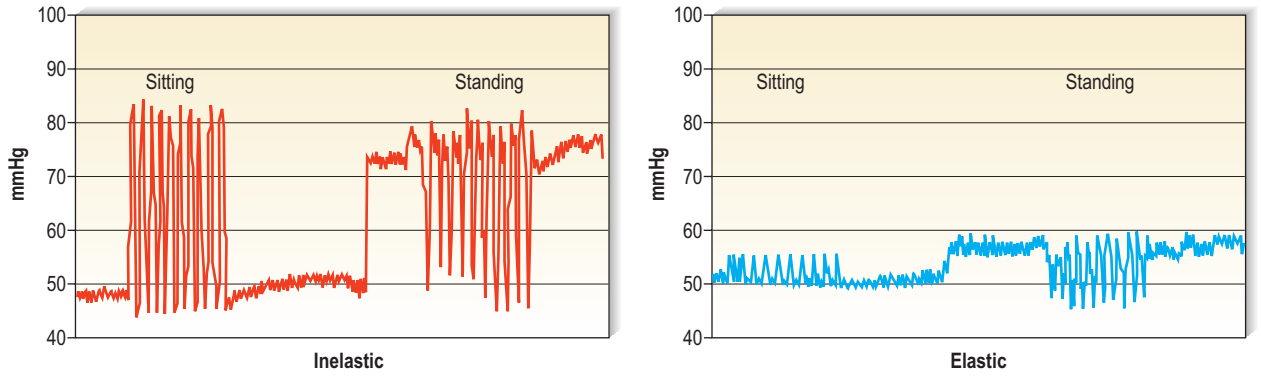

Figure 6.15 Resting and working pressure of an inelastic bandage *(left)* and an elastic bandage *(right),* measured at B1. During movement (dorsiflexions in the sitting position, tip-toes in the standing position) the pressure fluctuations are much higher with the inelastic bandage compared with the elastic bandage. By standing up from the sitting position the pressure rises by 23 mmHg under the inelastic bandage, but by only 8 mmHg under the elastic bandage. This increase of pressure characterizes stiffness.

Table 6.3 Categories of Compression Material

	'Inelastic'		'Elastic'
	No Stretch	**Short Stretch**	**Long Stretch**
Stretch	<10%	<100%	>100%
Application	Trained staff	Trained staff	Every patient
Stays on the leg	Day and night	Day and night	Daytime

Table 6.4 Classification of Compression Bandages by British Standard[77]

Bandage Type BS 7505	Level of Compression	Pressure British Standard (mmHg)
3A	Light	Up to 20
3B	Moderate	21–30
3C	High	31–40
3D	Extra high	41–60

Box 6.1 Types of Compression Device

Graduated Compression Stockings

- Ready-made 'off the shelf' stockings manufactured in fixed sizes
- Made-to-measure stockings, custom-made according to the length and the circumference of the leg
  - Below-knee hosiery
  - Mid-thigh hosiery
  - Thigh hosiery
  - Single-leg panty
  - Panty hosiery

Bandages

- Inelastic
  - No stretch (extensibility close to zero)
  - Short stretch (extensibility <100%)
- Elastic
  - Long stretch (extensibility >100%)
  - 'Nonadhesive', cohesive, adhesive
  - Single component
- Multiple components

Compression Boots

- Water, air
- Velcro-band devices (inelastic)

Intermittent Pneumatic Compression

- Single chamber
- Sequential chambers
  - Foot-pump
  - Lower leg
  - Full leg

of compression bandages,[77] which are summarized in Table 6.4.

By definition, the indicated pressure levels should be achieved on an ankle 23 cm in circumference when applied with a 50% overlap. This classification was constructed based entirely on in vitro measurements and does not correspond to the clinical reality. The resulting pressure of a bandage mainly depends on the stretch during application and far less on the material. Only a few measurements of compression pressure on the human leg have been reported, applying different materials with light, moderate and high strength.[90] It could be demonstrated that the interface pressure of a bandage on the human leg is on average one class higher compared with the values in Table 6.1 for compression stockings. Even with intentionally very loose bandaging in an attempt to achieve 'light compression', the pressure of the 5-m-long bandage, short stretch and long stretch, is always higher than 20 mmHg with one bandage and higher than 30 mmHg with a multilayer technique.

Table 6.5 Interface Pressure of Bandages Measured at B1 in the Supine Position[75]

Pressure (mmHg)	Mild	Moderate	Strong
Consensus proposal	<20	20–40	40–60

Because of these discrepancies, new proposals concerning a bandage classification were made in a consensus conference based on practical measurements in vivo.[75] The eponym 'PLACE' was proposed, containing the main characteristics to be considered when compression bandages are applied: P stands for pressure, LA for layers, C for components and E for the elastic property of the single bandage used. Table 6.5 shows the definition of different pressure ranges. Bandages are always applied with some overlap so that one-layer bandages do not exist. The only one-layer system is a compression stocking. Actually the so-called four-layer bandage is applied with much more than four layers and should correctly be called a 'four-component bandage' because it contains four different bandage materials. Use of the terms 'elastic' and 'inelastic' were proposed only for single bandages based on their elastic properties, but not for a final bandage consisting of different single bandages. In fact the elastic property of the final bandage cannot be predicted based on the elasticity of the single components. Adding several bandages does not only increase the sub-bandage pressure but also enhances the stiffness of the final bandage.

INELASTIC AND SHORT-STRETCH BANDAGES

Bandages with an extensibility close to zero, such as zinc paste (Unna boot) and rigid Velcro-bands like CircAid (CircAid Medical Products, San Diego, CA) or Hydro Boot, (Incappe Inc, Brandon, MS) are examples of completely nonelastic material. Nonelastic bandages must be applied with skill and some knowledge. If light compression is indicated they should be applied without extension of the fabric by molding the material to the leg without tension. When strong compression is indicated completely rigid zinc paste bandages need to be applied with full extension of the material and adjusted to the configuration of the leg. Figure 6.16 shows a bandage applied with zinc paste on the lower leg wrapped over with a short-stretch bandage, and with adhesive bandages over the knee and thigh of a patient with a proximal deep vein thrombosis (DVT).

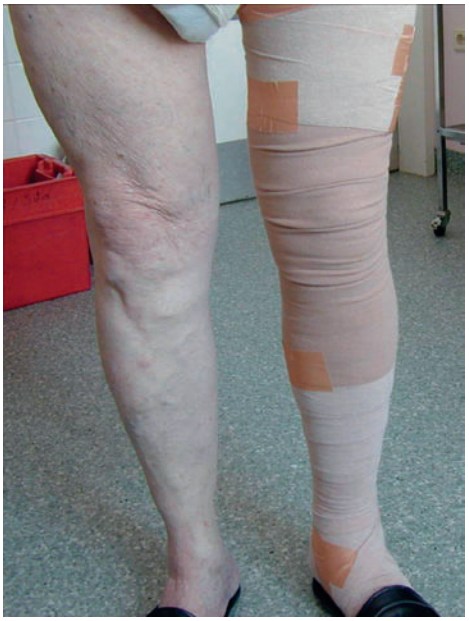

Fig. 6.16 Inelastic compression bandage with high stiffness consisting of a tightly applied zinc paste bandage, wrapped over by a short-stretch cotton wool bandage on the leg and of adhesive bandages over the knee and thigh in a patient with an acute proximal deep vein thrombosis. The initial interface pressure on the lower leg is between 50 and 60 mmHg in the supine position.

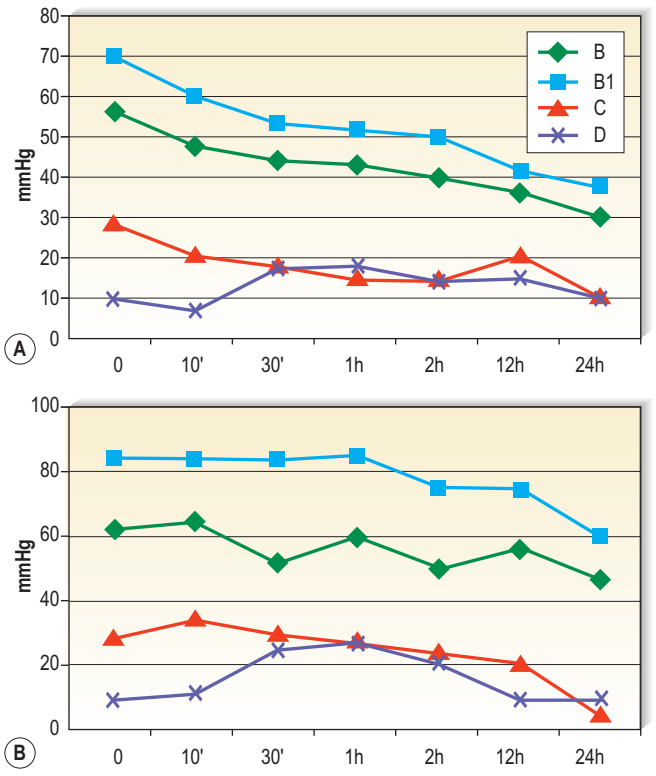

Figure 6.17 Interface pressure exerted by a multilayer short-stretch bandage (Rosidal sys, Lohmann) measured by an MST tester[130] on the medial leg in the supine **(A)** and in the standing position **(B).** Measuring points: B = behind the inner ankle, B1 = 8 cm above, C = 19 cm above, D = 27 cm above the ankle. The pressure drop of this multilayer short-stretch bandage is more pronounced in the supine than in the standing position.

Short-stretch bandages can be extended 30% to 100% and should be applied with a pressure of more than 50 mmHg on the distal leg if strong compression pressure is indicated. As a result of the immediate removal of edema, this pressure will fall to values that are also well tolerated in the supine position. After a few hours there will be a low to slight resting pressure, but still a high and very effective working pressure. Short-stretch bandages exert little pressure when the calf muscles are relaxed, but prevent expansion in calf diameter when the muscles are contracting during standing and walking ('high working pressure'). Therefore they are comfortable when patients are recumbent and they act to decrease venous pressure with ambulation.[40] The main disadvantage is that they may become loose after a few hours of wear, especially when applied too loosely. In immobile patients, correctly applied short-stretch and inelastic bandages are even more effective than long-stretch material. Even minimal toe movement or passive ankle mobilization performed by physiotherapists will produce a much higher massaging effect compared with elastic material.

Nonelastic bandages made of cotton may be washed and reused. Another category of short-stretch material is the cohesive or adhesive bandage. A cohesive bandage sticks only to itself, and not to skin or hair, whereas an adhesive bandage also sticks to the skin. These bandages cannot be reused after removal.

Stiff bandage material is not easy to handle. Most untrained persons apply inelastic bandages with too low a pressure. To obtain a resting pressure on the distal leg of about 40 mmHg, the initial pressure after application should reach about 60 mmHg. As can be seen from the example in Figure 6.17, the resting pressure in the supine position drops from 70 mmHg to 50 mmHg after 2 hours. This pressure exerted by an inelastic bandage is also well tolerated during nighttime. However, there is less pressure loss in the standing position, so an effective range of pressure values is still maintained after 24 hours (see Fig. 6.17). In the first days after bandage application, the reduction of swelling may be so pronounced that the bandages will get loose and have to be renewed. When edema reduction is stabilized, inelastic bandages may stay on the leg for several days.

A study of elastic minimal-stretch and nonelastic orthoses (CircAid) demonstrated that 4 hours after application, elastic bandages had 94% of their initial pressure, compared with 70% for minimal-stretch and 63% for the nonelastic orthose.[91] In the supine position, the decrease at 4 hours was 72% for elastic, 59% for minimal-stretch and 44% for nonelastic compression. One of the advantages of this particular orthosis is the fact that it can be readapted by the patient when it becomes loose (Figs 6.18 and 6.19). Smaller but significant decreases in pressure under short-stretch bandages were also found in studies on changes in pressure with exercising.[92,93] Measurement of compression after walking for 3 hours and then again 7 days later showed a decrease in pressure from 80.5 mmHg to 43.6 mmHg after 3 hours and to 26.3 mmHg after 7 days. In this study, Comprilan (Beiersdorf, Germany) with an extensibility of 70% was used.[92] In the second study, elastic bandages did not demonstrate a similar degree of compression loss after tip-toe exercise.[93] Although the authors speculate that the loss in pressure during exercise may be related to application technique

Figure 6.18 CircAid (San Diego, CA) ready-to-wear compression garment, Flex model.

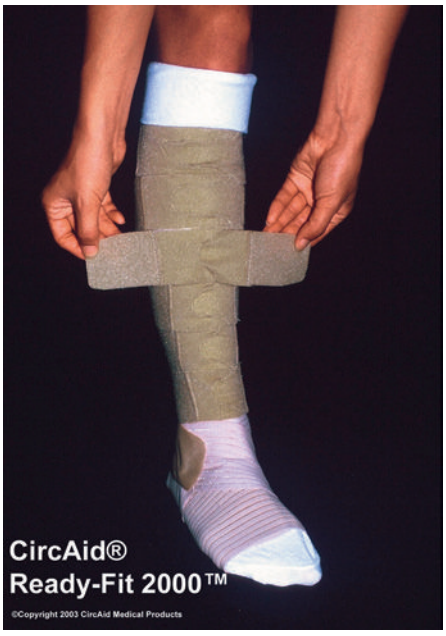

Figure 6.19 CircAid (San Diego, CA) ready-to-wear compression garment, Standard model.

of the short-stretch bandage with a maximum tension of 45% (Compridur; Beiersdorf, Germany), this could also be explained by an immediate volume reduction of the leg as shown in healthy volunteers and in lymphedema patients (Rosidal sys and Rosidal Lymphset; Lohmann & Rauscher, Germany).[94]

When the bandage becomes loose it should be renewed to prevent refilling of the extremity with edema and to avoid tourniquet effects from the down-gliding compression material. In patients with lymphedema, who are best treated with short-stretch bandages in the initial phase, renewal may be necessary once a day.[95]

Main indications for inelastic and short-stretch bandages are venous and mixed arteriovenous leg ulcers, DVT, superficial phlebitis, compression after surgery, sclerotherapy or endovenous therapy of varicose veins and lymphedema.

ELASTIC, LONG-STRETCH BANDAGES

Elastic bandages or compression stockings are usually applied in the morning, preferably before getting up, and are removed before going to bed at night. These highly extensible devices are relatively easy to apply and accommodate changes in leg geometry, expanding and contracting during walking. They sustain applied pressure for extended time periods, but may cause unpleasant feelings in the resting, sitting or lying positions.

Long-stretch bandages can be extended 140% to 200% and thus have a high resting pressure; that is, they exert pressure on the superficial venous system when the limb is at rest with a decreased working pressure as compared with short-stretch bandages (see Fig. 6.15). Because of their intrinsic high resting pressure, they can damage arterial, lymphatic and venous flow if not applied carefully, so they are best used while patients are ambulatory. Their advantage is that they may be molded around the heel and ankle more easily and can sustain their pressure better than inelastic bandages.

Elastic leg compression applied over a long period in the recumbent position may impede microcirculation and jeopardize tissue viability. New materials have been developed that provide effective compression pressures for a wide range of varying stretch. They are applied as multilayer bandages and may stay on the leg for several days and nights (Proguide; Smith & Nephew, UK).

Such bandages can be used to maintain a decongested condition when inelastic bandages are no longer required and may replace elastic stockings if these cannot be put on.

MULTILAYER BANDAGES

In the consensus paper mentioned earlier, it is stated that 'multilayer bandages' are actually multicomponent bandages consisting of different materials for padding, retention and compression.[75]

From these definitions it is quite obvious that many combinations of different materials are possible that will lead not only to an increasing pressure with each layer but also to variable elastic properties of the final bandage. In a comparative trial with different brands of four-layer bandages it was found that a bandage applied as part of a multilayered system achieves only about 70% of the pressure that it exerts when applied alone, thus challenging the commonly held assumption that the final pressure achieved by a multilayer bandaging system is the sum of the pressures exerted by each individual layer.[96] The elastic property of the final bandage will change toward a more inelastic bandage because of the friction of several layers, enabling it to be tolerated in the supine position[97] (Fig. 6.20). One example is the so-called four-layer bandage, which consists of several components of different material (wool, crepe, elastic and self-cohesive), and which may be worn day and night (Profore; Smith & Nephew, Hull, UK).

There were claims that such bandages have not lost pressure at 1-week follow-up.[98] Actually some of our own measurements revealed a pressure loss that started immediately

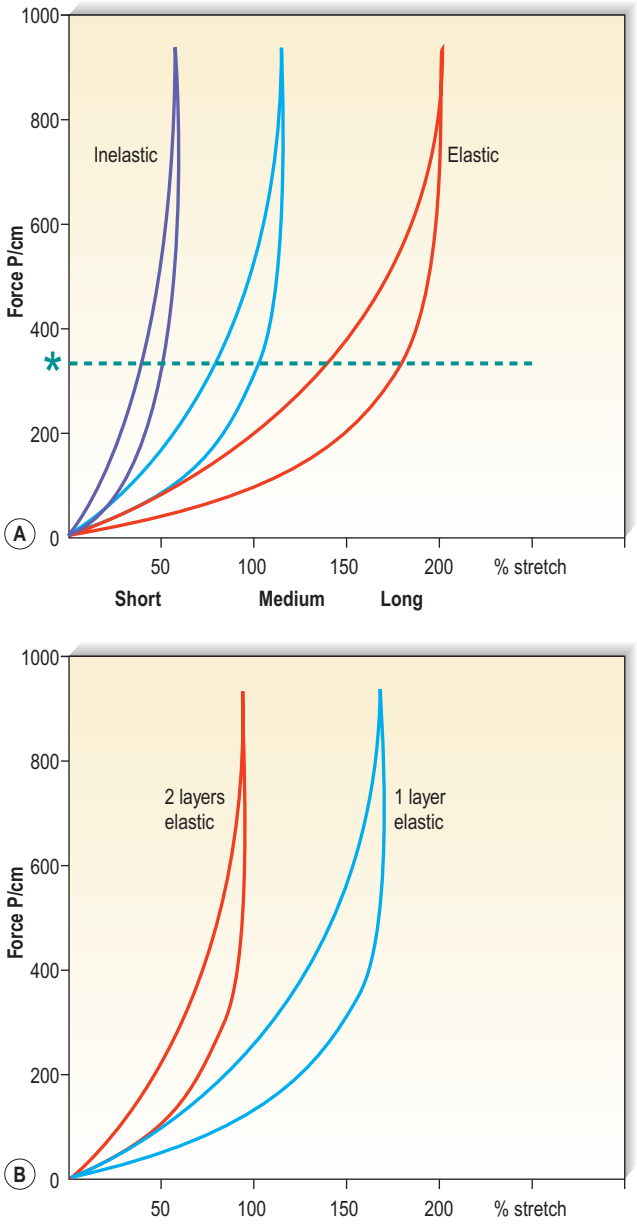

Figure 6.20 Hysteresis curves of different bandage materials. **A,** To achieve the same pressure level on the leg (*blue dashed line*) elastic bandages *(right)* need more stretch than inelastic *(left).* **B,** Compared with one layer of elastic material *(right),* two layers lead to a shift of the hysteresis curve towards the left. The elastic property of the final bandages is similar to a short-stretch bandage *(top).* (Redrawn from Partsch H, Rabe E, Stemmer R. Compression therapy of the extremities. Paris: Editions Phlébologiques Françaises; 1999.)

after application, which is less pronounced compared with short-stretch bandage systems.[99]

One study compared eight different compression bandages under standardized conditions.[97] Multilayer bandage systems composed of short- and medium-stretch bandages exhibit the smallest pressure loss with patient activity and have a significant pressure decrease when the patient is supine. These systems gave better postural and interface pressure changes than all types of single-layer bandages because of an increase in the stiffness of the final multilayer bandage.[84,90]

There are also multilayer systems consisting of short-stretch material, which are equally effective in ulcer healing when applied correctly.[100–103] Examples are the Pütter bandage (Hartmann, Germany), Rosidal sys (Lohmann & Rauscher, Germany), the adhesive Actico bandage (Activa Healthcare, UK), the Coban 2 bandage (3M, Minnesota, USA) and the Fischer bandage, consisting of a tightly applied Unna boot with a short-stretch bandage on top. This latter bandage was recommended by Heinrich Fischer, the pupil of Unna, in 1910 for the treatment of DVT[4] and is still one of the author's favorites in patients with DVT, post-thrombotic syndrome or venous leg ulcers (see Fig. 6.16). The tradition of using multilayer short-stretch bandages is rather restricted to central European countries and to the Netherlands, whereas many bandagers in the UK are more familiar with multilayer systems containing rather long-stretch material.

Several trials have compared multilayer long-stretch bandages with short-stretch, some showing better results with the short-stretch,[100–103] some better with long-stretch multilayer systems.[104,105] Frequently unfair comparisons have been made comparing properly applied versus inadequately applied bandages. In future trials, bandagers should be properly trained for both systems and interface pressure and stiffness should be measured.

One advantage of the multilayer bandages composed of short-stretch material is their reusability, in contrast to the single-use elastic multilayer systems. Short-stretch cotton wool bandages get stiffer with each washing procedure.

The principle of applying several compression layers over each other is also a promising concept for elastic stockings, with regards to an increase in both compression pressure and stiffness.[106,107]

TRAINING IN THE APPLICATION OF BANDAGES

A major drawback of bandages is their nonuniform application. A comparison of the range in pressures measured during application of a long-stretch elastic bandage by skilled nurses versus nursing students demonstrated that the skilled bandager's pressure ranged from 25 to 50 mmHg, and the unskilled bandager's pressure ranged from 15 to 70 mmHg.[108] A recent study checking the sub-bandage pressure showed that nurses with long professional experience tend to apply short-stretch bandages much too loosely (<20 mmHg) and that this can be greatly improved by training.[109]

In another study, similar results were demonstrated, and training programs were suggested that focus on practical bandaging skills.[110]

Several elastic bandages are marked with geometrical figures such as a rectangle that becomes a square when stretched to the proper length (e.g., Setopress; Seton Healthcare Group, Oldham, UK; Proguide; Smith and Nephew, UK; Velpeau; Lohmann & Rauscher, France) (Fig. 6.21). Setopress was studied with five skilled nurses and five unskilled assistants who also applied an Elastocrepe (Smith and Nephew, UK) bandage to the opposite leg. The Setopress bandage applied by experienced nurses most closely approximated target sub-bandage pressures, whereas the unskilled group differed significantly among themselves. As before, both groups differed significantly in applying sub-bandage pressure with the Elastocrepe bandage, with a

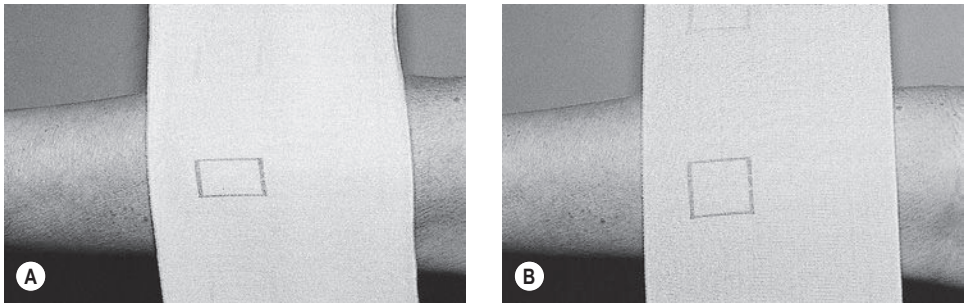

Figure 6.21 Appearance of a 30-mmHg, medium-stretch compression bandage without tension (Setopress, Seton Healthcare Group, Oldham, UK). **A,** Note rectangular boxes. **B,** Same bandage stretched to provide approximately 30 mmHg compression. Note that the rectangular boxes have now assumed a square shape.

significant difference noted between the skilled nurses and unskilled bandagers.[111] An additional study of 18 nurses applying an adhesive compression bandage showed ten nurses producing a tourniquet effect, five producing inadequate ankle pressure, two excessive ankle pressure and one appropriate ankle pressure but with an improper gradient in the calf.[112] Training significantly improved performance. Another study of 48 trained community nurses that compared one inelastic and two elastic bandages showed similar results.[113] The most common problem was production of a calf tourniquet.

In addition, even with physicians who are experts in applying bandages, a true graduation in pressure may not always be obtained. One study of five surgeons showed a range of 21.9 to 52.7 mmHg with application of a short-stretch bandage, with each individual surgeon having a range of 10 to 20 mmHg between bandage applications.[114] The coefficient of variation in each individual ranged from 9.9% to 25.2% with a mean (standard deviation) of 17.0 (4.9%).

Based on the information just presented, it is obvious that training in the application of bandages is very important.[109–116] This is especially true for inelastic bandages, which should be applied with a higher initial pressure compared with elastic material. Instruction of compression application with the use of interface pressure measurement has been shown to improve technique.[116] When teaching 156 persons at a wound healing course, the application of appropriate interface pressures required approximately ten exercises with the use of interface pressure transducers.

Important points to consider when applying a bandage are:

- Elastic bandages are easier to handle than inelastic bandages and may be applied by staff who are not specifically trained, in addition to the patients themselves. This is also true for compression stockings.
- Inelastic material like zinc paste should be applied with much higher resting pressure, pressing the bandage roll toward the leg as if molding clay. To obtain a homogeneous pressure distribution without creating constricting bands or folds, it is advisable to cut the zinc bandage when it does not exactly follow the cone-shaped leg surface during application. A 10-m bandage is recommended for one lower leg. After the lower leg has been covered with several layers, a 5-m-long short-stretch bandage is wrapped over and the patient encouraged to walk around immediately for at least 30 minutes. This short-stretch bandage can be washed and reused with each change of the bandage.
- After some walking the immediate removal of edema causes the pressure to drop to around 40 mmHg. Therefore, in the edematous phase the bandage will become loose after a few days, and it should be renewed or wrapped over with a short-stretch bandage. The same is advisable when exudates from ulceration penetrate the bandage. This may occur especially during the initial treatment phase and the patient should be advised to come back if this happens. Thereafter, the bandage is changed every 7 days on average.
- Bandaging should go up to the capitulum fibulae (Fig. 6.22). The initial turn may be placed around the ankle or between the heel and the dorsal tendon to fix the bandage. Then the bandage is taken down to the foot to the base of the toes. To avoid impeding ankle movement, it is not necessary to cover the whole foot, because slight morning edema developing distal to the bandage will disappear shortly after walking is started. The ankle joint is always bandaged with maximal dorsal flexion of the foot.
- When wrapping the bandage up the leg, overlapping can be done in a spiral fashion or with figures of eight. Circular turns over the conus-shaped part of the leg could lead to a constriction of the skin.
- With a knee-high bandage the proximal end of the bandage should cover the capitulum fibulae.
- Graduated compression is achieved by exerting higher pressure on the distal lower leg than on the proximal calf.
- Graduation in pressure is also ensured by applying even pressure on the bandage, which is stretched to a uniform degree while wrapping in the distal to proximal direction. This occurs according to Laplace's law, which states that smaller diameters have increased pressures as long as tension remains constant and the leg increases in diameter in a distal to proximal direction (see Fig. 6.22).
- Cotton wool padding or a thin polyurethane foam bandage underwrap should be placed on the distal anterior tibial area to protect the protruding tendon with its sharp curvature from pressure that is too high.
- Bandage materials must be nonallergenic to avoid the development of dermatitis.
- The bandage must be applied with no gaps so that each turn overlaps about 50% with the previous turn.

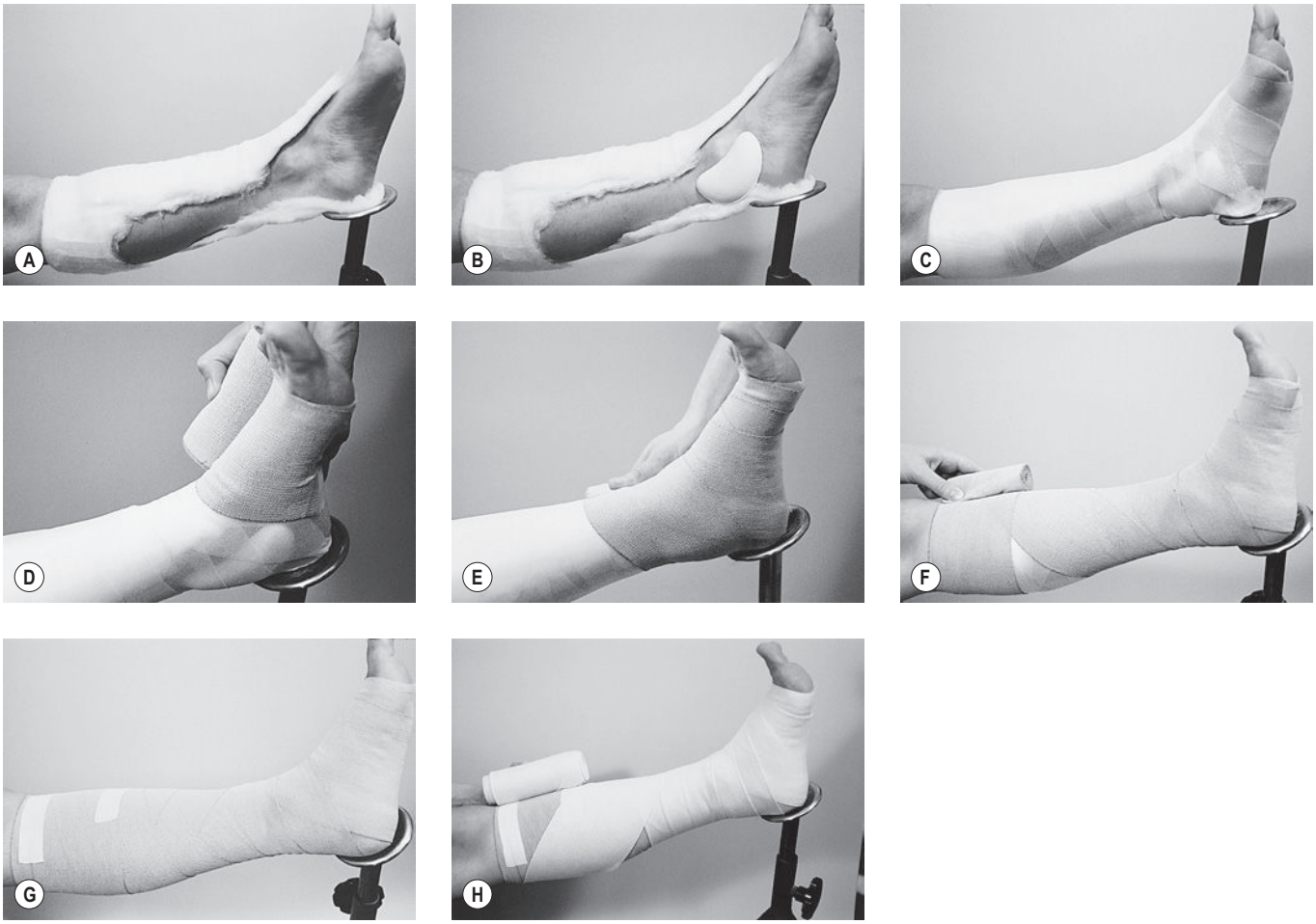

Figure 6.22 Preferred method for applying compression bandages. **A,** All areas with a pronounced curvature, such as ankles, Achilles tendon, instep and sharp edges of the tibia, are leveled and protected with cotton wool. **B,** The retromalleolar space is raised with a foam pad to prevent excess pressure on the medial and lateral malleoli. **C,** Cotton wool and pads are fixed to the leg with a light, absorbent dressing. **D,** Bandaging is begun at the medial dorsal foot with the foot in pronounced dorsiflexion. **E,** With each spiral turn, two thirds of the bandage is covered, except for the turn at the knee (**F**), where there is no circular bandaging, but the bandage turns across the leg and the contour of the leg is followed naturally. Uniform stretch on the bandage is applied at all times. **G,** Appearance of the completed first bandage. **H,** If a second bandage is to be applied, it is begun from the opposite direction from the lateral dorsal superior calf. (From Neumann HAM, Tazelaar DJ. Compression therapy. In Bergan JJ, Goldman MP, editors. Varicose veins and telangiectasia: diagnosis and treatment. St Louis: Quality Medical; 1993.)

- Local compression should be applied over the treated areas to avoid bruising, hematoma, edema and inflammatory reactions. Pads can increase local pressure over ulcers or firm lipodermatosclerotic areas.
- Ask the patient to walk and let them come back when the bandage is too tight. Pain may indicate arterial ischemia.
- Bandaging of the lower leg is sufficient for the majority of patients. Only in cases where there is extensive swelling or phlebitis of the thigh are compression bandages reaching up to the inguinal fold advisable. The flexor tendons in the kneehole should be protected by cotton wool. Adhesive short-stretch material, which does not slip down, is recommended for compressing the thigh. To keep the knee joint mobile, an adhesive two-way stretch bandage is used. To narrow the veins, the sub-bandage pressure at mid-thigh level should be at least 40 mmHg in the standing position.[42]
- Walking exercises are essential to optimize the effect of compression therapy.

COMPRESSION BANDAGES OR COMPRESSION STOCKINGS?

In general, compression bandages are able to achieve higher pressure than compression stockings.[90] Therefore, in severe stages of venous disease, treatment may be initiated with compression bandages.

Bandages are best indicated when temporary compression is required, such as in the acute phase of DVT, superficial phlebitis, in patients with venous ulcers, and in lymphedema and phlebolymphedema. As soon as the inflammatory signs and symptoms and the swelling are improved, compression stockings should be used to maintain the effect. Another benefit of bandages is that they can be reapplied as necessary as the edema in the affected limb is reduced. In this way the optimum compression needed for efficient therapy is obtainable.

Varying the strength of wrapping will alter pressure. The elasticity of bandages, although limited, changes somewhat according to the type used and functions as a fixed support.

Table 6.6 Some Practical Characteristics of Different Compression Products

Feature	CircAid* Legging	Unna Boot	Elastic Stocking	Inelastic Bandage	Elastic Bandage
Easy application	+	0	C	C	C
Unyielding	+	+	0	C	0
Compression maintained	0	0	+	0	+
Compression adjustable	+	0	0	0	(+)
Comfort level	+	+	C	+	C
Overnight removal	+	0	+	0	
Effective life	12 month	1 week	6 month	>6 month	6 month

+, Advantage; 0, disadvantage; C, conditional (depending on compression level and patient's physical conditioning).
*CircAid Medical Products, San Diego, CA.

Stockings, however, with elastic properties and graduated pressures fixed at the time of manufacture, undergo no change until the stocking is worn out and is no longer usable. In fact, stockings must be made of highly elastic materials to enable them to be pulled over the heel of the foot.

Elastic long-stretch bandages and elastic stockings may be handled and reapplied by the patients daily. Usually they are removed overnight. In contrast, Unna boot bandages and short-stretch bandages stay on the leg day and night, and should be changed by the bandager every few days. When they get loose they may be wrapped over by the patient preferably using a washed short-stretch bandage.

Multilayer bandages consisting of several layers of long-stretch material obtain the elastic property of short-stretch bandages (see Fig. 6.20) and may also stay on the leg for several days.

Table 6.6 gives an overview of some practical characteristics of different products.

COMPRESSION STOCKINGS

Graduated compression stockings are useful both for acute therapy after surgery or sclerotherapy treatment of varicose or telangiectatic leg veins and for long-term therapy in patients with CVI.[80,117] In the supine position, blood is pressed from the superficial to the deep veins. This effect may be used to improve the opacification of the deep veins when performing computed tomography (CT) venography.[118] During standing they achieve only a rather modest reduction of the venous diameters in the leg.[22,119,120] However, they provide an external support to prevent swelling. By virtue of their 'graduation' (see Fig. 6.12), it has been speculated that compression stockings help to propel blood toward the heart during walking.[39–47,121,122] Unlike nonelastic bandages they do not lose compression with time (except after months of continuous use).The importance of a graduated pressure profile for stockings was recently questioned by experimental findings showing a stronger effect of stockings on the venous pump if the stockings used exert a higher pressure over the calf.[123] Such stockings show superiority in reducing clinical symptoms in patients with chronic venous insufficiency.[124]

In general, compression stockings should be used only on legs in which the diameter has stabilized and edema is no longer a factor. When used in this manner, the stocking will correspond to the leg dimensions to prevent a renewed increase in leg circumference. For optimal performance, compression stockings should be fitted early in the day, when edema is reduced. However, even light stockings have been shown to be quite effective in reducing edema.[10]

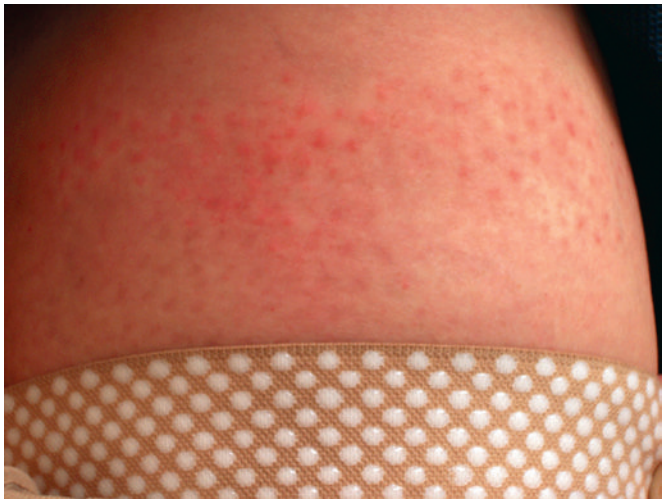

Figure 6.23 Allergic contact dermatitis from the silicone beads on this class II graduated compression stocking. Cutting the silicone band from the stocking and using a garter belt to hold it in place resolved this problem.

Although they usually do not have adverse effects when properly fitted, some types of elastic stockings may rarely cause an allergic reaction. This has been reported with elastic stockings composed of 76% nylon and 24% Elastane (Scholl Soft Grip; Scholl, UK) in less than 1% (2 of 126) of patients.[125] More commonly the silicone beads used to help hold the stocking up on the thigh cause an allergic reaction (Fig. 6.23).

CHARACTERISTICS OF MEDICAL GRADUATED COMPRESSION STOCKINGS

Most compression stockings are more or less two-way stretch stockings—elastic in both the longitudinal and transverse directions. This provides the stretch needed to apply a stocking that has the smallest diameter at the ankle and can be drawn over the heel. Two-way stretch stockings also have the characteristics of longitudinal bandages. The longitudinal elasticity of the stocking compensates for differences in limb length, thereby facilitating joint movements. In addition to

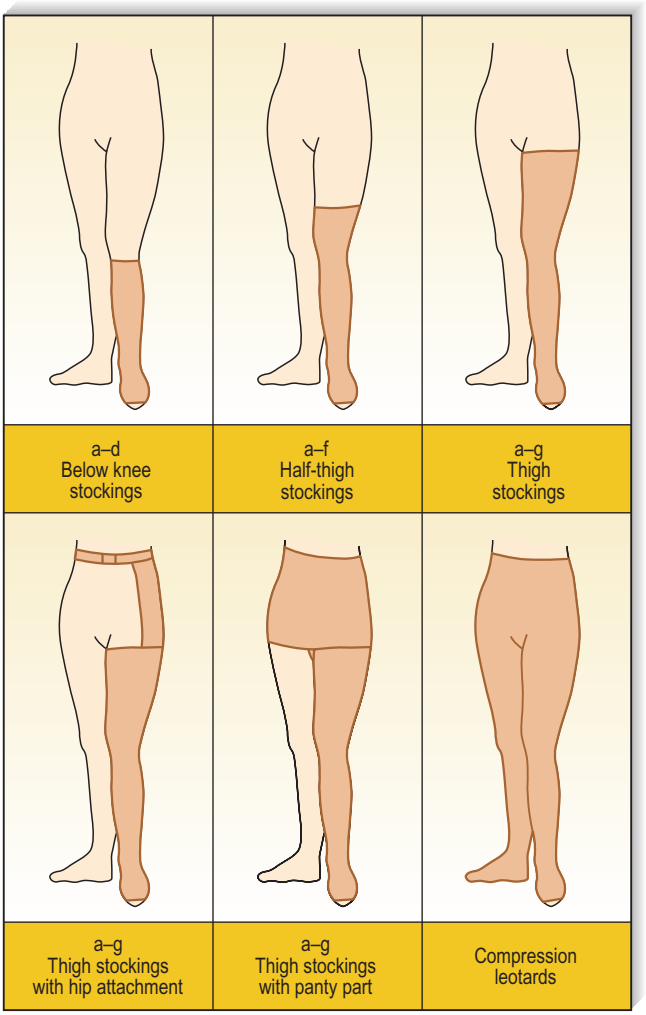

Figure 6.24 Six types of graduated compression stockings widely available. (Courtesy Juzo, OH.)

the compression generated by the stocking, another important parameter is the stiffness, elasticity or slope value of the stocking.

READY-MADE STOCKINGS

Ready-made or off-the-shelf stockings are manufactured in fixed sizes. Most manufacturers have several sizes varying in both length and width at various points on the ankle, calf and thigh (Fig. 6.24). Although the sizes are standardized to some degree by associations of stocking manufacturers, such as the Gütezeichengemeinschaft Medizinischer Kompressionsstrümpfe e.V. (Quality Seal Association for Medical Compression Stockings) in Germany,[78] there may be considerable variation between the sizings of different manufacturers. Therefore it may be prudent for distributors and physicians who dispense stockings to carry multiple brands in the event that some patients experience a poor fit with certain makes. It may be estimated that 80% to 90% of patients seeking treatment for venous disease can be fitted with some form of ready-made stockings.

CUSTOM-MADE STOCKINGS

Made-to-measure stockings are custom-made according to the length and circumference measurements of the patient's leg. Adjustments are made either by hand on flat-knitting machines, in which shaping is achieved by altering the width of the knit, or by machine in a circular-knit manner in which changes in the pressure and width are achieved by varying the tension of the weft and stitch size. Flat-bed knitted hosiery comes with a seam. Round-knitted stockings are seamless and can also be made to measure. For a good fit it is essential to get precise and accurate measurements of the patient. Custom-made garments will fit better than ready-to-wear. Several companies provide garments from woven fabric for patients of all body shapes and required compression levels.

Made-to-measure stockings should be prescribed under the following circumstances:

- For very large or small patients
- When there is a significant difference in the circumference between the right and left leg
- For the maintenance therapy of patients with lymphedema
- For patients with extreme deformities of the leg (e.g., 'champagne-bottle legs')
- When a special pressure gradient is required (e.g., increased pressure over the thigh)
- When the measurements of ready-made stockings do not correspond to the leg length and girth measurements of a patient (i.e., when there is a difference of more than 3 cm between the lower leg length and the standard 39-cm length used for ready-made stockings); this may not be applicable for all brands of stockings
- For patients who have a very large instep-to-heel circumference (i.e., one that is more than 12 cm larger than the smallest ankle circumference)[1]

PRESCRIPTION OF A STOCKING

Individual measurement of a compression stocking should be taken at the beginning of the day, when the leg is less edematous, in the standing position. The most important measurement location is at the ankle, where a graduated stocking exerts the greatest degree of pressure. Therefore, all ready-made stockings include the ankle as one of the measuring points. Measurements taken at various levels of the calf and thigh must also conform to the manufacturer's guidelines. If a calf or thigh diameter does not conform to the manufacturer's guide for that particular stocking size then a made-to-measure stocking should be used.

Recently a biometrical scanner combined with an 'intelligent ordering system' was introduced by the Bauerfeind company. Instead of measuring the leg circumference with a tape, digital photographs of the legs are taken against a structured background, which are then sent to the manufacturer for the production of a stocking to fit that individual.

A common error made by the physician attempting to avoid prescribing a made-to-measure stocking is to prescribe the next larger size of a ready-made stocking. This results in a lower pressure being exerted at the ankle; in addition, the counter-pressures are altered because the wider stocking is designed at all levels for different leg measurements. Proper measurement and fit of a compression stocking becomes increasingly important when higher compression classes are

required. Therefore made-to-measure stockings have particular application for compression classes above 40 mmHg, for example as used in lymphedema.[126]

The physician should note that differences of more than 15 mmHg could occur among different stocking manufacturers, not only by virtue of different types and strengths of elastic materials, but also by different methods of measuring the stocking to fit the leg. Some manufacturers provide only three ankle sizes of stockings, whereas others provide up to six or more ankle sizes. Thus there may be a large variation of applied pressure for different-sized legs among different stocking brands, as dictated by Laplace's law.

All manufacturers of compression stockings use a 'standard' wooden leg (the so-called Hohenstein leg), whose circumferences in each segment are circular.[1] This is also true for the B segment (see Fig. 6.11) representing the ankle area, which is taken as the reference point for indicating the pressure class of the stocking. This B segment is the area in which the crosssection through a human leg shows the most extensive deviations from a circle.[85] Here the radius varies dramatically, being small over the malleoli and the Achilles tendon and even 'negative' between the inner ankle and the tendon. According to the law of Laplace, the compression pressure will therefore also change considerably, which explains the discrepancy between in vitro and in vivo measurements of interface pressure especially in this segment. However, a good correlation could be shown between the pressure ranges declared by the producers of high-quality stockings and the actual interface pressure exerted on the human leg.[127]

STOCKING LENGTHS

Up to six styles of medical compression stockings are available, depending on the manufacturer: knee-length, mid-thigh or high-thigh pantyhose or leotard, one-legged pantyhose, thigh with waist attachment and maternity pantyhose. Some manufacturers have open-toed kinds available for some of the types, especially the single leg, high-thigh variety. Regardless of the style, most stockings are available in three lengths: knee length, mid-thigh and high-thigh. According to the standardized figure, a knee-length stocking is designated as 'AD', a mid-thigh stocking as 'AF' and a (high) thigh-length stocking as 'AG' (see Fig. 6.11).

There are specific indications and contraindications for the various stocking lengths. Knee-length stockings should be prescribed only if the 'C' circumference is approximately 2 cm greater than the 'D' circumference; otherwise it will have no hold on the leg and tend to slide down. In addition, if the 'A to D' length is too great, the excessive length interferes with movement at the knee. The patient usually folds the excess stocking down below the knee; this doubles the counter-pressure at point 'D' and thus may reverse the 'graduated pressure'. Likewise, if the 'A to D' length is too short, the patient will try to stretch the stocking beyond its natural point, thereby decreasing the effective circumferential pressure and thus defeating the purpose of wearing the stocking.

In patients with marked adiposity of the knee region, the upper edge of the stocking may produce skin bulging, which may be particularly bothersome on the inner aspect of the knee. In these cases it may be necessary to fit the patient with a mid-thigh stocking. Alternatively, tumescent liposuction of the bulging knee corrects this deformity and is a simple procedure.

To prevent or treat ankle edema or skin changes caused by CVI the majority of patients can be fitted with below-knee, ready-to-wear stockings.

PRESSURE GRADIENT

Graduation is not only a result of the leg circumference, it can also be added to a circular knit by altering the knitting construction from the ankle to the knee or thigh to reduce the tension from distal to proximal. Some studies have demonstrated that a pressure drop of 26% to 59% from the ankle to the thigh is desirable with graduated medical stockings.[128–130]

As previously explained, the postulated graduated pressure was recently questioned. The measurement of an ideal pressure profile on the human leg depends on several factors, especially on the shape of the measuring point.[131]

It has to be considered that the pressure gradient postulated for compression hosiery is based on pressure readings of the smallest segment of a wooden leg model in the laboratory (B-point) presenting a circular cross section. Owing to the fact that the human leg is flat or even concave at the corresponding medial ankle region, in vivo measurements at this point frequently show lower pressure values than at the B1-point 12 cm above (see Fig. 6.17).

There are many situations for which the dogma of a pressure gradient is unrealistic. Because of the changes of segmental circumferences and local curvatures that happen with every step, the local dynamic pressure fluctuations under a compression device may be very complex and pressure peaks may occur that are higher at a proximal level than distally. In general the necessity for a continuous gradient of pressure maximal at the ankle and diminishing up the limb is founded more on theory than on an evidence base.

New stockings have been introduced that exert a higher pressure over the calf than over the ankle area. These are easier to put on and are advocated not only in sports,[132] but also in venous patients.[133]

PROPER FIT AND POSITION

Because the efficacy of a compression stocking is directly related to a proper fit, its adherence to the leg to prevent vertical movement is important. Pantyhose stockings are the most expensive method to ensure the stocking remains in place by virtue of the attachment at the panty line. The only disadvantages are increased constriction on the lower abdomen and increased temperature and moisture retention in the groin generated by an additional undergarment.

With single-leg, thigh or calf stockings, various inexpensive methods such as adhesive tape, glues, clips or garter belts, serve to ensure proper positioning. Disadvantages of tapes or glues include the pain on removal of tape from hairy legs and the irritation of allergy caused by the adhesive portion of the tape. Various types of clips that secure the stocking to underwear are available. Disadvantages include tearing or stretching of the undergarment and cutaneous pressure and/or irritation by the clip itself.

Garter belts comprise a more elegant, practical and perhaps fashionable method for ensuring correct stocking placement. These belts may be built into the stocking as a

waist attachment or purchased separately in various styles. Disadvantages include the digging in of the belt into an obese thigh if the belt is too narrow and the possibility of the garter itself producing a tourniquet effect.

Finally a new type of silicone top-band on high-thigh- or mid-thigh-length stockings is available from many manufacturers of graduated compression stockings. It keeps the stocking in place without the disadvantages of glues, clips or garter belts.

DONNING MEDICAL COMPRESSION STOCKINGS

Before donning the stocking, the patient should be advised of the following considerations. Hand jewelry should be removed to avoid damaging the stockings. Fingernails should be smooth and relatively short. Rubber gloves are helpful and recommended both to prevent damage to the stockings from long fingernails and to grip the stocking. Talcum powder may be applied to the leg or a light Perlon pantyhose or stocking may be worn under the compression stocking to create a smoother leg over which to slide the stocking. Finally, satin foot 'socks' and foam-rubber foot pads provided by the stocking manufacturer are helpful in getting an open-toe stocking over the ankle (Fig. 6.25).

After preparing the foot and leg, turn the stocking inside out with the foot from the heel to the toe tucked into the stocking (Fig. 6.26A). Stretch the foot opening with the fingers or thumbs of both hands and pull the stocking foot over the foot up to the instep. Draw the stocking upward over the heel until pulling becomes difficult (Fig. 6.26B). Push the fold that forms across the instep and heel of the stocking over the heel. Finally pull the stocking up in sections, always remembering not to pull it over long distances all at once, but to proceed in small steps (Fig. 6.26C). When the stocking is applied without folds over the calf, the thigh

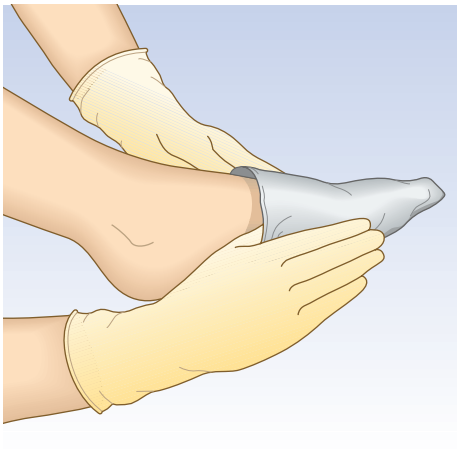

Figure 6.25 Foot sock, which is helpful for getting an open-toed stocking over the ankle.

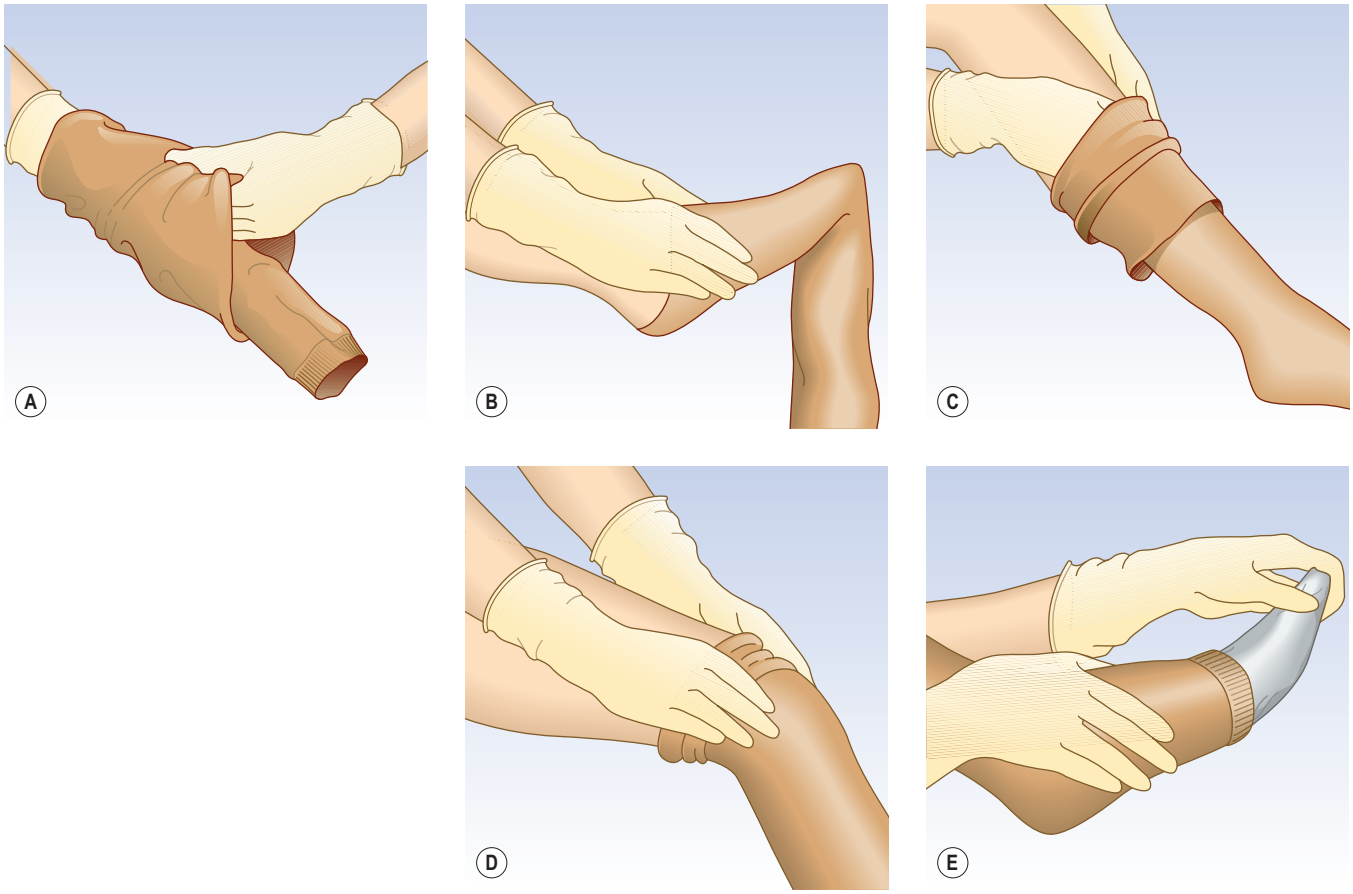

Figure 6.26 Schematic diagram illustrating the proper method for donning the compression stocking. **A,** Turn the stocking inside out. Tuck in the foot from the heel to the toe. **B,** Using both hands, pull the stocking over the foot up to the instep, drawing it upward over the heel. **C,** Continue pulling the stocking up in small sections. **D,** Pull the thigh section over the knee. **E,** Remove the foot sock. (Courtesy Juzo, OH.)

section is then pulled over the knee (Fig. 6.26D). Finally, remove the foot 'sock' (Fig. 6.26E).

It is very important for the physician or nurse to instruct and observe the patient applying the stocking. Compression is effective only when a stocking has been fitted correctly and is applied correctly. If the patient encounters difficulties in applying the stocking because of age, obesity, arthritis, etc., arrangements should be made to have an experienced helper on hand when needed. It is important to note that if patients have difficulty in applying higher-compression class stockings, wearing two layers of lighter stockings, one over the other, should be helpful. As discussed previously, the compressive effects of stockings are additive and stiffness increases exponentially. Zippers in stockings (available on some calf-length stockings) also make donning them easier.

Donning devices significantly improve the ability of elderly patients with CVI to don compression stockings successfully. However, there are differences in user-friendliness among the devices.[134]

An application aid for compression stockings is available from various compression stocking companies. These devices are cleverly-designed simple metal supports that make donning compression stockings easier, even when the stockings must be placed over compression padding (Fig. 6.27). The compression stocking is pulled over the half-circle bracket located on the front (open) side of the device so that the heel portion of the stocking is 2 to 3 inches (about 5–7.5 cm) below the top on the half-circle bracket. The heel portion is positioned facing the user and the toe of the stocking is facing toward the open side of the device. The patient's foot is then placed into the foot of the stocking until the foot is completely on the floor or until the heel is in place. The metal grips on either side are then used to pull the rest of the stocking onto the leg. Once the stocking is above the calf, the device may be pulled away and the remainder of the stocking then can be easily pulled up.

The Doff N' Donner device is an ingenious new donning aid (Sigvaris). Patients may be referred to web pages that also offer demonstrations on YouTube (http://www.supporthosestore.com/Categories/249-Patient-Assistance-Donning-Aids.aspx).

PATIENT COMPLIANCE

Noncompliance is the most important factor limiting the use of compression stockings. The reasons for noncompliance can be grouped into two interdependent major categories: (1) wear-comfort factors and (2) the intangible sense of restriction imposed by the stockings.[135]

In addition to a measurable improvement in multiple parameters of CVI, a study on symptoms of CVI has demonstrated an improvement after 1 and 16 months of wearing graduated compression stockings.[136] In this study 112 patients with CVI and significant CEAP classification [clinical state (C), etiology (E), anatomy (A) and pathophysiology (P)] were treated with a 30- to 40-mmHg graduated compression stocking. Patients rated on a five-point scale the degree of swelling, pain, skin discoloration, cosmetic problems, activity tolerance, depression and sleep problems caused by CVI. There were statistical improvements in all scores at 1 month, with continued improvement at 16 months. Most importantly 70% of patients were still wearing their stockings at 16 months, demonstrating their comfort over the symptoms of CVI. This is in contrast with the impression of poor compliance and indicates improved comfort with modern compression stockings. Similar degrees of improvement were also demonstrated in 31 patients with CVI wearing low- or medium-grade stockings.[137] There was no significant difference in the symptoms of these patients despite the difference in graduated compression. Therefore patients who cannot tolerate high compression classes should be fitted with lower class stockings. Mild compression is better than no compression.

Patients' compliance in wearing their compression stockings is frequently underestimated by the physicians. In a Canadian survey physicians estimated that 50% of patients after DVT would wear compression stockings daily, 30% occasionally and 20% would never wear them.[138] In this

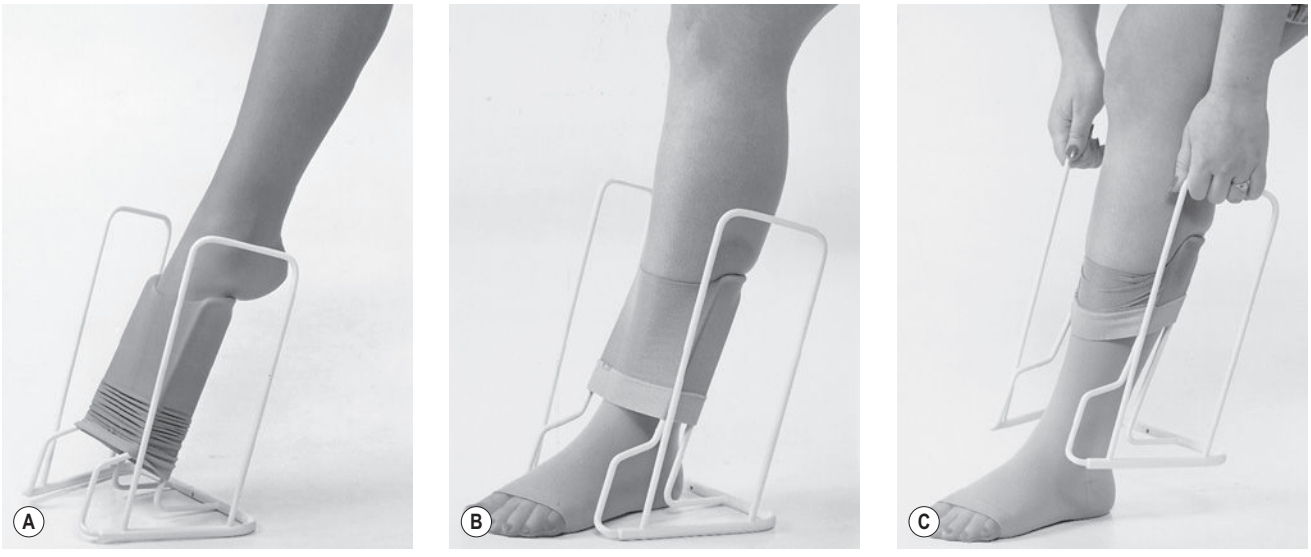

Figure 6.27 Medi Butler. **A,** After putting the compression stocking on the bracket, insert the foot. **B,** Continue until the foot is completely on the floor and the heel is in place. **C,** Pull up on the metal side grips until the Butler is above the calf, then remove it and continue until the stocking is in place. (Courtesy Medi USA, Whitsett, NC.)

study the most important reasons for noncompliance were thought to be discomfort (74%), hard to put on (71%) and high costs (53%). When the patients were asked, daily use was reported by 87%, once or twice weekly by 3%, less than once a week by 6% and never or rarely by 4%. In a European follow-up of patients, it was shown that there is less swelling of the thrombosed leg when the stockings are still being worn 2 years after DVT compared with patients who stop compression therapy before this time, and that most of those patients who still suffer from pronounced residual swelling use them.[139]

CARE OF THE MEDICAL COMPRESSION STOCKING

Because these stockings are worn on a daily basis in extremely close contact with the skin, they are subjected to considerable wear and tear. The chemical stresses from sweat, soaps, creams and body oils, in addition to the physical stresses of the nearly continuous stretch and relaxation with movements of the leg, result in a gradual decline in the compressive effect of the stockings. This decline was measured in class II and class III stockings. Flat-knitted and round-knitted European class II stockings showed a mean pressure decrease from 29.3 to 26.5 mmHg after 3 months of daily wear. Strong stockings had a similar rate of decreasing pressure from 47.5 to 44.2 mmHg.[140] Therefore compression stockings have a limited effective life. To ensure that they last as long as possible, special care is required.

The first lesson in proper stocking care is to avoid excessive trauma. Therefore rubber gloves should be worn when the stocking is put on to avoid tearing the threads with fingernails. Likewise, toenails should be trimmed and hard calluses, verrucas or other rough spots on the feet should be softened or removed. Also the stocking should be eased onto the leg, not pulled.

The stocking should not come into contact with ointments, creams, stain removers or other solvents, especially if it is composed of rubber threads. These substances can damage the fine elastic yarns by causing them to swell, thus reducing the strength and elasticity of the fabric. Some chemical components of topical steroid creams (chlorocresol and glyceryl mono-oleate) may have a negative influence on Lycra yarns, causing a decrease in elasticity and also discoloration.

Regular and careful washing is necessary to maintain the elastic properties of the fabric because of the harmful effects of sweat, skin oils and environmental dirt that accumulate in the fabric while the stocking is worn. These substances will penetrate deeper into the elastic yarns if allowed to remain on the fabric for long intervals between washings. Environmental dust is damaging to the yarn by virtue of its abrasive action when the elastomers are stretched and relaxed.

Ideally compression stockings should be washed every day. In fact, a study of six stocking types machine washed 15 times at 40°C demonstrated no decrease in resting pressure or elasticity.[98] Therefore, if long-term use is required, it is best to provide the patient with two pairs of stockings that can be alternated between washings. Most compression stockings incorporating spandex can be machine washed on a fine-gentle cycle with warm (40°C) water. This gives a better cleansing action than hand washing. (Consult the manufacturer's guidelines for specific instructions.) Gentle detergents without bleach or alkali are best. Gentle spinning after the washing cycle is harmless to compression stockings and quickens the drying process. Rather than being hang-dried from a line, compression stockings should be laid flat on a drying rack or towel. Low heat may be used in the drying process with most brands of compression stockings. With normal wear and proper care, compression stockings should have an effective life of 4 to 6 months.

If compression stockings are worn intermittently (during airplane flights or only after sclerotherapy or surgical treatments), they should be stored in a cool place after washing. Exposure to heat for prolonged periods can degrade the yarn and eliminate compression.

DANGERS, COMPLICATIONS AND CONTRAINDICATIONS

The most important caveat with any kind of compression therapy is the presence of an arterial occlusive disease that may be unrecognized.

Arterial ischemia can occur if the external compression pressure exceeds the intraarterial perfusion pressure. This is of concern particularly in the presence of venous leg ulcers during treatment. Two studies estimated the frequency of unsuspected arterial insufficiency among patients with chronic leg ulcers at 21%[141] and 31%.[142] Callam et al[143] surveyed consultants in general surgery in Scotland regarding their experience with compression therapy in the previous 5 years and found 147 cases of cutaneous ulceration caused by compression. Compression bandages accounted for 74 of 147 cases reported, with elastic and antiembolism stockings accounting for 36 and 38 cases, respectively. Also eight patients were reported who required amputations of the digits or feet as a direct result of arterial ischemia caused by an excessively tight compression bandage or stocking. It has been estimated that up to 50% of patients over 80 years of age with leg ulcerations also have significant arterial disease.[141] In a survey of 1416 venous reflux ulcers, 13.6% had moderate and 2.2% had severe arterial disease.[144]

Consequently the physician should always check arterial pulses before and after applying a compression bandage or fitting a compression stocking, especially in the elderly. Low-stretch bandages offer more safety in patients with arterial disease because these bandages can be applied with a very low resting pressure, achieving still-effective pressure peaks during ambulation. The natural history of such patients presenting with mixed ulceration has been described by Marston et al.[145] It was demonstrated that mixed, arterial–venous ulcers may heal without arterial therapeutic interventions, but healing time is prolonged in comparison with purely venous ulcers. This is in accordance with experimental findings reported by Mosti et al, that showed an increase in arterial inflow in patients with an ankle–brachial pressure index (ABPI; the ratio of ankle blood pressure to brachial blood pressure) between 0.5 and 0.8 as long as the pressure of the nonelastic bandages did not exceed 40 mmHg and at the same time showed an improvement of the ejection fraction of the venous calf pump.[58] Doppler ultrasound allows measurement of arterial pressure, which has to be done in every case before a high-pressure bandage is applied for the first time. An ABPI below 0.5 corresponds to critical

ischemia and is considered to be a contraindication for compression.[1,81,117]

Sensory disturbances should be a warning for reevaluating the degree of compression in the posttreatment period (see Chapter 8). If the patient suffers from diabetic neuropathy, minimal pressure damage to the skin may stay unrecognized and may be the starting point of skin necrosis when the bandage or the stocking is not removed.

When firm compression bandages are applied to both legs, a considerable volume of blood can be shifted toward the heart.[146] This can lead to an increase of the preload of the heart and affect cardiac output. Therefore severe decompensated heart failure should be considered as a contraindication for bilateral firm bandages.

CLINICAL INDICATIONS FOR COMPRESSION THERAPY

A review of all randomized controlled trials (RCTs) assessing the clinical efficacy of compression in venous and lymphatic disorders of the lower extremity has been published.[147]

Compression is the basic treatment modality in patients with chronic venous insufficiency; however, it is still underused.[148]

THE USE OF COMPRESSION ALONE IN PREVENTING VARICOSE AND TELANGIECTATIC LEG VEINS

Although clinical evidence is still lacking that compression is able to reduce a progression of venous disorders, some theoretical considerations support its use.

The cause of varicose veins is unknown. Several data support the assumption that the primary lesions leading to circumscribed dilation of the venous wall are defects at the molecular level in the vessel wall that result in a derangement of the collagen fibers and of the matrix. These anatomic abnormalities cause a disturbance of the hemodynamics, promoting the progression of the disorder.

Varicose and telangiectatic leg veins progress when the volume and subsequent pressure of blood within the vessel lumen exceed the vessel's capacity to enclose that volume. The deep venous system, by virtue of its position within a musculofibrous sheath, can accommodate such changes. Major parts of the superficial venous system are not enclosed in a rigid sheath. Thus to accommodate the increase in flow the vessel lumen increases in diameter. When this increase in diameter is supraphysiologic, the one-way valve cusps no longer meet and they become incompetent. This causes excessive pressure, with blood volume routed into smaller branching vessels, producing an abnormal dilation. This hemodynamic explanation of varicose vein development is best regarded as a vicious cycle (Fig. 6.28).

The primary method of reversing the changes just mentioned is to normalize the quantity of blood within the vessel lumen. This can be accomplished by sealing off incompetent perforator veins or junctions between the deep and superficial systems through surgical ligation, endoluminal radiofrequency closure or sclerotherapy-induced endofibrosis. Compression of the leg provides a sheath around the vessel so that blood flow will be propelled upward toward the heart instead of laterally against the vein wall. Bandages, and to a lesser degree graduated compression stockings, provide the external support needed to produce this effect.

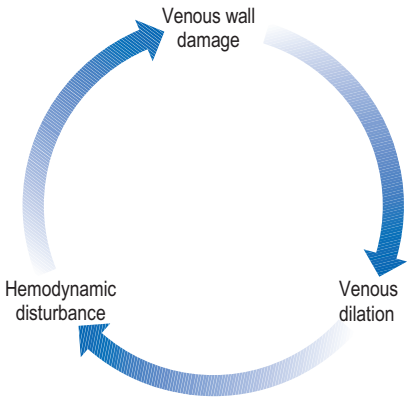

Figure 6.28 Vicious cycle of varicose veins.

Externally supporting untreated varicose veins will narrow their diameter and decrease retrograde blood flow.[149] External pressure may also provide a normalization of cutaneous blood flow. In support of this theory, improvement in cutaneous oxygenation has been demonstrated with the use of compression in patients with venous stasis after only 10 to 15 minutes.[150]

The most important indication for compression in patients with varicose veins is the relief of aching symptoms with all classes of compression stockings.[36,37,121] This has also been shown in an RCT in patients with symptomatic varicose veins of pregnancy.[151] Patients with postphlebitic limbs find that the 30- to 40-mmHg and 40- to 50-mmHg stockings control edema and symptoms better than do 20- to 30-mmHg stockings. Graduated compression stockings of 20 to 30 mmHg are best used for conservative treatment of symptomatic varicose veins and stronger stockings may best be used for conservative treatment of CVI (see previous discussion).[47]

There are no RCTs available showing that compression is able to prevent the progression of venous disease.[147,152]

RATIONALE FOR THE USE OF COMPRESSION IN VARICOSE VEIN SCLEROTHERAPY

The basic concept of Fegan's 'empty vein technique' is to keep the blood clot after injection of the sclerosing agent as small as possible.[153–155] Postsclerotherapy compression primarily eliminates a thrombophlebitic reaction and substitutes a 'sclerophlebitis' with the production of a firm fibrous cord.[156] Compression serves at least six purposes:

1. Compression, if adequate, may result in direct apposition of the treated vein walls to produce a more effective fibrosis (Fig. 6.29).[155,157,158] Therefore weaker sclerosing solutions may be used successfully.
2. Compression of the treated vessel decreases the extent of thrombus formation, which inevitably occurs with the use of all sclerosing agents[158,159]; this may decrease the subsequent risk of recanalization of the treated vessel.[153,154]
3. A decrease in the extent of thrombus formation may also decrease the incidence of postsclerosis pigmentation[158–162] (see Chapter 8).

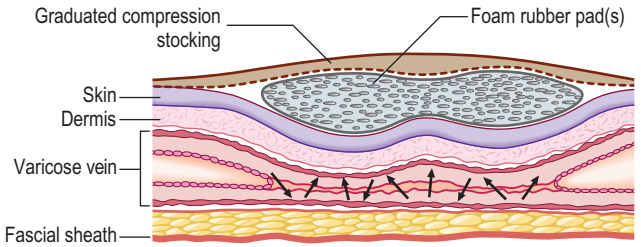

Figure 6.29 Schematic diagram demonstrating idealized compression of a treated varicose vein segment using foam rubber pads under a compression stocking. (Redrawn from Wenner L. Vasa 1986;15:180.)

4. The limitation of thrombosis and phlebitic reactions may prevent the appearance of telangiectatic matting[160] (see Chapter 8).
5. The physiologic effect of compression is to improve the function of the calf muscle pump, which is accompanied by subjective improvement.[163]
6. Compression stockings increase blood flow through the deep venous system.[22] This acts to rapidly clear any sclerosing solution that has inadvertently made its way into the deep venous system and thus prevents damage to valves in the deep venous system.

HOW MUCH PRESSURE IS NECESSARY FOR VARICOSE VEINS?

The optimum interface pressure required to compress the varicose vein after sclerotherapy has yet to be defined.

Initial compression measurements taken during manual wrapping of the leg with Crevic crepe bandages by multiple surgeons using the technique of Fegan[153] show an average between 20 and 100 mmHg with a mean of 54 mmHg at calf level.[128] In addition, experimental varicose vein models have shown this level of compression to cause a reduction of the vessel lumina by 94%.[128] Thus the classic technique for compression sclerotherapy is theoretically sound.

The physician should consider the posture of the patient when prescribing compression stockings. If higher compression pressures are used (e.g., through the use of double stockings), care must be taken to inform patients to remove the outer stocking when not ambulatory. A sustained external pressure above 30 mmHg with elastic material applied to the leg of supine patients is hardly tolerated and may impair peripheral blood circulation and skin temperature.[108] Patients may perceive this as achiness in the ankle area that occurs during sleep and resolves with walking after 30- to 40-mmHg compression stockings have been worn to bed following sclerotherapy.

By having compression of 30 to 40 mmHg at the ankle, the compressive strength at other locations on the leg may be between 10 and 20 mmHg, depending on the site and amount of underlying bone, adipose tissue and muscle.[33] Experimental models have demonstrated that external pressures of 10 to 15 mmHg reduce the capacity of the underlying varicose vein in the upright position only minimally.[22,42,128,164] Therefore with the use of this degree of compression one does not attempt to completely empty intravascular blood from the treated veins.

LOCAL PADS AND ROLLS

To occlude a vein completely, the external pressure should exceed the intravenous pressure. In the standing position, the intravenous pressure is about 70 mmHg at the lower leg and about 30 mmHg at thigh level, depending on the body height. The pressure exerted by a compression stocking at thigh level is about 10 to 15 mmHg, which is too low to occlude the vein.[22,119]

By applying small rolls with different materials over the injected vein, this difficulty may be overcome, as demonstrated in Figure 6.30. When the injected vein is covered by a small rubber roll, a thigh-length compression stocking with a pressure of 15 to 20 mmHg may compress the vein even in the standing position.

The increase of pressure in a localized area by using narrow foam rubber pads under compression stockings has been described by several authors.[165–170] Foam Sorbo pads (STD Pharmaceuticals, Hereford, UK) (Fig. 6.31) are widely used in Great Britain.[156] A new wedge-like rubber foam device (postop device; Medi, Bayreuth, Germany) has been developed specifically for compressing the great saphenous vein on the thigh (Fig. 6.32) and a very satisfying outcome after stripping operation was reported.[48]

Different types of pads do provide different pressures. A study by Hirai et al[168] demonstrated pressure over the anterior tibia with a moderate-pressure stocking to be 20.3 mmHg without pads, 59.1 mmHg with a cotton pad or gauze pad, 73.5 mmHg with a foam rubber pad, and 76.5 mmHg with a hard rubber pad.

In addition to producing an increase in cutaneous pressure, their use, especially in the popliteal region, has decreased the incidence of abrasions from pressure stockings and tape, thereby improving patient comfort. In one physician's practice,[169] foam rubber pads have been noted to produce minor skin irritation (erythema) in up to 28% of patients. Another device for increasing local pressure is Molefoam (Scholl, UK). This product comes in sheets of 7-mm thickness that may easily be cut to size. The adhesive side is covered with paper that is peeled away. Molefoam has a decreased incidence of local irritation (14% versus 28% for Sorbo pads). One study that compared the efficacy of sclerotherapy with Sorbo versus Molefoam showed no difference between the two groups.[169]

Another clever method for increasing local pressure is the use of rolls of cotton wool (Fig. 6.33).[170] The roll is secured with a nonelastic material. This method is advantageous for compressing long lengths of veins. A study of 100 patients (120 legs) with varicose veins treated with sclerotherapy, followed with long cotton wool rolls under compression stockings, found good results in all patients.[170] Compression was given by a combination of European class I (daytime and nighttime) and class II (daytime only) compression hosiery. Only three patients developed intravascular blood clots. The mean pressure under the pads was 84 mmHg (68–122 mmHg). In this study, cotton rolls and class I stockings were removed at 1 week and patients continued to wear class II stockings for an additional 3 weeks.

Local padding of the injected vein may considerably improve the emptying of the vein. A satisfactory compression of the veins by compression stockings may be a problem because of a markedly low pressure especially in the thigh

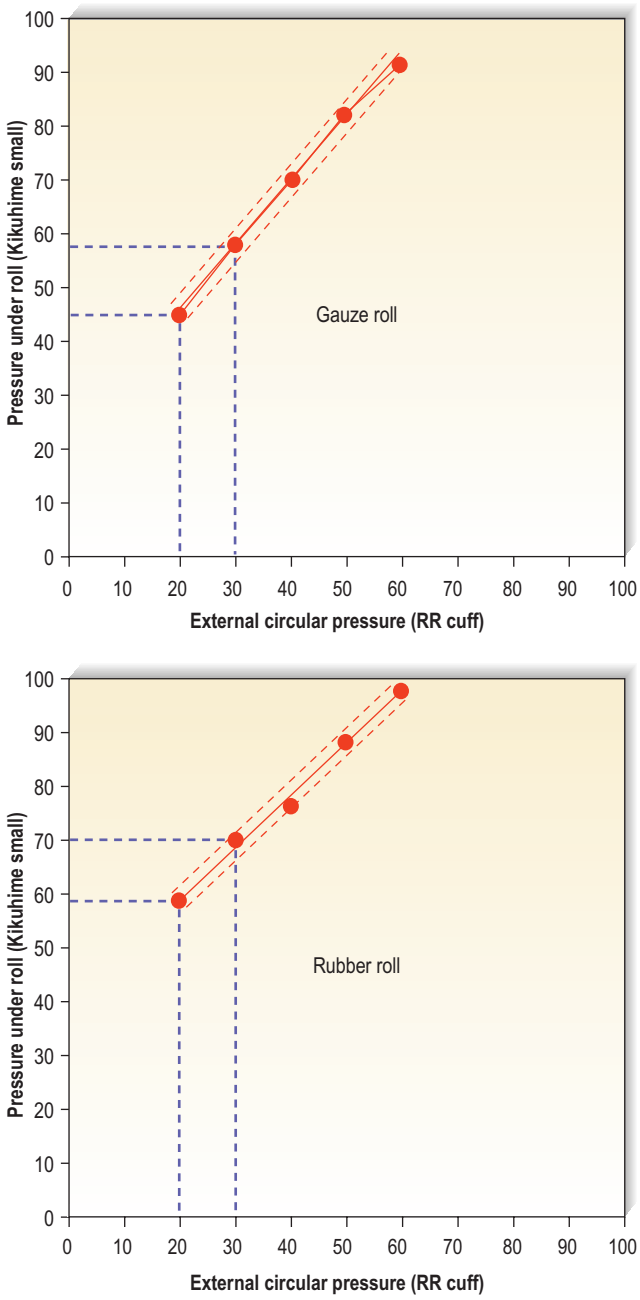

Figure 6.30 A blood pressure cuff ('RR cuff') is applied on the thigh and inflated in a stepwise fashion from 20 to 60 mmHg (*x axis*). The local pressure over the great saphenous vein is measured using a small Kikuhime pressure transducer (MediTrade, Soro, Denmark), which is placed under a 2-cm-thick gauze roll *(top)* and then under a rubber roll with the same dimension *(bottom).* With the soft padding material *(top),* the local pressure over the vein *(y axis)* can be doubled; with the rubber pad *(bottom)*, a cuff pressure of 20 mmHg will increase the local pressure under the pad close to 60 mmHg.

region. In such cases, compression bandages with adhesive material applied over the local pressure rolls may be a good alternative.[48,171]

HOW LONG SHOULD COMPRESSION BE MAINTAINED?

In addition to the degree of compression needed to effect optimal sclerotherapy, the duration needed to maintain

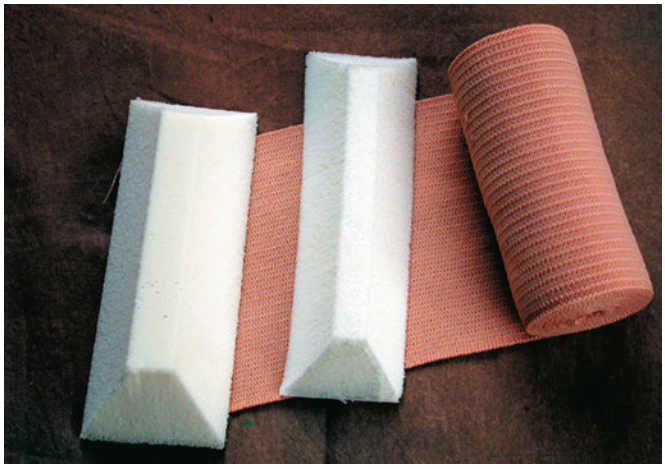

Figure 6.31 Foam Sorbo pads. (STD Pharmaceuticals, Hereford, UK.)

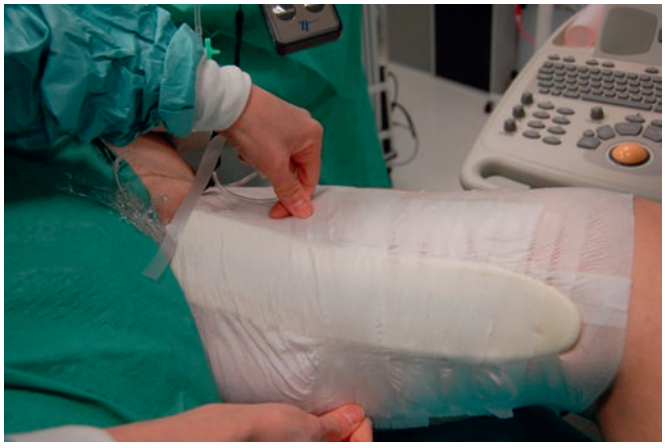

Figure 6.32 A wedge-like foam pad (Postop device, Medi, Germany) is attached to the thigh by crosswise taping after endovenous laser ablation of the great saphenous vein. (Courtesy M. Lugli and O. Maletti, Modena, Italy.)

compression is also open for debate.[172] The classic technique for sclerosis of varicose veins described by Fegan[153,154] and used by Hobbs,[173] Doran and White[174] is to continue compression for 6 weeks. This period was not arrived at randomly but through multiple histologic examinations of sclerotherapy-treated varicose veins at intervals of 30 seconds; 1 and 5 minutes; 12, 24 and 36 hours; 6, 8, 12 and 14 days; 3, 4, 7, 10, 16 and 20 weeks; and 0.5, 1 and 5 years.[175] Fegan concluded that organization of the fibrous occlusion required at least 6 weeks. However, a randomized study found no difference in clinical results at 2 years when compression was maintained for 3 weeks as compared with 6 weeks.[176] Thus many phlebologists recommend a maximum of 3 weeks of compression for varicose veins.

A review on RCTs regarding this question was published in 2006.[145] Studies have shown that compression bandages maintain significant compression for only 6 to 8 hours while patients are ambulatory and lose up to 50% of their initial compression pressure in recumbent patients at 24 hours,[165] thus questioning the rationale for prolonged use. After phlebectomy, bandaging for 1, 3 and 6 weeks did not show a difference in efficacy at 2 months postoperatively.[177]

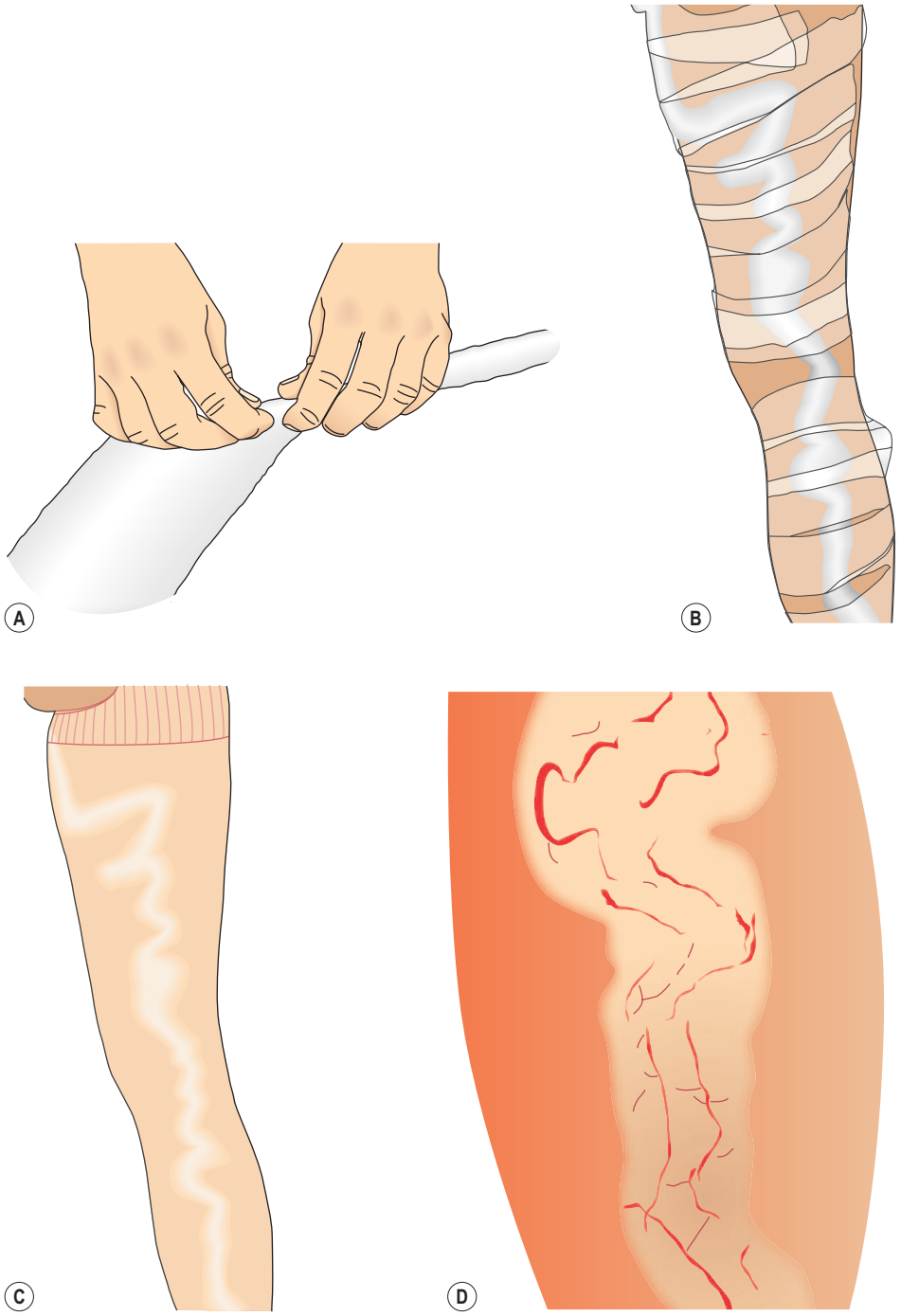

Figure 6.33 **A,** A flat piece of cotton wool is twisted into a firm roll with a diameter of approximately 2 cm. **B,** The cotton wool roll follows the course of the varicose vein and is secured to the skin with 5-cm-wide Leukopore bandage (BSN-Jobst, Charlotte, NC). **C,** Appearance after application of a 30- to 40-mmHg compression stocking. **D,** Appearance after stocking and cotton wool are removed in 2 weeks. Note compression of both the varicose vein and overlying tissues.

However, in this study compression with an elastic bandage was given to all groups for only 1 week, with the variable being a Tubigrip tube gauze (Seton Products, Montgomeryville, PA) applied only during the day, which provided minimal compression. Finally, a randomized study of the use of compressive bandages in the treatment of varicose veins with a 3-month follow-up was reported.[178] The study demonstrated through both subjective and objective findings that 3 days of compression equaled the results at 6 weeks. This study used a Coban bandage dressing that may not maintain effective pressure beyond 8 hours.

A corollary to the amount of time necessary to effect adequate compression is whether it is necessary to continue compression while the patient is lying down or asleep. The authors recommend that some degree of compression be maintained at all times to ensure optimal contraction of

the treated vein. In fact, studies have demonstrated that veins become more distensible during sleep.[179] This has been postulated to occur as a result of respiratory factors or emotional factors during dream states. In addition, thrombogenesis after the sclerotherapy-induced injury to vascular endothelium is maximal 8 hours after treatment, which may be when the patient wishes to lie down (see Chapter 8). Compression here speeds deep venous blood flow to prevent thrombosis in the deep system after treatment. Finally it may be impractical for patients to remove and reapply the stocking at night if they must get out of bed for any reason. Therefore if a high degree of compression is required after treatment, the use of double stockings appears practical, because one of the stockings can be removed while the patient is lying down.

Some anatomic sites necessitate inventive measures to effect compression of the underlying varicose veins. Perhaps the most difficult area to compress on the leg is the vulvar region. The authors have found the 'vulvar pad' described by Nabatoff,[180] and the V2-Supporter (Prenatal Cradle Inc, Hamburg, MI.) described by Ninia,[181] to be useful in this area.

There are colleagues who do not perform any compression after sclerotherapy of large veins, especially in France.[182] Based on a comparative study the general recommendation of using compression after foam-sclerotherapy of the great saphenous vein as a routine has recently been questioned.[183] It has to be emphasized that in this study French compression class II stockings were used corresponding to a pressure range between 15 and 20 mmHg on the leg (around 10 mm Hg at thigh level). This pressure is much too low to narrow veins in the upright position.

SCLEROTHERAPY OF SMALL VEINS

RATIONALE FOR THE USE OF COMPRESSION IN THE TREATMENT OF TELANGIECTASIAS

Although compression sclerotherapy is now standard practice in the treatment of varicose veins, its use in the treatment of smaller abnormal leg veins and telangiectatic 'spider' veins has never been adopted uniformly. Many European colleagues do not use any kind of compression after sclerotherapy of small veins.[182] However, the same justification for the use of compression in larger veins should hold true for its use in smaller veins. Convincing results from a randomized controlled study are favoring the use of compression 23- to 32-mmHg hosiery for 3 weeks after sclerotherapy of small veins.[184]

Duffy[185] has classified unwanted leg veins into six types based on clinical (and possibly functional) appearance (see Box 2.6). Types 1, 1A and 1B are probably dilated venules, possibly with intimate and direct communication to underlying larger veins from which they are direct tributaries.[186] Both Bodian[187] and de Faria and Moraes[188] have found on biopsy examination that such 'telangiectasias' are actually ectatic veins. Therefore because a significant percentage of smaller spider veins occur in direct communication with larger varicose or reticular superficial veins, compression of the 'feeder' vein should decrease, if not eliminate, the blood flow to the smaller connected vessels. Thus in addition to the effects of compression on the treated vessels themselves, compression of the entire leg should lead to a relatively stagnant blood flow in the feeder veins, which should allow for more effective endosclerosis of the treated vessel and a subsequent decreased risk of recanalization. In addition to these hemodynamic reflections the analgesic and antiedema effect of compression, even with low pressures, has to be considered.

HOW MUCH PRESSURE IS NECESSARY TO COMPRESS TELANGIECTASIAS?

The only reported study measuring the pressure necessary to empty superficial 'capillaries' (telangiectasias) on the leg demonstrated that a sudden emptying of superficial cutaneous capillaries occurred between 40 and 60 mmHg at a point 5 cm above the medial malleolus with the patient recumbent.[189] However, 80 mmHg was required to produce a complete emptying of blood with the patient in a standing position. This degree of pressure can be obtained with a bandage wrapped over a local pad but not with graduated compression stockings on areas of the leg above the ankle.

One limitation to the use of compression stockings in treating leg telangiectasias is the lack of complete emptying of the treated telangiectasias when only one stocking is used. Theoretically the incorporation of foam pads directly over the injected vessels and a double layer of compression stockings for daytime use, with one stocking removed on recumbency, should produce a more complete vascular occlusion (Fig. 6.34).

As shown in Figure 6.35 even very high pressure applied by a circular compression device is not able to compress small skin veins.

Based on serial biopsies performed by L. Wenner after sclerotherapy of small veins, Staubesand and Seydewitz were able to demonstrate by electron microscopy less thrombus formation using powerful local compression.[190]

A multicenter, bilateral comparative study through the North American Society of Phlebology (now the American College of Phlebology) examined the necessity for the use of a class II (30- to 40-mmHg) single stocking when treating leg telangiectasias.[191] Thirty-seven women with bilaterally symmetric telangiectatic leg veins of less than 1 mm in diameter were evaluated. One set of vessels was compressed for 3 days with a 30- to 40-mmHg compression stocking (MediUSA, Arlington Heights, IL) over a cotton ball dressing. The alternate set of vessels had a cotton ball dressing applied for 2 hours with paper tape without an overlying compression stocking. With the stocking, a greater clinical resolution occurred after treatment with one sclerotherapy injection on vessels located on the distal leg or when vessels were greater than 0.5 mm in diameter. Vessels located elsewhere or less than 0.5 mm in diameter showed no significant difference when this form of compression was used.

The main benefit of compression treatment was noted in the evaluation of adverse sequelae (Table 6.7).[191] The most significant finding in this study was that 20 to 30 mmHg compression produced a relative decrease in postsclerotherapy hyperpigmentation, which fell from an incidence of 40.5% to 28.5% with the use of compression. In addition, ankle and calf edema were lessened if a graduated compression stocking was worn immediately after sclerotherapy.

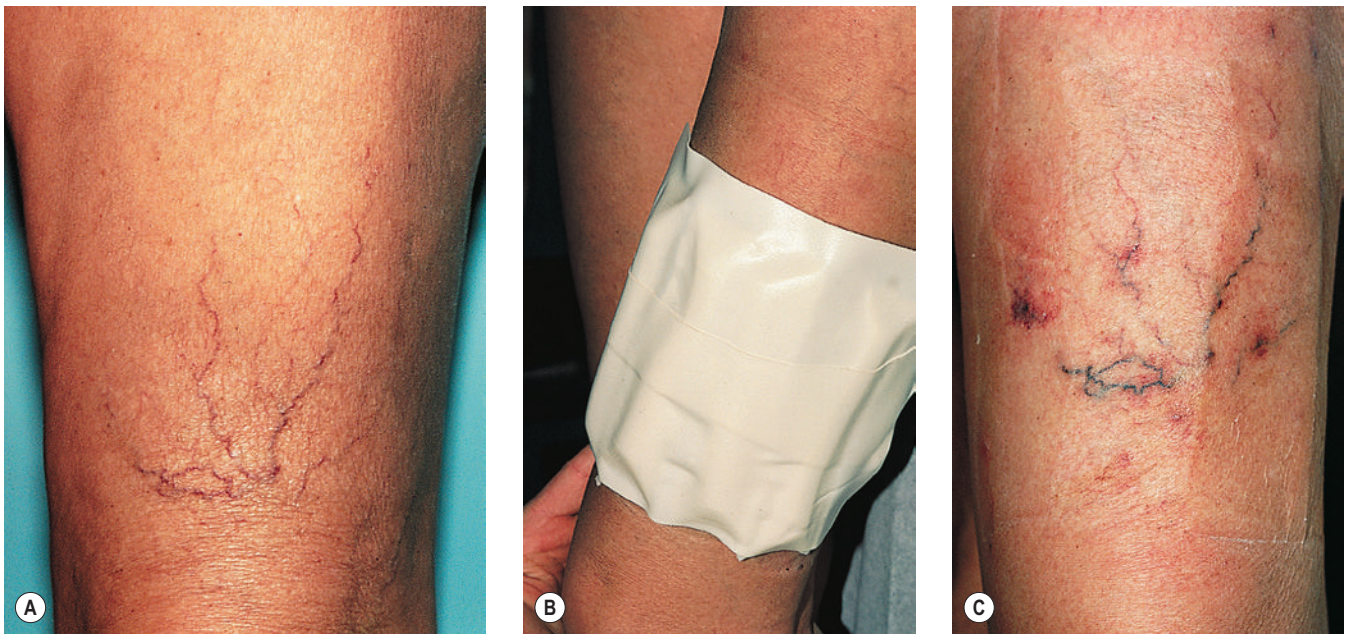

Figure 6.34 **A,** Clinical appearance of venules and telangiectasia on the anterior thigh of a 42-year-old woman, measuring 0.2 to 0.6 mm in diameter, without evidence of an obvious feeding reticular or perforating vein. **B,** Immediately after sclerotherapy with polidocanol 0.5%, STD foam pads were applied over the injected veins and secured with Microfoam tape under a 30- to 40-mmHg graduated compression stocking. **C,** Three days after treatment, immediately after the removal of both the stocking and the pads. There is significant thrombosis of the treated veins even with a high degree of compression, as noted by the indentation of the foam pad on the skin overlying the vessel.

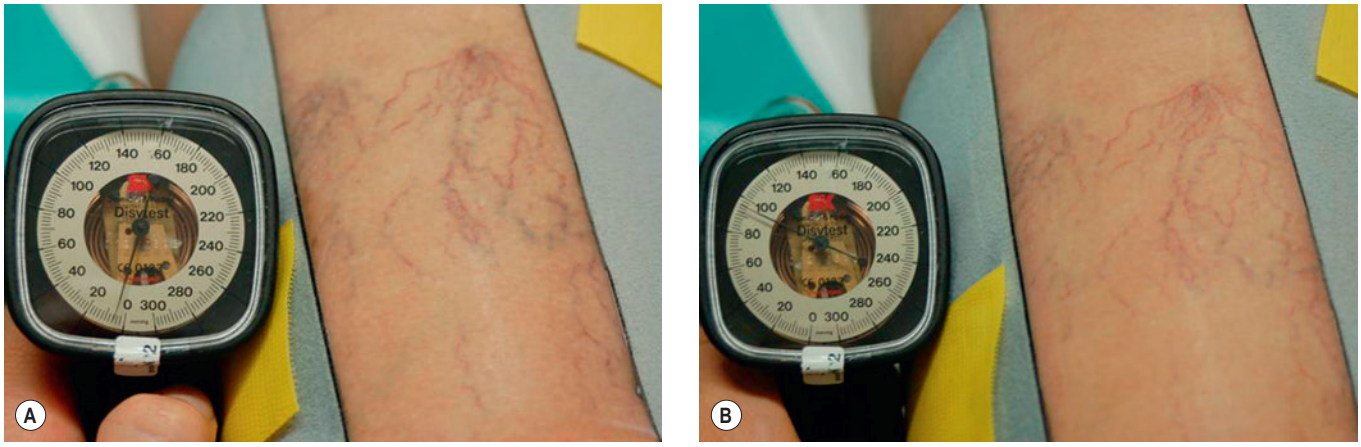

Figure 6.35 Using a blood pressure cuff with an acetate window (Echocuff, VNUS, CA, USA) the effect of compression on the diameter of spider veins on the thigh was investigated. **A,** Loosely applied cuff (6 mmHg); **B,** cuff inflated to 100 mmHg. The experiment shows that small skin veins cannot be compressed by circular compression devices. (Courtesy B. Partsch, Vienna.)

Table 6.7 Adverse Sequelae of Sclerotherapy

	Pigmentation	Ankle edema	Calf edema
Compression	28.5%	33%	–
No compression	40.5%	66%	40%

Modified from Goldman MP et al. J Dermatol Surg Oncol 1990;16:332.

An additional nonrandomized study of 386 patients with leg telangiectasias was conducted without bilateral paired comparison. In this study, 436 legs received graduated elastic stockings (compression class not stated) for 48 to 96 hours, and 182 legs were not compressed. Disappearance of more than 70% of telangiectasias occurred in one treatment in 85.7% of patients who wore compression stockings versus 72.5% of patients without compression ($P < 0.01$). In addition, compression reduced the incidence of pigmentation from 12.2% to 6.7%.

HOW LONG SHOULD COMPRESSION BE MAINTAINED AFTER SCLEROTHERAPY OF SMALL VEINS?

Formal studies on the use of compression in the treatment of leg telangiectasias are rare. A 3-day period for compression of leg telangiectasias is common based on the empirical report of Ouvry and Davy,[160] who advised a minimum of 3 days to limit the development of peripheral inflammation and intravascular thrombosis. Without supporting information, Harridge[192] recommended a 1-week period of compression for spider veins, using a local pressure band of elastic adhesive only. In a methodologically very convincing study showing clear benefits after compression stockings, a wearing time of 3 weeks was recommended.[184]

A review concerning compression and its effects on compression sclerotherapy of reticular and telangiectatic legs veins has been reported.[193] Forty patients were treated with sclerotherapy in three centers, followed by no compression or compression with 20- to 30-mmHg graduated stocking for 3 days, 1 week or 3 weeks. A statistically significant improvement in hyperpigmentation and resolution was seen in patients treated with 3 weeks of compression. Patients treated with compression for 3 days or 1 week also had a greater degree of improvement than patients not treated with compression. Patients treated with compression for 1 or 3 weeks had the least amount of postsclerotherapy hyperpigmentation. The full benefits of compression were seen when patients were examined 6 months after a single treatment. The authors concluded that patients are best treated with either 1 or 3 weeks of compression after sclerotherapy, but that even 3 days of compression offers some improvement over no compression.

In another RCT, the outcome of sclerotherapy with subsequent Elastoplast bandages was compared with the results after 35- to 40-mmHg stockings.[194] After 3 to 6 weeks, the stocking group showed a higher success rate, less thrombosis and less pigmentation.

COMPRESSION THERAPY AFTER VENOUS SURGERY AND ENDOVENOUS CATHETER PROCEDURES

Compression therapy is routinely performed after surgery of large varicose veins.[195,196] According to Perrin, the possible short-term benefits of compression after surgery include prevention of superficial thrombophlebitis and DVT, improvement of wound healing, and reduction of pain, bruising and hematoma. The level of activity, namely ambulation, is improved and return to work can be accelerated.[197]

Prolonged use of compression might provide benefits that include decreased incidence of recurrent varicosities. The progression of chronic venous disease may also be impeded by long-term use of compression. The same applies to the ablation of varicose veins by catheter procedures. However, these ideas are conceptual and supported only by few data that are summarized in a consensus paper on evidence-based compression.[147]

It could be demonstrated that high local compression achieved by using rubber foam pads on the thigh after surgery and after laser abolition of the great saphenous vein, is able to reduce pain and hematoma (see Fig 6.32).[48,198]

RCTs have underlined that after stripping, strong compression, mainly by compression bandages, is advisable especially in the first days after intervention only, whereas prolonged use of stockings would have no benefit.[199,200]

PREGNANCY

Pregnancy is an excellent model for observing the development of varicose veins in a relatively short time period. If the valves are allowed to remain incompetent for prolonged periods, fibrosis of the cusps may occur and cause irreversible damage. This effect is noted commonly in multiparous women who first note the temporary development of varicose veins during their first or second pregnancy. When the factors responsible for dilation of pregnancy-induced varicose veins (excessive blood volume, hormonally-induced relaxation of the vein wall, etc.) resolve, the veins return to normal. However, after repeated pregnancies varicose veins may become permanent. This progression is probably related to recurrent insult on the valves resulting in fibrosis and permanent incompetence. Therefore the use of graduated compression stockings for pregnancy-induced varicose veins could be considered preventive medicine, the goals being to maintain valvular competence and to prevent sustained valvular damage.

One RCT came to the conclusion that compression stockings may be ineffective in preventing the development of small varicose veins and side branches during pregnancy, but they alleviate leg symptoms and reduce the incidence of great saphenous vein reflux at the saphenofemoral junction.[201]

At the first indication of pregnancy, patients should be fitted with a 10- to 30-mmHg graduated pantyhose. In multiparous women or in those with a history of varicose veins, a stronger (30- to 40-mmHg) pantyhose should be worn. In women with large legs or in patients who are too uncomfortable with a 30- to 40-mmHg pantyhose, a calf-length, 20- to 30-mmHg compression stocking can be worn over a 20- to 30-mmHg pantyhose. One study comparing venous emptying between 13- and 25-mmHg ankle compression stockings used during pregnancy found no significant difference between the two compression levels.[202] Patient compliance between the two classes of stockings was the same, with 82% of the 50 women continuing to wear the stockings throughout their pregnancy.[202] Another study showed an improvement in maternal and fetal circulation, with best effects in the range of a 40-mmHg compression.[203]

Even for women in their 35th week of pregnancy, graduated compression stockings are able to increase expelled venous volume, whereas the refilling rate is influenced to a lesser degree, thus minimizing venous congestion in the leg.[204] This has been demonstrated to decrease postural changes in heart rate, preventing the uterovascular syndrome.[203,205] Using these guidelines, compression stockings worn during pregnancy can prevent or lessen the development of venous insufficiency. At the very least, the use of 25-mmHg graduated compression stockings decreased subjective discomfort from 82% to 13% in pregnant women between 30 and 40 weeks gestation and decreased edema from 75% to 14% in these pregnant women.[205]

EDEMA CAUSED BY SITTING AND STANDING; OCCUPATIONAL EDEMA

The rationale described in the previous section also applies to most other forms of venous stasis disease. Compression stockings are helpful to patients in occupations that necessitate standing for long periods. Light-compression stockings may be effective.[206–208] By measuring the physiologic swelling of the legs after a working day using water-displacement volumetry it could be demonstrated that light support stockings were able to significantly reduce evening edema. Compression stockings with an interface pressure of 18 mmHg on the distal leg were able to prevent the swelling after a working day completely.[6]

Light-compression stockings may also improve subjective symptoms of heaviness that occur after long sitting or standing.[7,36,37] A long flight or a car or bus drive for several hours is a typical situation in which leg swelling is a common sign, frequently also connected with subjective symptoms.[209–212] Considerable fluid accumulation in the legs of about 250 mL was measured after long-haul flights. The increase of skin thickness over the shin was even maintained for some days after the flight.[211]

Hagan et al showed that low-ankle-pressure stockings (5 mmHg at ankle, 17–20 mmHg at calf) reduced flight-induced ankle edema and subjectively rated travel symptoms of leg pain, discomfort and swelling, and improved energy levels, ability to concentrate, alertness and postflight sleep.[213]

The clinical benefits of lightweight compression stockings were also shown in flight attendants.[37] A crossover prospective study of 19 flight attendants wearing 8- to 15-mmHg and/or 15- to 20-mmHg graduated stockings demonstrated a statistically significant reduction in leg discomfort, ankle swelling, aching and tiredness in the leg. Interestingly, in this population in which almost all patients had leg telangiectasia (with one person having varicose veins), wearing 15- to 20-mmHg stockings did not significantly improve symptoms over the lighter-strength stockings. Light stockings have been reported to reduce the incidence of flight thrombosis.[214]

Severe stages of edema can be dramatically improved by compression bandages (Fig. 6.36). In chronic edema leading to lipodermatosclerosis on the distal leg, the lymphatics ultimately decompensate. Consequent compression therapy is able to reverse the skin changes and restore normal lymphatic drainage (see Fig. 6.2). For patients who have difficulty donning and doffing compression stockings or compression bandages, the CircAid legging is a viable option and may aid in patient compliance and comfort.[215]

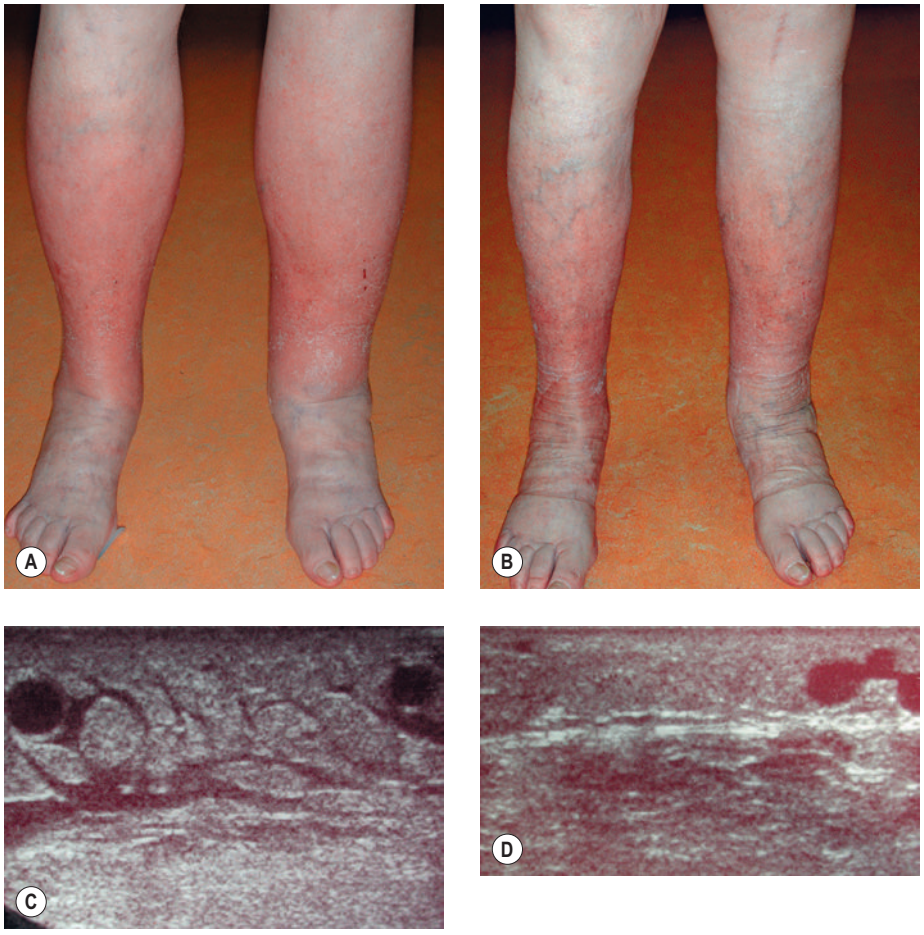

Figure 6.36 **A, B,** Before and after removal of edema in a patient with swollen legs (result of prolonged sitting; 'dependency syndrome') by a multilayer short-stretch compression bandage. After 5 days, the circumference of the calf decreased by 5 cm. **C, D,** Duplex examination before and after treatment shows that the water-filled clefts in the skin have disappeared and that the dermal thickness has halved.

Immobility edema in patients spending most hours of their life in an upright position, e.g., in a wheelchair, is an increasing practical problem. Recommendations that only elastic bandage material can be used on these patients is based on the misconception that inelastic material would work only in active patients who are able to walk. In fact inelastic bandages applied with adequate pressure produce a much higher massaging effect, even with small toe movements or passive mobilization of the ankle, than elastic material.

Additional intermittent pneumatic compression can further help to reduce edema in these patients.[216]

PREVENTION OF DEEP VEIN THROMBOSIS AND POSTTHROMBOTIC SYNDROME

Several RCTs and systematic reviews have shown the beneficial effects of compression in preventing venous thromboembolic diseases in bedridden patients. More convincing studies have been performed with intermittent pneumatic compression than with stockings.[197,217–220] Recent guidelines recommend combined pharmacologic and mechanical prophylaxis, assuming that mechanical methods may increase efficacy and reduce death and morbidity rates without increasing bleeding risk.[221]

Signs and symptoms of a postthrombotic syndrome after proximal DVT may be dramatically reduced if compression stockings are worn in the following years.[222–225] Immediate compression and mobilization in the acute stage of DVT seems to further reduce the incidence and severity of postthrombotic syndrome.[139] However, a large study, which is very much under dispute, was unable to find benefits from wearing compression stockings for preventing postthrombotic syndrome.[226] Delayed start with compression after acute DVT and poor compliance of the patients were the main counter-arguments which were discussed about this study.[227] We recommend wearing the stockings for 2 years and to continue when signs and symptoms of swelling and pain are still present.

TREATMENT OF SUPERFICIAL PHLEBITIS, DEEP VEIN THROMBOSIS AND POSTTHROMBOTIC SYNDROME

Acute superficial phlebitis is an excellent indication for strong compression, preferably by adhesive bandages, especially when thigh veins are also involved. The same is true for phlebitic reactions after sclerotherapy. The patient should be encouraged to walk with a strong bandage as shown in Fig. 6.16. This regimen is completely based on experience. Up to now there is only one RCT available demonstrating modest beneficial effects of compression stockings (20-30 mmHg) in this important indication.[228] Future trials would be desirable using bandages exerting higher pressures.

In acute DVT of mobile outpatients, good compression and immediate ambulation is able to reduce pain and swelling and to prevent thrombus growth.[229,230] This adjunctive treatment always has to be accompanied by exact anticoagulation, preferably with therapeutic doses of low-molecular-weight heparin (LMWH). Firmly applied Fischer bandages in addition to an adhesive thigh bandage exerting a pressure of 40 mmHg showed better results than a thigh-length European class II compression stocking (Sigvaris 503; Ganzoni, Switzerland). Either methods, bandage or stocking, were much better than bed rest.[229,230] However, for those centers that are not familiar with applying appropriately strong short-stretch bandages, good compression stockings may be a valuable alternative. In 1289 consecutive patients with DVT treated by compression bandages, walking exercises and LMWH, the complication rate of symptomatic pulmonary embolism and of fatal events was much lower than in reports from the literature regarding immobilizing the patients.[231] Our recommendation of immediate walking exercises with good compression is in contrast to the clinical routine in many countries. A survey from Canada reported that compression stockings were prescribed in the acute stage of DVT only by 26% of physicians and that 68% prescribed stockings only if venous signs and symptoms were present.[138]

In a subanalysis of the disputed SOX trial[226] no pain relieving effect of compression stockings could be found 2 to 3 weeks after acute DVT.[232] This is very different from our recommendation of immediate mobilization of the patient with acute DVT with good compression, which leads to an instant relief of pain and swelling enabling the patient to walk again.[229,230] This procedure is also able to reduce the incidence of postthrombotic syndrome.[139] Reports on the treatment of patients with a manifest postthrombotic syndrome are scarce.[233]

VENOUS ULCERS

Compression is considered to be the most important conservative treatment modality to heal venous ulcers. However, its importance is still widely underestimated compared with local treatment modalities.

There is no other indication for which the clinical efficacy of compression treatment has been so well established by numerous RCTs.[102,104,105,147] The different compression devices in use require more work in conjunction with measurement of interface pressure and stiffness in the individual patients who are enrolled in comparative trials to achieve reliable comparisons between various products.

Most studies have been undertaken using compression bandages. The following conclusions may be derived from several RCTs and systematic reviews[104,105]:

- Compression increases ulcer healing compared with no compression.
- Multilayered bandages are more effective than single-layered systems.
- High compression is more effective than low compression.
- The conflicting results achieved with different types of compression occur mostly because of inadequate application technique with one product and not because of its inferior elastic property. Four-layer bandages and inelastic multilayer bandages show equal results if both systems are adequately applied.[100,102,103]

Compared with local therapy alone, compression achieves significantly faster healing rates of venous ulcers. The

augmentation of sustained compression with sequential pneumatic compression promotes ulcer healing.[234,235] With adequate compression therapy, 70% of consecutive outpatients with venous ulcers should be healed after 12 weeks. Reports with healing rates lower than 50% raise the suspicion that the technique used was inadequate.[1] This is also true for randomized studies comparing different compression regimens or trying to demonstrate the supplementary effect of drugs. In future studies comparing different materials, it is highly recommended that the sub-bandage pressure be measured, because this parameter is of deciding importance for the healing of venous ulcers.[104,105,236] With optimal compression therapy, baseline ulcer area and ulcer duration are significant predictors of ulcer healing.[237]

If the ulcers are not too large and not too longstanding, favorable results can also be achieved with compression stockings.[107,238–243] Some stockings were developed specifically for treating venous ulcers: 'two-layer stockings' with a basic liner to keep the ulcer dressing in place, and a second outer stocking, thereby enhancing pressure and stiffness, e.g., UlcerCARE which comes with a zip (Beiersdorf-Jobst, Charlotte, NC), Mediven ulcer kit (Medi, Bayreuth, Germany), Venotrain ulcertec (Bauerfeind, Zeulenroda, Germany) with a specifically designed knitting pattern to increase the stiffness in the gaiter area,[241] and Tubulcus (Innothera, Paris, France), which is a ready-made tubular compression device.[244,245]

It can be more difficult to keep a venous ulcer closed than to heal it. Noncompliance of the patient regarding wearing compression stockings is associated with a higher recurrence rate.[246] Recurrence after healing of leg ulcers was shown to be significantly lower if compression stockings with higher pressure were used.[247] For the insurance companies, it would be much cheaper to reimburse for compression stockings after the ulcers are healed than to pay the costs for ulcer recurrences.[248]

LYMPHEDEMA

Conservative management of lymphedema is based on complex decongestive therapy. This treatment modality consists of manual lymph drainage, exercises, skin care, and most importantly, compression.

Multilayer short-stretch bandages are essential to achieve optimal edema reduction.[95,249] Bandaging and subsequent elastic hosiery is more effective than elastic hosiery alone in reducing lymphedema.[249,250] As a result of the fast diminution of limb volume the bandages will loosen rapidly[94] and should be reapplied in the initial phase at least once a day. To maintain the effect and to prevent refilling of the extremity with edema, lifelong wearing of compression hosiery preferably made-to-measure is essential.

OTHER INDICATIONS

Compression is also indicated in many other conditions like posttraumatic hematoma (Fig. 6.37), vasculitis, burns, keloids or after any kind of surgery on the lower extremity. The main reason for the effectiveness of adequate compression on the leg is its action against gravity, preventing swelling and impeding inflammation.

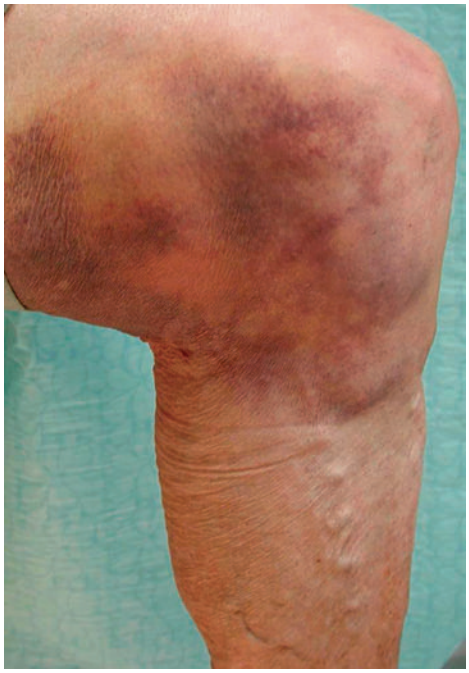

Figure 6.37 Posttraumatic hematoma in a patient who wore compression stockings because of his varicose veins at the time of the trauma. The compressed skin areas are spared from hematoma.

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7 Mechanism of Action of Sclerotherapy

Mitchel P. Goldman, Jean-Jérôme Guex, with contributions by Joanna Bolton

GENERAL MECHANISM FOR PRODUCING ENDOTHELIAL DAMAGE

Sclerotherapy refers to the introduction of a foreign substance into the lumen of a vessel, aiming to create venous wall damage leading to occlusion of the vessel (Fig. 7.1). This procedure, when performed on telangiectasias, is referred to as microsclerotherapy.[1]

The mechanism of action for sclerosing solutions is that of producing endothelial damage (endosclerosis) that causes endofibrosis. The extent of damage to the blood vessel wall determines the effectiveness of the solution. Endothelial cells are highly complex and represent the largest cell type in the human body. In addition to their function as a conduit for blood, these cells react to mechanical forces and multiple substances produced locally or circulating in the blood. They have a broad range of metabolic activities, including, but not limited to:

- Uptake and degradation of circulating norepinephrine (adrenaline), epinephrine (adrenaline), bradykinin and serotonin
- The conversion of angiotensin I to the vasoconstrictor angiotensin II
- Production of plasminogen activator inhibitor
- Production of heparin and/or heparin-like substances
- Production of prostacyclin, which acts both on vascular smooth muscle and on platelet aggregation
- Production of endothelium-derived relaxing factor
- Storage and secretion of histamine
- Synthesis of basic fibroblast growth factor (FGF)
- Modulation of inflammation through interactions with tumor necrosis factor (TNF) and interferon-γ[2–5]

In addition, endothelial cells in one organ and in one location may act differently than endothelial cells elsewhere. They appear to be specialized to their area. Thus it is paradoxical that sclerotherapy treatment is not without significant adverse sequelae (see Chapter 8).

Endothelial destruction by sclerosing solutions is both dose- and time-dependent.[6] In vitro studies of cultured endothelial cells demonstrated activation of calcium signaling and nitric oxide pathways followed by cell death after exposure to sclerosing solutions. Cell death occurred within 15 minutes with 0.3% polidocanol (POL) or 0.1% sodium tetradecyl sulfate (STS). At less than 0.003% POL or 0.005% STS cells remained alive after 60 minutes. Combined with protein-binding of detergent sclerosing solutions and a 10,000-fold dilution after release into the circulation, these studies demonstrate the safety of sclerotherapy, because sclerosing solutions are rapidly diluted to 'safe' concentrations distal to the point of injection.

Total endothelial destruction results in the exposure of subendothelial collagen fibers, causing platelet aggregation, adherence and release of platelet-related factors. This series of events initiates the intrinsic pathway of blood coagulation by activating factor XII. Ideally, sclerosing solutions should not otherwise cause activation or release of thromboplastic activity because this would initiate the extrinsic pathway of blood coagulation. Excessive thrombosis is detrimental to the production of endofibrosis because it may lead to recanalization of the vessel as well as excessive intravascular and perivascular inflammation and its resulting sequelae (see Chapter 8). This is thought to be prevented or at least minimized with postsclerotherapy compression (see Chapter 6). However, thrombosis usually occurs to some degree as a result of sclerotherapy.

If a thrombus is formed, it should be well anchored to the venous wall to prevent embolization. Wolf[7] in 1920 established that effective sclerosis causes thrombosis that penetrates the full thickness of the adventitia of the vessel wall. Schneider[8] has shown in histologic examinations of sclerosed varices that the strongest fixation of a thrombus occurs in areas where the entire endothelium is destroyed. Therefore, endothelial damage must be complete and should result in minimal thrombus formation with subsequent organization and fibrosis (Fig. 7.2). In addition, after sclerotherapy, maximum full-thickness fibrosis of the treated segment occurs after 6 weeks of compression.[9] Therefore, in addition to limiting the extent of thrombosis, compression may facilitate endofibrosis (see Chapter 6). Chleir and Vin[10] have described the differences between a clot observed during a spontaneous thrombosis 'thrombus' and during the sclerosing process, for which they suggested the neologism 'sclerus' (Table 7.1).

In a pilot study, analysis of the content of sclerosed veins has shown that an important number of fibroblasts are often detected at the 6th week. Evidence of correlation with durable occlusion of the vein is still lacking.

The fate of vasa vasorum during the process is not clear either. Secondary recanalization after lysis of the clots which cause obstruction early in the reaction, and the subsequent bleeding after several weeks, could explain why foam-sclerosed veins fill up again with blood around the 6th week.

Endothelial damage can be provoked by a number of mechanisms, such as a change in the surface tension of the plasma membrane or modification of the physical–chemical

milieu of the endothelial cell through a change of intravascular pH or osmolality. The endothelium can be destroyed directly by caustic chemicals or by other physical factors such as heat and cold. For sclerotherapy to be effective without recanalization of the thrombotic vessel, the endothelial damage and resulting vascular necrosis must be extensive enough to destroy the entire blood vessel wall.[11]

Destruction of the entire vessel wall and not just the endothelium is necessary, as demonstrated in animal studies described later in this chapter. The reason may relate to the multifunctional nature of vascular smooth muscle cells. These cells, which are found in significant concentration within superficial veins (see Chapter 2), have a large number of functions, including the synthesis of collagen, elastin and proteoglycans.[12] It is hypothesized that if they remain viable, they can regenerate a foundation that promotes migration of undamaged adjacent endothelial cells that allow recanalization of the treated vessel.[13,14]

In addition, for effective destruction of a varicosity or telangiectasia, the entire vessel must be sclerosed to prevent recanalization. Recanalization occurs easily in vessels where only a section of endothelium is damaged. This is caused by

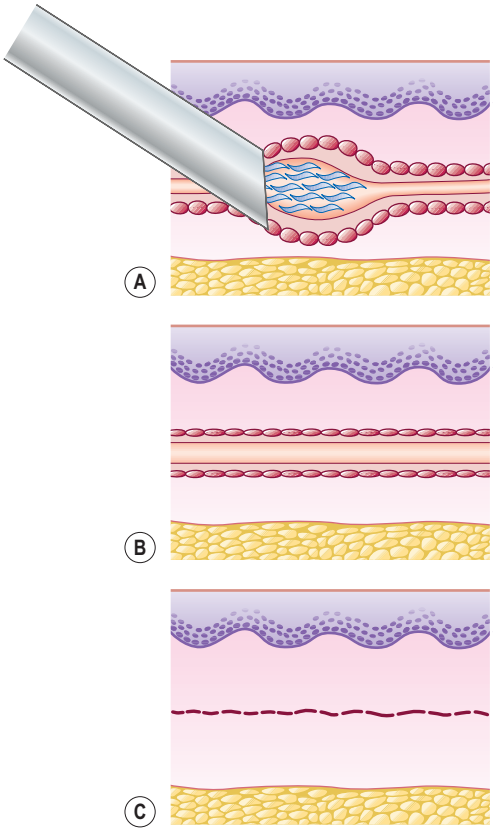


Figure 7.1 Diagrammatic representation of the mechanism of action for sclerotherapy. **A,** Proper placement of needle into the vein and release of sclerosing solution. **B,** Early stage of endothelial destruction and minimal organizing thrombosis. **C,** Late stage demonstrating fibrous cord formation.

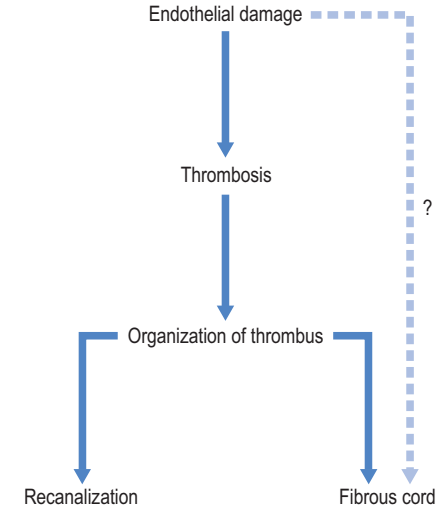


Figure 7.2 Chain of events occurring after sclerotherapy. Ideally, the treated vessel will progress directly from damaged endothelium to a fibrous cord. However, some degree of intravascular thrombosis usually occurs.

Table 7.1 Thrombus Versus Sclerosis: Comparison of Vein Content During a Thrombosis and During a Sclerosing Process

	Thrombus	Sclerosis
Pathophysiology	Hematological phenomenon	Tissue phenomenon
	Activation of Virchow triad	Parietal mechanism
	Recanalization without fibrosis	Fibrosis
Clinical	Painful	More discomfort than pain
	Inflammatory	No inflammation
	Indurate plaques	No indurate plaque
Biology	Positive d-dimers	Negative d-dimers
B-mode ultrasound	Convex toward junction	Concave toward junction
	'Rosette' picture	Parietal thickening
	No parietal adhesion	Parietal adhesion
	Dilatation	Retraction
Pathology	No parietal lesion	Inflammatory infiltration of venous wall
	Thrombus rich in RBCs and platelets	Sclerosis contains more WBCs and less RBCs than thrombus
	Rare WBCs	

From Chleir F, Vin F. Actua Vasc Inter 1995;35:18.
RBCs, red blood cells; WBCs, white blood cells.

rapid endothelial regeneration, which has been measured at a turnover rate of 0.1% to 10% per day or higher.[15] Endothelial migration has been estimated to proceed at a rate of 0.07 mm/day in the circumferential direction and six times faster in an axial direction in rat aortas.[16] In fact, endothelial cell regeneration may be sufficiently rapid to replace dying endothelium after small areas are denuded.[17] In the future, the practitioner may be able to estimate total endothelial destruction as a marker for effective sclerosis by counting circulating endothelial cells.[18,19]

CATEGORIES OF SCLEROSING SOLUTIONS

All sclerosing solutions can be placed into three broad categories based on their mechanisms for producing endothelial injury:

- Detergent
- Osmotic
- Chemical

There are an infinite number of potential solutions that, when injected intravascularly, can cause endothelial and vascular wall necrosis. In addition, an infinite variety of combinations or mixtures of solutions can be used to produce endosclerosis. The ideal sclerosing solution should be painless on injection, free of all adverse effects and specific for damaged (varicose) veins. Although such a solution has not been discovered for all types of vein, this chapter examines solutions commonly used for this purpose.

DETERGENT SOLUTIONS

Detergent sclerosing solutions commonly used to treat varicose and telangiectatic veins include sodium morrhuate (SM), ethanolamine oleate (EO), STS and POL (lauromacrogol 400, laureth-9). They produce endothelial damage through interference with cell surface lipids (Fig. 7.3). Strong detergents, such as STS and SM, produce maceration of the endothelium within 1 second of exposure.[20] The intercellular 'cement' is disrupted, causing desquamation of endothelial cells in plaques. Because the hydrophilic and hydrophobic poles of the detergent molecule orient themselves so that the polar hydrophilic part is within the water and the hydrophobic part is away from the water, they appear as aggregates in solution (micelles) or fixed onto the endothelial surface (Fig. 7.4). Because the practitioner cannot ensure that the solution is entirely in contact with the endothelial surface (if the injected vein contains blood), the decrease in surface tension on the endothelial cells may not be in direct proportion to the concentration of the solution. Strong detergent sclerosants therefore have a low safety margin.[20]

Detergents act as micelles when injected into a nondetergent environment (blood). Their destructive action on endothelial cells is enhanced when they act as aggregates rather than monomers. Thus, the concentration of the sclerosing solution in the vessel is an important factor regarding endothelial destruction and activity (Fig. 7.5). Detergents have been found to aggregate to a significant extent at lower temperatures as opposed to room temperatures (Fig. 7.6).

Detergent sclerosing agents have been studied regarding their direct toxic effects on the formed elements of blood. One study found that the addition of SM, EO, STS or POL

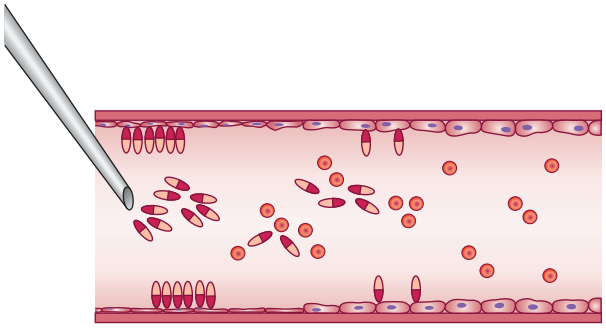


Figure 7.3 Diagrammatic representation of the action of a detergent sclerosing solution on the vessel wall, showing formed elements of the blood.

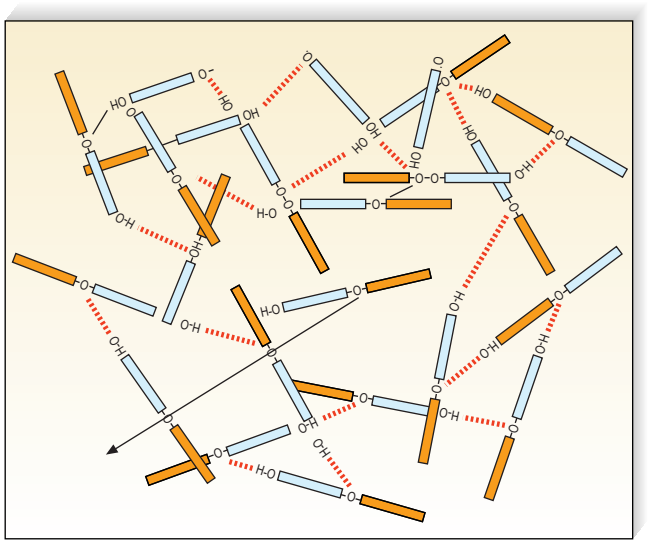


Figure 7.4 Diagrammatic representation of the probable molecular orientation of detergent sclerosing solutions into aggregates.

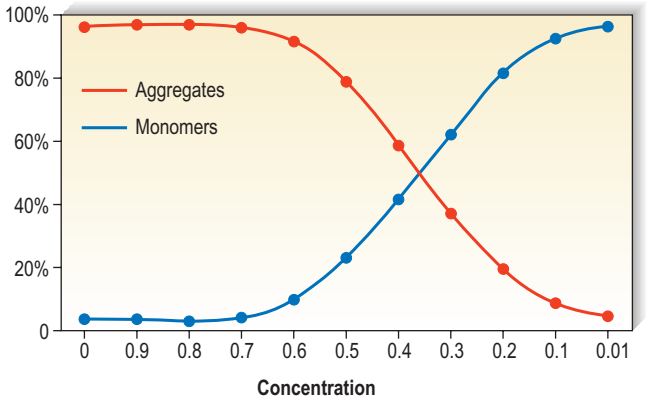


Figure 7.5 Diagrammatic representation of the percentage of detergent aggregates versus monomers is a correlation of the solution concentration. (From Feid C. Presentation at the American College of Phlebology Sclerotherapy Workshop, Atlanta, GA, November 2000.)

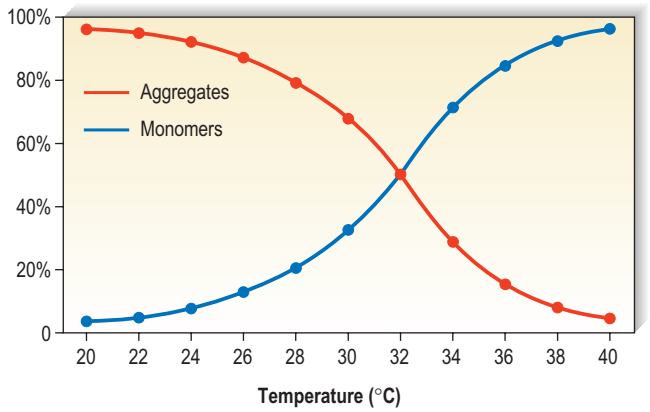


Figure 7.6 Diagrammatic representation of the percentage of detergent aggregates versus monomers is a correlation of the solution temperature. (From Feid C. Presentation at the American College of Phlebology Sclerotherapy Workshop, Atlanta, GA, November 2000.)

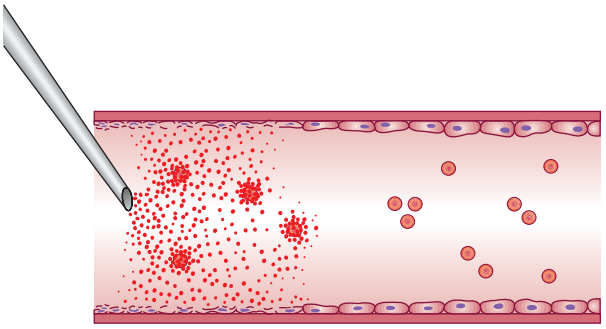


Figure 7.7 Diagrammatic representation of the action of a hypertonic sclerosing solution on the vessel wall, showing formed elements of the blood.

to citrated plasma did not cause clotting nor shorten either the prothrombin time (PT) or the partial thromboplastin time (PTT).[21] However, all of the sclerosing agents examined were directly toxic to both granulocytes and red blood cells (RBCs) at dilutions of up to 1:1000. When tested against cultured endothelial cells, all solutions were toxic to approximately 60% to 80% of cells at 1:100 dilutions, but only SM and EO were toxic at a further dilution of 1:1000. None of these tested solutions were toxic at 1:10,000 dilutions. Therefore this study confirms that effective endosclerosis occurs through damage to endothelium and not through thrombosis induced by destruction or damage to red and/or white blood cells. Another in vitro study, however, found that the activated PTT was prolonged in proportion to the fall of factor XII and prekallikrein activity when POL was added to citrated serum.[22] This indicates that in addition to its action on endothelial cells, POL is capable of acting on blood coagulation through activation of the early phase of the intrinsic pathway. The clinical relevance of this finding is unclear because additional studies have failed to demonstrate its significance, as explained later in this chapter.[23,24]

OSMOTIC SOLUTIONS

Hypertonic solutions, such as hypertonic saline (HS), probably cause dehydration of endothelial cells through osmosis, causing endothelial destruction (Fig. 7.7).[22] It is speculated that fibrin deposition with thrombus formation on the damaged vessel wall occurs through modification of the electrostatic charge of the endothelial cells.[20] For the vessel wall to be completely destroyed, the osmotic solution must be of sufficient concentration to diffuse throughout the entire vein wall.[25] In contrast to the immediate action of detergent sclerosing solutions, experimental studies have shown that endothelial destruction with HS 22% or glucose 66% occurs only after 3 minutes.[20] The destroyed endothelial cells do not appear to be desquamated as with detergent sclerosing solutions.[20]

Hypertonic solutions have a predictable destructive power that is proportional to their osmotic concentration. This was demonstrated in a comparative study of multiple hypertonic solutions used on the superficial and internal saphenous veins of 27 dogs.[26] The degree of endothelial damage was assessed histologically at multiple time points from 30 minutes to 8 weeks after sclerotherapy. The authors ranked the solutions from strongest to weakest as follows:

1. Sodium salicylate 40%
2. Sodium chloride 10%/sodium salicylate 30%
3. Invert sugar 75%
4. Saccharose 5%
5. Phenol 1%
6. Dextrose 66%
7. Sodium chloride 20%
8. Sodium salicylate 30%
9. Glycerin

The authors concluded that maximal endothelial destruction occurred as early as 30 minutes to 4 days after injection, after which time the injected vessel went through either a reparative or a fibrotic process. Because dilution occurs with intravascular serum and blood, osmotic solutions have their greatest effect at or near the site of injection. In contrast, detergent sclerosing solutions can exert effective sclerosis for 5 to 10 cm along the course of the injected vessel. Sadick[27] examined the sclerosing effect of HS 23.4% and POL 0.5%. He found equal sclerosing effect (length) for these two solutions injected in a similar type of vein using identical techniques. Unfortunately, HS 23.4% is more potent (about two to three times more) than POL 0.5%. Therefore, he inadvertently demonstrated that detergent solutions have about twice the therapeutic efficacy of osmotic solutions. A better comparison would have been with HS 11.7%.

CHEMICAL SOLUTIONS

Chemical irritants also act directly on endothelial cells to produce endosclerosis. Lindemayr and Santler[28] studied the sclerosing effect of 4% polyiodinated iodine (PII; Variglobin) with standard and immunofluorescent microscopy and demonstrated fibrin deposition on the sclerosed veins only. Platelets fixed only to elastin, collagen, the basement membrane and the amorphous material of the subendothelial layer, not to intact endothelial cells. It is also thought that the chemical destruction is in part related to the dissolution

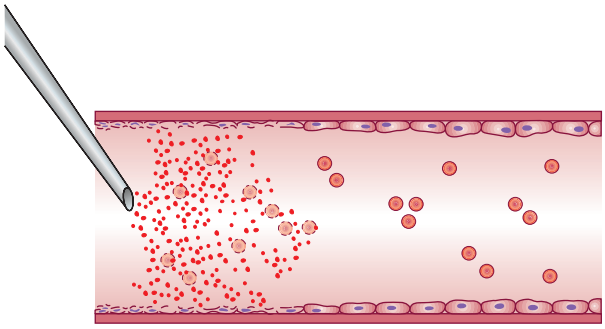


Figure 7.8 Diagrammatic representation of the action of a caustic chemical sclerosing solution on the vessel wall, showing formed elements of the blood.

of intercellular cement, which has been demonstrated to occur after 30 seconds of exposure.[20] Thus, this chemical irritant sclerosing solution produces its end result of vascular fibrosis through the irreversible destruction of endothelial cells with resultant thrombus formation on the subendothelial layer (Fig. 7.8).

The aforementioned mechanism of action has been demonstrated visually with scanning electron microscopy of sclerosed rabbit veins (agent not noted) by Merlen.[29] He demonstrated intimal cracks and fissures that left intimal connective tissue fibers and elastic lamina exposed. Ultrastructural damage involving stasis of blood and platelet aggregation on intact endothelial intima occurred in 5 minutes in the dorsal rabbit ear vein.

FACTORS PREDISPOSING TO THROMBOSIS

As discussed previously, optimal clinical results occur when sclerotherapy-induced thrombosis is minimized. Factors predisposing to thrombus formation include decreased velocity of blood flow, hypercoagulability and endothelial cell damage.[30] The velocity of blood flow is unaffected by the sclerosing agent itself, but flow in general is usually slower in varicose veins and telangiectasia. This relative decrease in blood flow may predispose to thrombus formation in varicose veins and may be a significant contributing factor to the increased incidence of thrombophlebitis and deep vein thrombosis (DVT) in patients with varicose veins (see Chapter 2).

Hypercoagulability predisposes the patient to thrombus formation. Wuppermann[31] studied fibrinolysis in subjects injected with POL and found a slight, statistically insignificant hyperfibrinolysis in blood drawn from the antecubital vein. He hypothesized that because coagulation factors II, VII, VIII and IX and platelet function are damaged directly by the sclerosing solution, coagulation at the injection site is delayed. Endosclerosis, as measured by fibrinogen, gradually occurred over 5 days only at the injection site and did not result in systemic hypercoagulability. Therefore, sclerotherapy should not cause a sudden thrombosis. In fact, a hemolytic effect was detected with STS even at a 0.1% concentration, with POL at a 0.05% dilution and with PII at a 2% concentration.[23] The PTT, PT and thrombin time (TT) were unchanged with injection of these agents into whole blood. Earlier work also demonstrated the lack of effect of POL on coagulation parameters in rabbits.[32] MacGowen et al[33] combined STS with whole normal blood, causing a homogeneous RBC lysate without the formation of thrombin. In vivo studies have also demonstrated a lack of hypercoagulability from sclerosing solutions. Cepelak[24] found that platelet aggregation occurs only at the site of the sclerosing solution injection, with aggregation-inhibiting effects occurring in the efferent deep veins distal to the femoral vein. Thus, endothelial damage probably causes a release of various factors that produce anticoagulant effects, lowering the risk of thrombotic complications of sclerosing therapy. This effect was confirmed by Raymond-Martimbeau and Leclerc,[34] who measured fibrinopeptide A and fibrin degradation of D-dimer fragments after injection of sodium iodine. They found no evidence for activation of blood coagulation. Therefore, experimental findings do not support the theory of intrinsic hypercoagulability of sclerosing solutions as the mechanism of action for thrombus formation during sclerotherapy (see Chapter 1).

The lack of hypercoagulability just mentioned correlates with clinical experience using POL. When POL is used in patients who are taking systemic anticoagulants, a decrease in its sclerosing action does not occur.[35] The addition of heparin to STS also had no effect on the sclerotherapy results in a paired comparison of 100 patients.[36] Thus it appears that the mechanism of action of POL and STS is to produce endothelial damage[37] but not thrombus formation associated with platelet aggregation. This mode of action is also seen with other (nondetergent) sclerosing agents. The low incidence of DVT after sclerotherapy (less than 1 per 10,000 sessions[38]) is the ultimate evidence that thrombosis is an epiphenomenon of the sclerosing process, not a goal.

FACTORS PREDISPOSING TO ENDOFIBROSIS

Whether vessels altered by changes from being varicose or stretched are more susceptible to the action of sclerosing agents than are normal vessels is unknown. At times, human varicose and telangiectatic vessels are noted to sclerose focally after the injection of various solutions. The focal nature of endothelial necrosis and thrombus formation may be related to toxic effects of the sclerosing solutions on the surrounding media. This effect is commonly observed when injecting varicose veins under duplex control. With this technique (described in Chapter 9), the sclerosing solution is injected and/or held in place until the varicosity is seen to spasm. This indicates effective sclerosis. Venograms of varicose veins injected with STS demonstrate segmental, intense and diffuse spasm, both proximally and distally, at the time of injection and 6 minutes after injection.[39] Effective endosclerosis occurs at points of vessel spasm where the entire endothelium is adherent. This agrees with the clinical impression that total compression of the sclerosed vessel is necessary for ideal, long-lasting and complication-free sclerosis.[40,41]

At one time it was thought that 'any solution which will not produce a slough when injected perivenously will generally not be strong enough to obliterate a vein.'[42] However, some very effective sclerosing solutions are thought to act

selectively on 'damaged' varicose endothelium. In fact, experimental studies have documented that effective sclerosing solutions do not have to produce tissue necrosis on intradermal injection (see Chapter 8). The manufacturers of POL state that this agent acts selectively on damaged vessels.[a] In addition, a number of histologic studies of the effect of sclerotherapy on varicose veins have also concluded that damaged varices are preferentially sclerosed.[b,8,20,29] However, experimental injection of sclerosing agents into normal dorsal veins of rabbit ears yields effective vessel sclerosis in a concentration-dependent manner.[43,44] Therefore, in addition to the type and concentration of sclerosing solution, other factors, including vessel diameter, rate of blood flow and anatomic site of the vessel, may also be important.

Sclerosing solutions affect arteries in a different manner than they do veins. Although thrombosis occurs, intimal damage may not. MacGowen et al[33] studied the local effects of intra-arterial injection of STS. They injected STS 3.0% into the central auricular artery at the base of the rabbit ear and visualized the resulting chain of events through a Perspex ear chamber (Lucite International, Southampton, UK) with high-power and oil-immersion lenses. Spasm was not noted in any vessels, but within minutes the erythrocytes appeared distorted and broken, with the formation of a central homogeneous thrombus that moved down the arteriole and lodged in a capillary. Intimal damage did not occur. Thus, the major effect of STS was on the blood cell mass that it destroyed and converted into an intravascular embolus. Subsequent biopsies of the ears at 1 hour and at 5 days demonstrated thrombus only, without evidence of intimal damage. These results are distinctly contrary to the effects of sclerosis on veins.

The reason for the different mechanism of action is unknown but may relate to the difference in velocity of blood flow in arteries and veins. Specifically, STS injected intra-arterially may not have enough time to react with endothelium, being both absorbed and inactivated by formed elements in the blood and serum factors and thereby being diluted to a 'safe' concentration by the more rapid arterial flow. Safe is a relative term, because inadvertent intra-arterial injections of STS have produced gangrene through thrombosis of vessels downstream of injection (see Chapter 8).

EXPERIMENTAL EVALUATION OF SCLEROSING SOLUTIONS

As physicians in the United States are especially limited in the type of sclerosing solutions available, an analysis of the following studies was performed to compare the efficacy of various sclerosing agents.

An important question regarding the studies in this section is whether the experimental animal model is an appropriate system in which to compare the efficacy of various sclerosing solutions. The dorsal marginal rabbit ear vein is similar in size (0.35–0.45 mm in diameter) to telangiectasias in humans. Reiner[45] found that it was difficult to measure the rate of dilution of sclerosing solutions in the rabbit ear vein because of the greater number of collaterals and rapid blood flow caused by the thermoregulatory nature of the ear. Therefore, after injection of the solution, 20 seconds of occlusion on the proximal and distal aspects of the injected vein wall caused by firm pressure helped simulate the more sluggish blood flow of human telangiectasias.[43,44] In vitro studies of the effect of sclerosing solution on saphenous veins harvested for coronary bypass surgery have confirmed the histologic effect of sclerosing solution type and concentration with the rabbit ear vein model.[46] However, study of an animal model may not produce accurate data because the researcher is comparing the action of a sclerosing solution on a normal vessel. In addition, the injected vessels are not compressed in rabbit ear vein studies, thereby resulting in the formation of a larger thrombus, which may allow for a more rapid or increased incidence of recanalization. Finally, thrombogenesis and thrombolytic effects are different in the rabbit ear than in the human artery and vein (Feied C, Kessler CM. Personal communication, 1993). However, despite all these shortcomings, as a model the rabbit ear vein does allow the physician to compare the mechanism of action of various sclerosing solutions both clinically and histologically. On the basis of these studies, the physician can achieve a similar therapeutic effect in humans by varying the concentration and type of solution (Table 7.2).

Table 7.2 Relative Potency of Sclerosing Solutions

Vein Diameter	Sclerosing Solution
0.4–1 mm	Nonchromated glycerin 72% Chromated glycerin 50%–100% (Sclermo) Polidocanol 0.25%–0.5% Sodium tetradecyl sulfate 0.1% Hypertonic saline 11.7% Sodium chloride solution with dextrose (Sclerodex) Ethanolamine oleate 2% Polyiodinated iodine 0.1% Sodium morrhuate 0.25%–0.5%
1–3 mm	Sodium tetradecyl sulfate 0.25% foam Polidocanol 0.5% foam Polyiodinated iodine 0.5%–1.0% Ethanolamine oleate 5% Hypertonic saline 23.4% Sodium morrhuate 1.0%–2.5%
3–5 mm	Polidocanol 1% foam Sodium tetradecyl sulfate 0.5%–1.0% foam Sodium morrhuate 5% Polyiodinated iodine 2%
>5 mm	Polidocanol 3%–4% foam
Perforators	Sodium tetradecyl sulfate 2%–3% foam
Saphenofemoral/ popliteal junctions	Polyiodinated iodine 3%–12%

[a]Product description on hydroxypolyethoxydodecane, Dexo SA Pharmaceuticals, France, May 1985; product insert for Aethoxysklerol, Kreussler, Wiesbaden-Biebrich, Germany, 1985.

[b]Henschel O. Sclerosing of varicose veins sclerotherapy with Aethoxysklerol-Kreussler (product booklet), Kreussler, Wiesbaden-Biebrich, Germany.

In the 1920s, the first studies to elucidate the mechanism of action of sclerosing agents were performed using the dorsal vein of the rabbit ear. Sclerosing agents tested included 1% bichloride of mercury,[47] 30% sodium chloride and 50% grape sugar,[48,49] 30% sodium salicylate,[50] 50% to 60% calorose[51,52] and SM.[53,54] All of these solutions achieved venous obliteration through endothelial cell alteration, with inflammation resulting in thrombus formation and the eventual production of a fibrous cord.

An evaluation of foamed sclerosing solutions has also been performed in vivo on isolated saphenous veins before stripping.[55] Pathologic damage from 3% STS foam prepared with 1 mL of STS and 4 mL of air was extremely rapid, with complete damage to the endothelium within 2 minutes. Edema of the intima with progressive separation from the tunica media and formation of thrombus occurred at 15 and 30 minutes.

SODIUM TETRADECYL SULFATE

The mechanism of sclerosis for intravascular STS was elucidated by Schneider[8] and by Schneider and Fischer[54] in human varicose veins, by Dietrich and Sinapius[56] in rabbit external jugular veins and by Imhoff and Stemmer[20] in the dorsal rabbit ear vein. With STS, endothelial damage is dependent on concentration and occurs immediately after injection, with resulting rapid thrombus formation leading to vascular sclerosis.

In two studies, sclerosis with STS produced similar results in a concentration-dependent manner.[43,44] Endothelial damage occurred within 1 hour (Fig. 7.9), followed by the rapid onset of vascular thrombosis with subsequent organization (Fig. 7.10). Histologic recanalization occurred after 30 days with solution concentrations of 0.1% to 0.5%. The histologic findings explained the clinical appearance, which demonstrated initial thrombosis, followed by partial reappearance of the vessel injected with STS 0.1%. Therefore, there may be a concentration gradient in which an ideal concentration depends on many factors, including vessel diameter, rate of blood flow, animal model and anatomic region within each animal model.

SODIUM MORRHUATE

Sodium morrhuate, a mixture of sodium salts of the saturated and unsaturated fatty acids present in cod-liver oil, has been studied in the rabbit ear vein model.[57] A 0.5% concentration of SM produced no clinical evidence of endothelial damage. Temporary histologic evidence of thrombosis was noted at 1 hour only, with a mild perivascular mixed cellular infiltrate (MCI). There was no evidence for extravasation of RBCs. Vessels injected with SM 1.0% were thrombosed between 2 and 10 days, after which the vessels normalized. Histologically the vessel injected with SM 1.0% demonstrated a partially destroyed endothelium with extravasation of RBCs. The vessels injected with SM 2.5% demonstrated clinical fibrosis with histologic evidence of microangiopathic recanalization through a fibrotic cord at 45 days after injection. A unique finding noted with injection of SM, both 1.0% and 2.5%, was the presence of large numbers of perivascular mast cells (Fig. 7.11). This finding may correlate with the increased inflammatory nature and allergenicity of SM as compared with other sclerosing solutions.

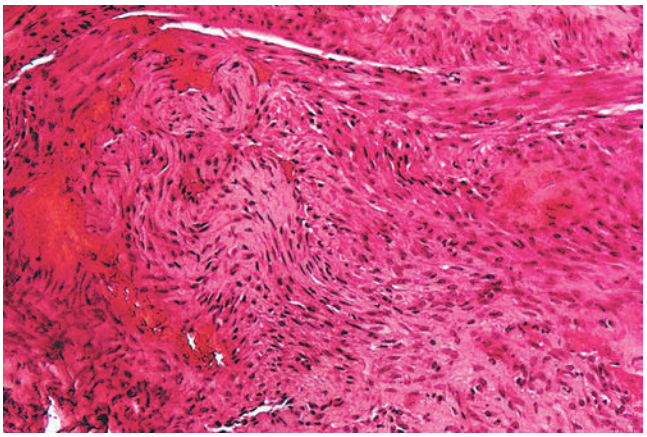


Figure 7.10 Microangiopathic recanalization is apparent 14 days after injection with sodium tetradecyl sulfate 0.5% (hematoxylin–eosin, ×100). (From Goldman MP et al. Arch Dermatol 1987;123:1196.)

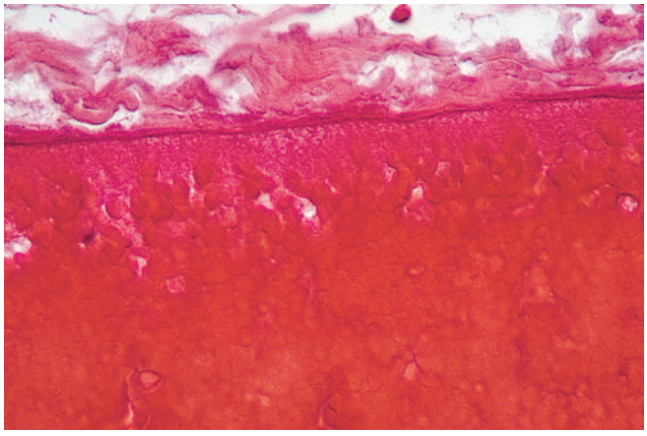


Figure 7.9 Endothelial cells and the vascular wall are entirely destroyed 1 hour after injection of sodium tetradecyl sulfate 0.5%. Hemolysis of red blood cells and early thrombosis are also present. (Hematoxylin–eosin, ×200.)

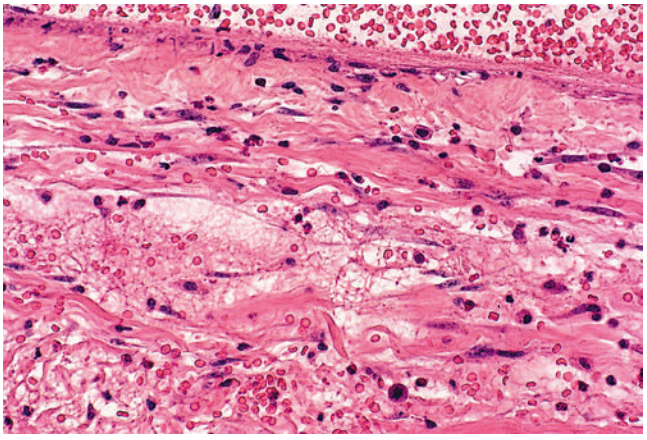


Figure 7.11 Vessel 2 days after injection of sodium morrhuate 1%. Note the large numbers of perivascular mast cells (hematoxylin–eosin, ×400).

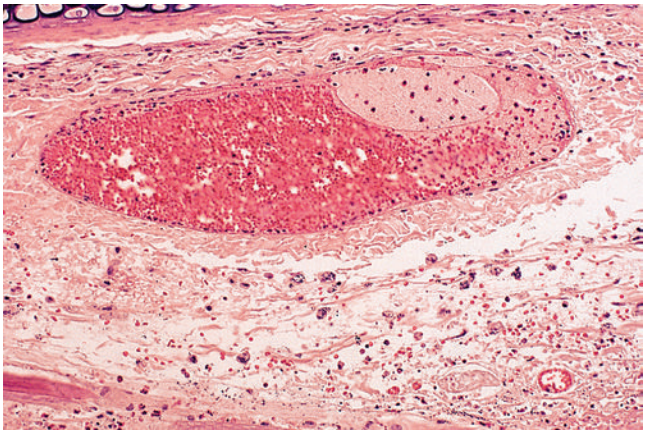


Figure 7.12 Vessel 2 days after injection of ethanolamine oleate 2.5%. Note the extensive phagocytosis of lipid-like globules (hematoxylin–eosin, ×200).

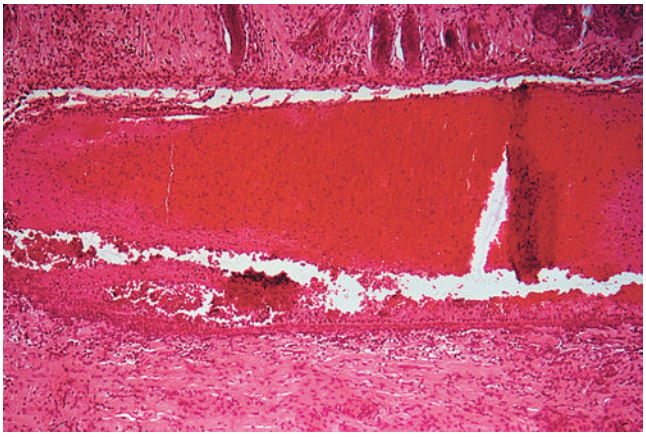


Figure 7.13 Partially damaged endothelial cells with thrombosis are seen 8 hours after injection of polidocanol 0.25% in the rabbit ear vein (hematoxylin–eosin, ×40).

ETHANOLAMINE OLEATE

A synthetic mixture of ethanolamine and oleic acid, EO is another sclerosing solution that has been studied in the rabbit ear vein model.[57] No histologic or clinical changes were noted with injection of EO 0.5%. Although an organizing thrombus was produced, complete recanalization occurred in the vessel injected with EO 1%, causing the returned clinical appearance of the injected vessel. Vessels injected with EO 2.5% had a partially destroyed endothelium followed by luminal recanalization. Evidence of phagocytosis of lipid-like material was noted in a vessel injected with EO 2.5% at 48 hours (Fig. 7.12). This may indicate extravasation of sclerosing solution either during injection or with endothelial destruction. Large numbers of perivascular mast cells were also noted 2 days after injection with EO 1% and 2.5%. Extravasated RBCs occurred in vessels injected with EO 1% and 2.5% at 1 hour and 2 days, but not in vessels injected with EO 0.5%.

A previous study comparing EO with STS was performed using the rat tail vein model.[58] In this model, EO 5% was compared with STS 3% and 1%. Solution measuring 0.1 mL was injected and the veins were biopsied at 4 weeks. In this study, EO 5% was effective in sclerosing only 25% of the treated veins, as opposed to a 73% efficacy with STS 1% and a near 100% efficacy with STS 3%. Therefore, results in the rabbit ear vein compare well with those in the rat tail vein.

POLIDOCANOL

A concentration gradient was also demonstrated in a study of POL in concentrations of 0.25%, 0.5% and 1.0%.[43] Only vessels injected with POL 0.5% and 1% were clinically sclerosed, and only the vessels injected with POL 1% maintained sclerosis without revascularization by 60 days.

An examination of the histologic effects of POL on the endothelium specifically, between 1 hour and 4 days after injection, illustrates the effect of varying the concentration of sclerosing solutions. Endothelial cells exposed to POL 0.25% were at first only partially damaged (Fig. 7.13). Mitotic figures indicating endothelial regeneration were noted 4 days after injection (Fig. 7.14). Likewise, with POL 0.5%, partial luminal recanalization occurred through an initial fibrotic cord in vessels (Fig. 7.15). Only vessels sclerosed with POL 1.0% developed complete endosclerosis (Fig. 7.16). Therefore, POL is a weaker detergent type of sclerosing solution than STS, and higher concentrations are necessary to produce complete vascular sclerosis.

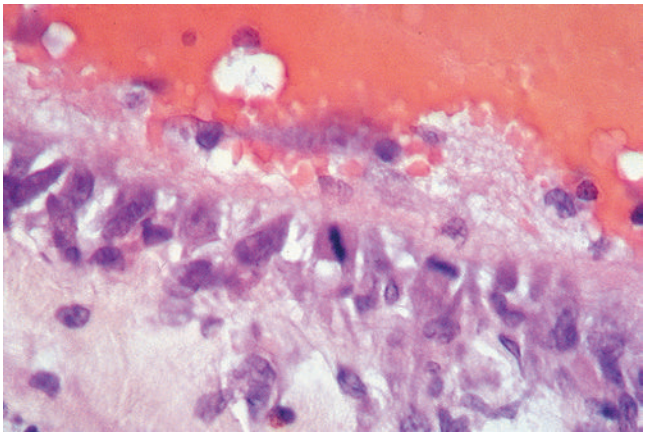


Figure 7.14 Endothelial regeneration is apparent 4 days after injection of polidocanol 0.25% in the rabbit ear vein (hematoxylin–eosin, ×100).

POLIDOCANOL: LIQUID VERSUS FOAM

Hamel-Desnos et al and Wollmann have demonstrated both clinical[59,60] and microscopic[61] superior efficacy of foam versus liquid. In vitro studies have been conducted on single layers of endothelial cells in contact for 1.5 seconds with various concentrations of foam and liquid POL. Histologic examination demonstrated identical cell destruction with 0.5% foam and 3% liquid. As indicated by Hamel-Desnos et al, better efficacy had been supposed to be related to a longer time of contact; they have observed that the effect happened in a very short time, therefore there should be missing explanatory links. From a macroscopic point of view, foam seems to work because of the delayed dilution and closer contact between nondiluted sclerosing agent and endothelium; some microscopic phenomena will perhaps

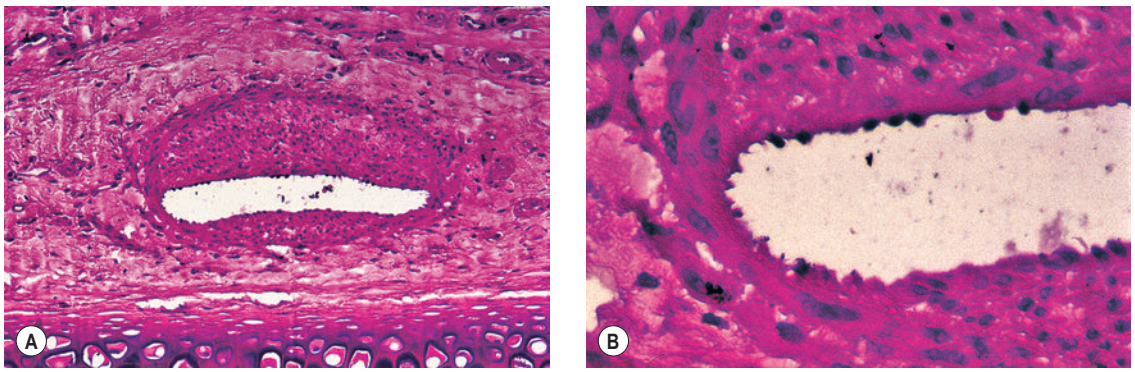


Figure 7.15 Advanced luminal recanalization is present 60 days after injection of polidocanol 0.5%, as seen in cross-section. **A,** ×100. **B,** ×200; note endothelial lining on recanalized lumen (hematoxylin–eosin). (A from Goldman MP et al. Arch Dermatol 1987;123:1196.)

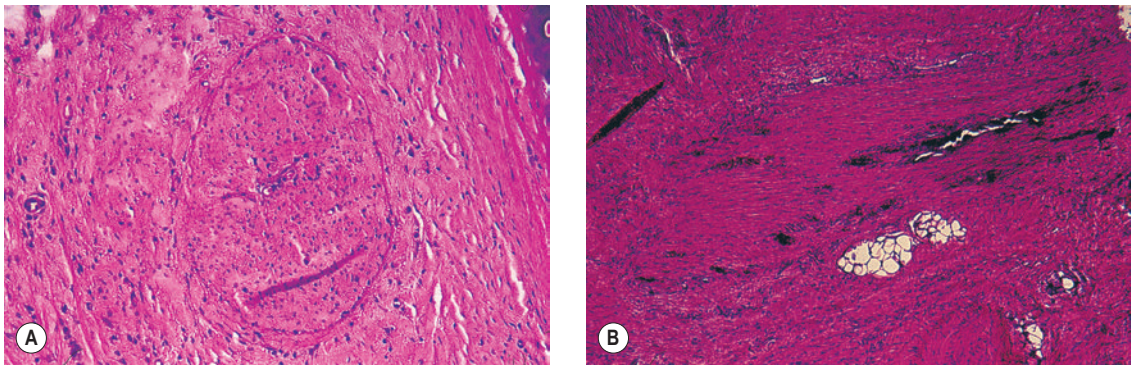


Figure 7.16 Fibrous cord formation is present 30 days after injection of polidocanol 1.0%. The darker areas within the fibrous cord represent hemosiderin-laden macrophages. **A,** Cross section, ×40. **B,** Longitudinal section, ×100 (hematoxylin–eosin). (B from Goldman MP et al. Arch Dermatol 1987;123:1196.)

be found explaining more precisely what happens. (Foam sclerosants are described in detail at the end of this chapter and in Chapter 9.)

HYPERTONIC SALINE

The sclerosing effect of HS was examined histologically in the external jugular vein of the dog by Kern and Angle[62] and in human varicose veins by McPheeters and Anderson.[52] These investigators noted endothelial damage with thrombus formation within 1 hour of injection, with ultimate conversion into a fibrous cord within 2 to 4 weeks. This was confirmed in the rabbit ear vein model[43] both clinically and histologically. Examination of the marginal ear vein 1 hour after exposure to HS 23.4% demonstrated complete endothelial destruction (Fig. 7.17).

However, subsequent evaluation of HS 11.7% in the rabbit ear vein model[57] demonstrated an immediate thrombosis that lasted only 48 hours before complete normalization. Endothelial destruction was patchy at 1 hour with perivascular and intraluminal margination of polymorphonuclear cells and eosinophils. There was no evidence of extravasation of RBCs in the veins injected with HS 11.7%, whereas extravasation was noted in 30% of vessels injected with HS 23.4%. Therefore, the degree of endothelial damage and resulting extravasation of RBCs is proportional to the concentration of HS used.

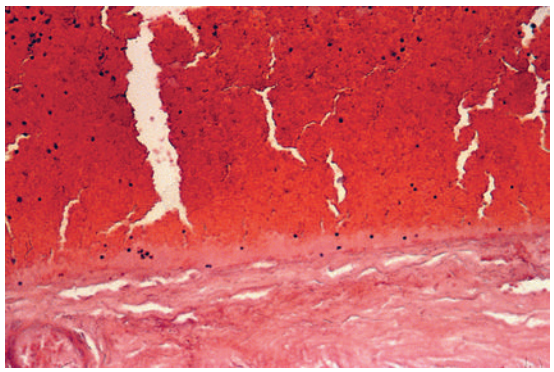


Figure 7.17 The endothelial cells and vascular wall structure are completely homogenized 1 hour after injection of the rabbit ear vein with hypertonic saline 23.4%. Longitudinal section, ×40 (hematoxylin–eosin).

HYPERTONIC GLUCOSE/SALINE

Sclerodex (SX; Omega Laboratories, Montreal, Canada) is a mixture of dextrose, sodium chloride, propylene glycol and phenethyl alcohol. When SX was studied in the rabbit ear vein model,[57] it produced an immediate thrombosis that lasted for 2 days, after which the vessel recanalized. At 1 hour, perivascular and intraluminal margination of polymorphonuclear cells and eosinophils were present with

patchy endothelial destruction. Endothelial mitoses were present at 2 days within a regenerative endothelium. Extravasation of RBCs was not noted. Therefore, SX has a potency similar to HS 11.7%.

GLYCERIN: CHROMATED VERSUS NONCHROMATED

The effect of chemical irritant sclerosing solutions has been studied in the rabbit ear model.[44] Chromated glycerin (CG; Sclérémo, Laboratoires Bailleul, Paris, France), 50% and 100%, was injected into the dorsal marginal rabbit ear vein, producing clinical and histologic thrombosis that lasted only 2 to 8 days, after which the vessel appeared clinically and histologically normal. As noted with POL 0.25% mentioned earlier, the endothelium 1 hour after biopsy was almost undamaged. Therefore, in this experimental model, CG is a weak solution with a sclerosing effect similar to POL 0.25%. This correlates well with its clinical profile. The chromium alum component of CG is a potent coagulating factor that increases the sclerosing power of glycerin but also poses the issue of allergenicity. Fortunately, the sclerosing effect of CG is not dependent upon chromium. Excellent results without evidence of hypersensitivity can be achieved in treating leg veins less than 1 mm in diameter with the use of a nonchromated 72% glycerin solution mixed 2:1 with 1% lidocaine with epinephrine, as described later in this chapter.

POLYIODINATED IODINE

Various iodine solutions, with or without hypertonic solutions, have been examined in the rabbit ear vein model.[63] Sclerodine (Omega Laboratories, Montreal, Canada) is a mixture of iodine USP (United States Pharmacopeia; 60 mg/mL) and sodium iodide USP (90 mg/mL). This solution was compared with an American iodine formula consisting of iodine and sodium iodide, compounded by the Women's Hospital of Texas in Houston. The two sclerosants were identical in composition. After being mixed with either normal saline, SX or a solution of dextrose 250 mg/mL and sodium chloride 100 mg/mL (compounded by the Women's Hospital of Texas in Houston), each sclerosant was injected in concentrations of 0.1% and 0.5%. Thrombosis occurred with all solutions at 1 hour, with an attenuated endothelium and focal endothelial necrosis. A mild perivascular mixed cellular infiltrate consisting of eosinophils and polymorphonucleocytes was present with margination along the endothelial border. With the 0.1% solutions, the endothelium was hyperplastic, with regenerative changes noted by 8 days (Fig. 7.18) and complete normalization by 28 days. With the 0.5% solutions, the endothelium was necrotic with multiple brown spherules approximately 1 μm in diameter seen within the endothelial wall (Fig. 7.19). These may represent iodine crystals. By 28 days, a fibrous cord was present without inflammation. Interestingly, veins treated with iodine/normal saline mix showed a greater incidence and extent of extravasated erythrocytes compared with those treated with iodine/SX (hypertonic saline/dextrose) solutions. The PII 0.1% solution had an experimental efficacy equivalent to HS 11.7%, SM 2.5%, STS 0.25% and POL 0.5%. The PII 0.5% solution had an experimental efficacy similar to HS 23.4%, STS 0.5% and POL 1.0%.

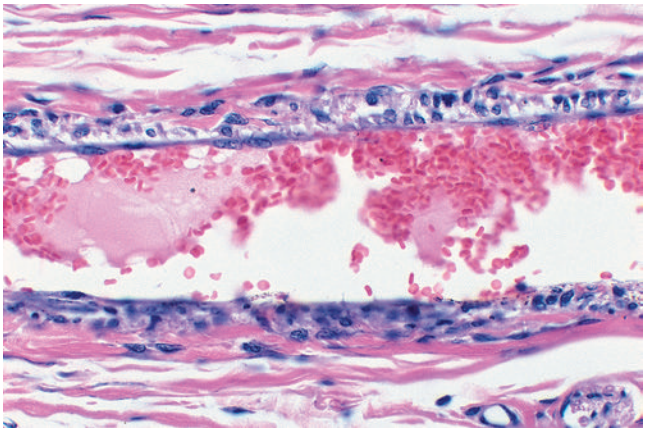


Figure 7.18 Regenerating hyperplastic endothelium is present 8 days after injection of the rabbit ear vein with 0.1% polyiodinated iodine diluted with Sclerodex (hematoxylin–eosin, ×20).

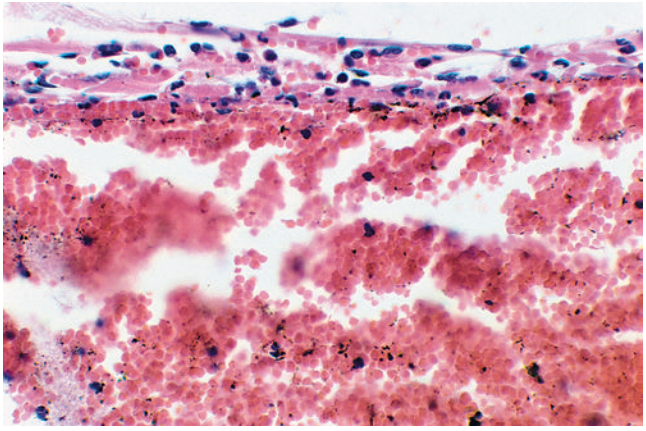


Figure 7.19 Multiple brown spherules approximately 1 μm in diameter are noted within necrotic endothelium at 8 days in the rabbit ear vein injected with 0.5% polyiodinated iodine (hematoxylin–eosin, ×40).

COMPARATIVE EFFICACY IN THE ANIMAL MODEL

The mechanism of action for all sclerosing solutions injected into veins in the aforementioned studies was basically similar; that is, endothelial damage and simultaneous thrombus formation occurred almost immediately after injection. Endothelial damage was less in the vessels injected with CG, POL 0.25%, SX and EO 0.5%, which showed early recanalization and a continued normal clinical appearance. POL 0.5%, SM 0.5% and 1%, EO 1% and HS 11.7% produced endothelial attenuation, not necrosis. Although an organizing thrombus was produced, recanalization occurred, causing the returned clinical appearance of the injected vessel. Vessels injected with PII 0.1%, STS 0.5%, SM 2.5% and EO 2.5% also demonstrated recanalization, although endothelial necrosis was demonstrated. In contrast to the luminal recanalization that occurred with POL 0.5% and EO 2.5%, recanalization with STS 0.5% and SM 2.5% occurred with multiple minute vascular channels. Vessels sclerosed with STS 0.25% and 0.5% and with SM 2.5% never totally reappeared clinically in the 60-day span of this study.

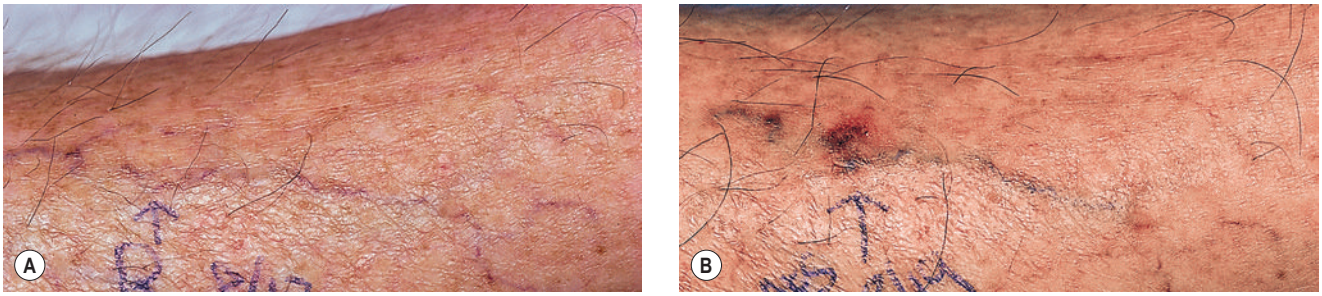


Figure 7.20 Anterior tibial telangiectasia. **A,** Before treatment and, **B,** 48 hours after injection of polidocanol 0.5%.

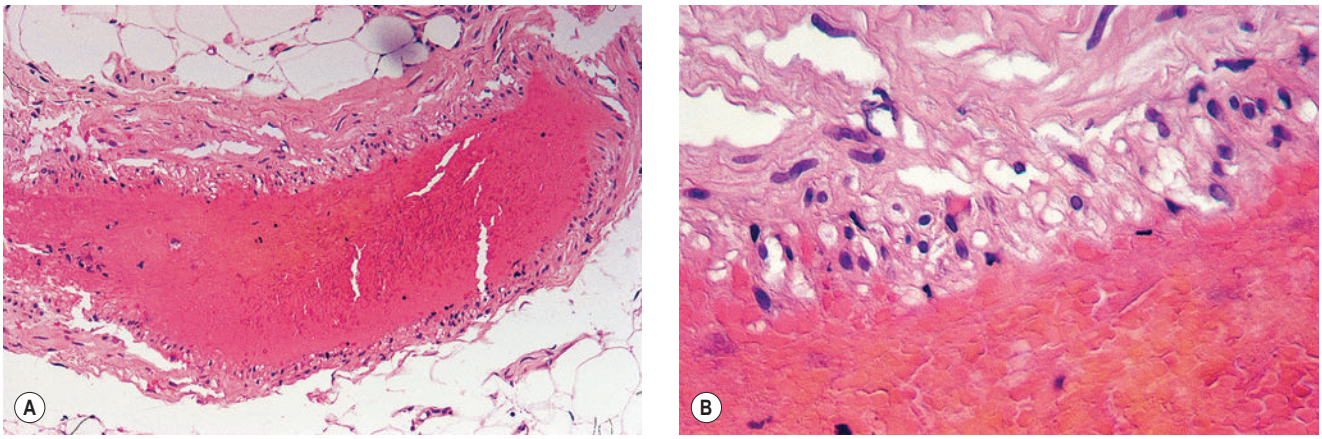


Figure 7.21 Histologic examination of vein in Figure 7.20. **A,** ×40. **B,** ×100; shows endothelial cell vacuolization with thrombosis (hematoxylin–eosin).

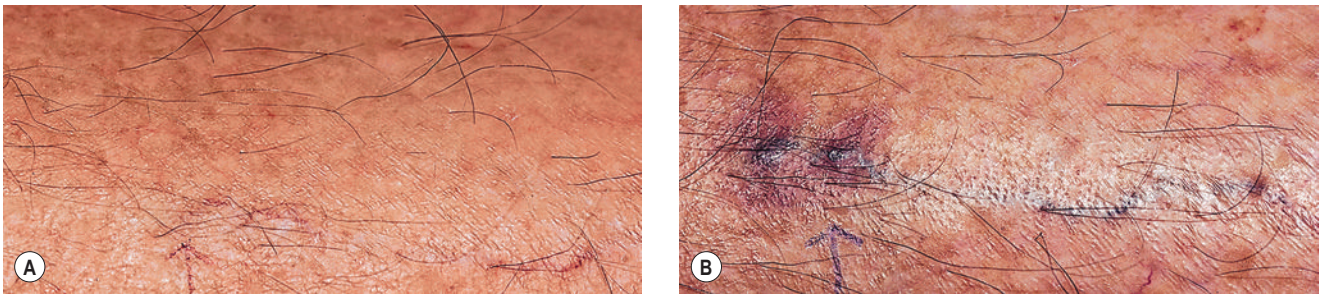


Figure 7.22 Anterior tibial telangiectasia. **A,** Before treatment and, **B,** 48 hours after injection of sodium tetradecyl sulfate 0.5%.

The only vessels to histologically demonstrate fibrous cord formation that did not recanalize were sclerosed with PII 0.5%, HS 23.4% and POL 1.0%. Therefore there is a minimal sclerosant concentration (MSC) that is essential to produce endosclerosis. This term, coined by Neil Sadick,[64] is useful in determining which solution and concentration is best at sclerosing a specific vessel.

COMPARATIVE EFFICACY IN THE HUMAN MODEL

In an effort to assess the effect of sclerosing agents in human leg telangiectasias, the author injected 0.1 mL of either POL 0.5% or STS 0.5% into two nearly identical telangiectasias (0.4 mm in diameter) over the anterior tibia in a 65-year-old man. The vessels did not have any associated 'feeding' reticular veins, and there was no evidence of associated varicose veins or signs of venous insufficiency. Neither injected vessel was compressed, and a biopsy of each was taken 48 hours after treatment. The vessel injected with POL 0.5% demonstrated a blue thrombus (Fig. 7.20) that was histologically confirmed, and an endothelium that was relatively intact with extensive cellular vacuolization (Fig. 7.21). The vessel injected with STS 0.5% demonstrated a deep blue thrombus (Fig. 7.22). Histologically, the endothelium was totally destroyed, showing extensive intravascular thrombosis and early organization (Fig. 7.23). Therefore, this limited human study correlates with the aforementioned studies on the marginal rabbit ear vein, demonstrating that STS is a stronger sclerosing agent than POL.

CLINICAL USE OF SCLEROSING AGENTS

The sclerosing agents approved for use in the United States by the Food and Drug Administration (FDA) are SM, EO, STS and POL. SM, EO and STS were approved for use

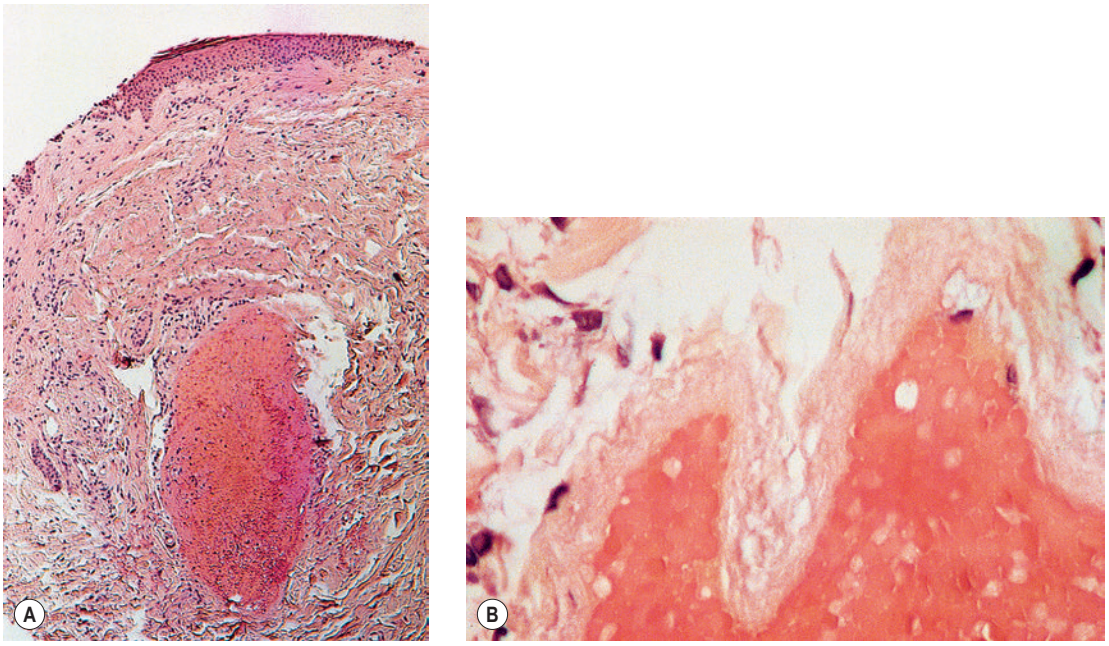


Figure 7.23 Histologic examination of vein in Figure 7.22. **A,** ×40. **B,** ×100; shows endothelial cell homogenization/necrosis with thrombosis (hematoxylin–eosin).

before 1950 and thus were not subjected to the rigorous toxicity and efficacy studies that would be required by the FDA today. Although probably the most commonly used sclerosant in the world, POL was not widely available in the United States until its FDA approval in 2010. SM and EO, although approved by the FDA, have a safety profile and allergenicity not suitable for treatment of leg veins.[65] Although HS in a 23.4% concentration is available and FDA-approved for use as an abortifacient, it is widely used off-label for sclerotherapy largely because of unrealistic fears regarding the allergenicity associated with detergent sclerosants and the low cost of HS. It is commonly used in various concentrations, with and without the addition of heparin, procaine or lidocaine, for sclerosis of telangiectasias and superficial varicosities. SX is commonly used in Canada for sclerosis of superficial varicosities and telangiectasias, but lacks FDA approval and can only be obtained in the United States through compounding pharmacies. Chromated and nonchromated glycerin are perhaps the most widely used nondetergent sclerosing agents worldwide for the treatment of leg telangiectasias. Although both lack FDA approval, Ouvry[66] and Goldman[67] have popularized their use in the English literature. PII is the most powerful sclerosing agent and is commonly used outside of the United States for sclerotherapy of the saphenofemoral junction (SFJ). It is not approved by the FDA for use in the United States but is discussed because of its importance in sclerotherapy. Another solution rarely used now, sodium salicylate, is briefly discussed.

OSMOTIC AGENTS

HYPERTONIC SALINE

Hypertonic saline (HS) was first used to sclerose varicose veins by Linser[20] in 1926 and Kern and Angle[61] in 1929. With the advent of more effective, synthetic, detergent sclerosing solutions in the 1940s, its use declined. Renewed interest in its use occurred in the 1970s, spurred on by numerous publications in the dermatology literature and multiple lectures on its use presented at major medical meetings.

A double-blind, paired-comparison study of various concentrations of HS, with and without heparin, was performed in different-sized varicose and telangiectatic leg veins.[64] It was found that an 11.7% HS solution was as effective as a 23.4% solution in treating vessels less than 8 mm in diameter, and more effective than a 5.8% solution, with less burning, pigmentation and cramping. The addition of heparin only decreased thrombosis formation requiring puncture evacuation in vessels greater than 4 mm in diameter. This demonstration of MSC produced superior cosmetic results with an improved therapeutic-to-complication index.

Advantages

Part of the previously experienced popularity stems from the lack of allergenicity of unadulterated HS solution compared with the exaggerated claims of allergenicity associated with all other sclerosing agents. However, HS is not without significant adverse sequelae (see Chapter 8).

Disadvantages

Unlike detergent sclerosing solutions, all hypertonic solutions act nonspecifically to destroy all cells (including RBCs) within their osmotic gradients by dehydration. Osmotic agents damage cellular tissues and readily produce ulceration if injected extravascularly or if diffused through the vessel extravascularly (see Chapter 8). Therefore, injection technique is critically important with use of this type of sclerosing agent.

Because HS diffuses to some extent through the blood vessel wall, nerves in the adventitia of the vein may be stimulated, causing pain (see Chapter 3). This diffusion may also

lead to transient muscle cramping. Hemolysis of RBCs occurs through hyperosmosis, causing the release of hemosiderin, which may readily diffuse across the damaged endothelium. This may lead to posttreatment hyperpigmentation, especially in a punctate pattern. Finally, because osmotic agents are rapidly diluted in the bloodstream, they lose their potency within a short distance of injection, which means injections should be made at close intervals for effective treatment. Thus, these agents are only rarely effective in treating veins larger than 3 to 4 mm in diameter. HS is probably the agent that has created the most negative connotations associated with sclerotherapy because of its burning, stinging and cramping pain following injection plus the potential for ulceration and extravasation.[65]

For decades HS was probably the best-known scerlosant in the United States, with patients frequently asking for 'saline injections' when requesting injection sclerotherapy. Today the more efficacious, less painful and safer detergent and chemical sclerosants have surpassed HS in popularity and clinical use in reputable facilities. The author no longer offers HS or any other hyperosmolar solution as an injection option for sclerotherapy.

Modification of the Solution and the Technique

Various modifications of the HS solutions have been made in an effort to increase the efficacy and decrease the pain of injection and other adverse sequelae. In 1975, Foley[68] described the microinjection of 'venous blemishes' with a 30-gauge needle using 20% hypertonic saline, 100 U/mL of heparin and 1% procaine, which he patented as Heparsal. He reported no allergic or anaphylactic reactions and only rare pigmentary problems in more than 1000 treatments to more than 100 patients. Foley theorized that the addition of heparin helped to prevent thrombi in larger vessels, and the addition of procaine helped alleviate the pain on injection. Sadick,[64,69] in randomized, double-blind, 800-patient and 600-patient, paired-comparison studies, found that the addition of heparin to HS provided no benefit in the treatment of varicose and telangiectatic veins less than 4 mm in diameter. Bodian,[70,71] because of his personal clinical comparison experience, also did not believe that the addition of heparin was necessary for effective sclerosis. Finally, it has been demonstrated that the addition of heparin to the culture medium enhances proliferation and increases the lifespan of endothelial cells.[72] Therefore its use may be counterproductive.

A number of modifications in injection technique have also been made to limit the pain of HS. Bodian[71] found that muscle cramps occurring at the site of injection last 3 to 5 minutes and are relieved with gentle massage or ambulation. To limit the risk of extravasation, he recommended injecting a small air bolus before injecting 0.5 to 1 mL of HS; this ensures undiluted contact of the HS with the intima to produce maximum irritation of the vessel. He believed that hemolysis caused by the sclerosing solution may lead to or exacerbate hemosiderin staining and thus should be lessened by the prior injection of air, which washes out the RBCs from the vessel.[73] Finally, regarding the possible exacerbation of hypertension with injection of a large sodium bolus, he stated that 1 g of sodium chloride injected during a 'long treatment session' (5 mL of a 20% HS solution) is well tolerated.

Alderman[74] was the first to advocate dilution of the HS solution to better adjust the osmotic damage to the caliber of the vessel. From his experience with 150 patients with telangiectasias treated over 8 years with 18% to 30% HS, he recommended the following HS concentrations for sclerosis of varicose and telangiectatic veins: 18% to 25% HS for 'venous telangiectasias' (blue telangiectasias), 22% to 25% HS for 'arterial lesions' (red telangiectasias) and 30% HS for rare, large 'arterial' lesions. He diluted the saline with lidocaine to achieve a 0.4% concentration of lidocaine. The only adverse side effects reported were mild, temporary burning at injection and residual brownish pigmentation that occurred in up to one third of patients. The pigmentation usually resolved, for the most part, over 1 year.

Lidocaine, when used as a diluent, can be used with or without epinephrine. Animal studies have demonstrated that solutions with less than a 1% concentration of lidocaine are vasoconstrictive.[75,76] In addition, the author routinely uses it with epinephrine as a diluent to enhance vasospasm and partially stabilize perivascular mast cells.

HYPERTONIC GLUCOSE–SALINE

Sclerodex, another hyperosmolar sclerosant, is a mixture of dextrose 250 mg/mL, sodium chloride 100 mg/mL, propylene glycol 100 mg/mL and phenethyl alcohol 8 mg/mL (as a local anesthetic/preservative) at a pH of 5.9, mainly used in Canada for sclerosis of telangiectasias and small-diameter superficial varicosities.[77] It is essentially a hypertonic solution with a mechanism of action similar to HS. The manufacturer states that the sodium chloride reinforces the sclerosing potency of dextrose.

It is interesting to note that a similar product was manufactured by Abbott Laboratories (Abbott Park, IL) in the 1950s and 1960s under the trade name Varisol. This compound consisted of 30% invert sugar and 10% sodium chloride, with a mixture of preservatives and stabilizers (benzyl carbonate phenethyl, propylene glycol) in water. It was withdrawn from the market in 1963 in conjunction with the FDA's new requirements for efficacy and toxicity testing. The author's past correspondence with Abbott Laboratories has not spurred their interest in development or production of this solution (Diane Rennpferd, Coordinator, External Technology Evaluation, 15 August 1991).

The manufacturer of SX recommends that the maximum quantity to be injected during one visit is 10 mL in divided doses, with a 5-cm interval between each site of injection.[a] (The maximum recommended amount to be injected at any one site is 1 mL.) The average dose per treated vein varies from 1 mL in the upper thigh to 0.1 mL in the lower leg. The reason for these recommended doses by the manufacturer is unclear.

Advantages

Omega Laboratories, which produces SX, claims that the addition of dextrose allows for a reduction in the concentration of sodium chloride, thereby minimizing the pain and local discomfort that would occur with injection of sodium chloride alone.[a] However, it is probably the decrease in

[a]Correspondence received from Laboratories Ondee Ltee, 280 Milice Longueuil, Montreal, Canada (1986).

osmolarity relative to 23.4% HS that allows SX to produce less pain and muscle cramping.

Disadvantages

Despite the lower osmolarity of SX, like HS, it is slightly painful for the patient on injection.[78] Superficial necrosis may occur rarely, with an incidence of less than that with HS.[a,77,79] The author has noted postsclerotic pigmentation occurs with a frequency similar to that of other sclerosing agents, although Mantse[79] noted a decreased incidence of complications with SX as compared with POL and STS (see Chapter 8).

Another disadvantage of SX use is that the solution becomes sticky in the syringe when blood is withdrawn to ensure an intravenous position. Unfortunately, unlike unadulterated HS, allergic reactions may occur to the phenethyl alcohol component of the solution.[a] Mantse[77] noted one allergic reaction in 500 patients treated with SX, giving an incidence of 0.2%.

SODIUM SALICYLATE

Sodium salicylate (SS; Saliject, Omega Laboratories, Montreal, Canada) is provided in a 10-mL multiuse vial. Each milliliter contains 570 mg of SS, with benzyl alcohol 1% and sodium metabisulfite 0.1% added as preservatives. Because SS is painful on injection, especially if it diffuses or is injected extravascularly, it is recommended to be diluted with lidocaine 1% without epinephrine. The manufacturer recommends a maximum daily total quantity of 8 to 10 mL. It may also be added to other sclerosing solutions such as glycerin to achieve a final concentration between 6% and 30%. In this concentration, it can be used for telangiectasias less than 1 mm in diameter.

Recommended concentrations are 20% for reticular veins of 2 to 4 mm in diameter and 15% for telangiectasia 1 mm or less in diameter. To make 30 mL of a 15% solution, dilute 5 mL of Saliject with 12 mL of 1% lidocaine and 13 mL of normal saline. To make 30 mL of a 20% solution, mix 10 mL of Saliject with 10 mL of 1% lidocaine and 10 mL of normal saline.

This solution causes muscle cramping after use, especially if volumes greater than 0.1 mL are injected in a single location. Like other osmotic agents, SS produces necrosis on extravasation in a concentration-dependent manner. Because of the intense pain produced with arterial or extravascular injection, SS is often mixed with STS to ensure that injection of STS is intravascular (STS is nearly painless when injected extravascularly). Anaphylactic reactions are possible because, albeit rarely, patients can be allergic to salicylates.

CHEMICAL IRRITANTS

CHROMATED GLYCERIN/GLYCERIN

Chromated glycerin 72% (Sclérémo, Laboratories Bailleul, Paris, France; Chromex, Omega Laboratories, Montreal, Canada; Skleremo, Elvetium-Alet Laboratorios, Buenos Aires, Argentina) is a sclerosing solution that is popular in Europe, whereas clinical experience in the United States remains limited. The maximum recommended amount per injection session is 10 mL of pure solution. Concentrations of 25% to 100% have been used.[80] Its clinical efficacy has been shown to be dose dependent. Although not approved by the FDA, CG is a widely used sclerosing agent for leg telangiectasias in the world; 500,000 vials were sold in 1986.[a] More recent information is not available from the manufacturers.

The glycerin component of CG is rapidly absorbed by the intestine and transformed into carbon dioxide or glycogen or is directly used for the synthesis of fatty acids.[81] Therefore, this solution must be used with caution in diabetic patients. One case of reactive hypoglycemia to an infusion of glycerol occurred in a child, resulting in a comatose state within 4 minutes of infusion.[82]

The sclerosing quality of glycerin was first studied in 1925 by Jausion et al,[83] who found that it induced a mild, rapid and complete endosclerosis. Isosmotic glycerol (2.6% m/v) produces 100% hemolysis in 45 minutes.[81,84] This usually occurs with rapid infusions of 60 g in 15 minutes, 70 g in 30 minutes and 80 g in 60 minutes.[85] However, a review of 500 patients who received glycerol intravenously (at 50 g/500 mL) 6 hours a day for 7 to 10 days demonstrated hemoglobinuria in less than 1% of patients.[86]

The chromium alum component of CG is a potent coagulating factor that increases the sclerosing power of glycerin. It also prevents the mild hematuria induced through the use of glycerin alone.[81,87,88]

Mihael Georgiev (personal communication, 1994) has produced a 70% glycerin solution, sterile for injection, and has seen a sclerosing effect with this agent that is identical to CG. Hobbs (personal communication, 2000) has confirmed this effect with a 72% solution mixed with lidocaine 0.5% (Laboratorio Terapeutico M.R., Florence, Italy). As glycerin is obtainable on formulary for use in cerebral edema and acute glaucoma, its availability makes it a promising alternative to more caustic sclerosing agents. Its use for these applications indicates that glycerin alone has an osmotic effect as well.

We compared the effects of STS 0.25% with those of glycerin 72% mixed 2:1 with lidocaine 1% with epinephrine in 13 patients, to determine the relative safety and efficacy of the two sclerosant solutions.[67] Each patient's leg veins from 0.2 to 0.4 mm in diameter that did not have incompetence from the SFJ, and whose feeding reticular veins had been already treated in a prior sclerotherapy session, were randomly treated with either STS 0.25% or glycerin 72% solution. Patients were evaluated from 2 to 6 months postsclerotherapy for overall clinical improvement and incidence of adverse sequelae. We found that glycerin was comparable to STS in the discomfort of injection, but demonstrated a significant decrease in bruising, swelling and postprocedural hyperpigmentation. Glycerin also demonstrated a better, more rapid clearance of treated telangiectasias. Thus, the chromate salt addition to glycerin was not necessary for effective sclerotherapy.

Advantages

The relatively weak sclerosing power of CG corresponds to its promotion as a mild sclerosing solution with more

[a]Correspondence received from Laboratories Ondee Ltee, 280 Milice Longueuil, Montreal, Canada (1986).

[a]Correspondence received from Laboratories Ondee Ltee, 280 Milice Longueuil, Montreal, Canada (1986).

versatile use and a low incidence of side effects. Pigmentation and cutaneous necrosis are exceedingly rare at recommended dosages, and minimal extravascular injection causes only a small temporary ecchymosis without any cutaneous damage.[89,90] Reportedly, the incidence of adverse sequelae is very low.[a,41,80]

Disadvantages

The disadvantages of CG are its high viscosity and local pain at injection.[91,92] Both of these drawbacks can be overcome partially by dilution with lidocaine. Hypersensitivity is a rare complication.[93,94] Hematuria associated with ureteral colic can occur transiently after injection of large doses. Ocular manifestations, including blurred vision and a partial visual field loss, have been reported by a single author, with resolution in less than 2 hours.[95] These latter two complications may be a result of excessive, nonspecific destruction of RBCs.

A case of fatal anaphylaxis has been reported with chromated glycerin.[96] The case is well documented and little doubt remains regarding responsibility of the sclerosing agent. This case is the only one published and no known cases of anaphylaxis with glycerin alone exist.

ETHANOL

Ethanol is a sclerosing agent most commonly used for treating arteriovenous malformations. It kills cells by fixation, preserving cell morphology and is thus listed as a 'chemical' sclerosing agent. The precipitant thrombus-forming effect makes it useful for high-flow lesions. Using an in vitro model, Mol et al found that almost all cells die within 5 seconds when exposed to a 30% concentration.[97] A 3% concentration, to which cells were exposed for 12 hours, did not cause any damage. As a comparison, all cells exposed to 0.025% POL for 5 seconds also died. As discussed previously, POL kills cells by disrupting the cell membrane through protein-theft denaturization.

DETERGENT SCLEROSING SOLUTIONS

SODIUM MORRHUATE

Sodium morrhuate (Palisades Pharmaceuticals, Tenafly, NJ; American Regent Laboratories, Shirley, NY) is a mixture of sodium salts of the saturated and unsaturated fatty acids present in cod-liver oil (Table 7.3). It is prepared by the saponification of selected cod-liver oils. Each milliliter contains morrhuate sodium, 50 mg; benzyl alcohol, 2% (as a local anesthetic); water for injection (as much as will suffice); and hydrochloric acid and/or sodium hydroxide to adjust the pH to approximately 9.5. It is available as a 5% concentration that can be diluted with normal saline (to the appropriate concentration) for the vessel to be treated.

This sclerosing agent was first prepared for injection by Ghosh[98] or Cutting[99] and was met with enthusiasm in the United States by Biegeleisen[53] and others. However, extensive cutaneous necrosis occurs when SM is inadvertently injected perivascularly. Many cases of anaphylactic reactions within a few minutes after injection have been reported. More commonly, these reactions occur when therapy is reinstituted after a few weeks. Anaphylaxis has resulted in fatalities, albeit rarely (see Chapter 8). The FDA has approved the usage of SM for sclerosis of varicose veins. However, because of its extremely caustic nature, it is not recommended for use as a sclerosing agent for telangiectasias, although Gallagher[89] advocates its use diluted to a 0.25% to 0.5% concentration.

Table 7.3 Fatty Acid Composition of Sodium Morrhuate

Component	Percentage
Linoleic acid	28.2
Unknown	20.8
Eicosadienoic acid	15.5
Palmitoleic acid	12.1
Arachidonic acid	8.2
Palmitic acid	8.1
Myristic acid	4.2
Oleic acid	1.8
Stearic acid	1.1

From Monroe P et al. Gastroenterology 1983;85:693.

Most patients have minimal discomfort after injection, with an occasional tenderness at the injected site for a few days.[100] Gallagher's 25-year experience with 20,000 patients treated with SM is notably free of significant adverse sequelae, with only one episode of 'full anaphylactoid reaction'. He describes more than 20 patients who had immediate postinjection 'early anaphylactoid reactions' manifesting as chest pain, shortness of breath, tachycardia and hypotension, who responded to intravenous dexamethasone and intramuscular diphenhydramine (Benadryl). Gallagher states that STS has a higher incidence of adverse reactions than SM, so he prefers the latter for telangiectasia.

ETHANOLAMINE OLEATE

Marketed under the name of Ethamolin (QOL Medical, USA), ethanolamine oleate (EO) is a synthetic mixture of ethanolamine and oleic acid with an empiric formula of $C_{20}H_{41}NO_3$. It is available as a 5% aqueous solution containing approximately 50 mg of EO per milliliter. Benzyl alcohol, 2% by volume, is used as a preservative. The pH ranges from 8.0 to 9.0. The minimum lethal intravenous dose in rabbits is 130 mg/kg.[101]

The oleic acid component is responsible for the inflammatory action. Oleic acid may also activate coagulation in vitro by release of tissue factors and Hageman factor XII. It is not known whether EO is secreted into breast milk, so its use during lactation cannot be recommended. A 5% concentration used in gross varicose veins (diameter not specified) completely destroyed the veins 8 weeks after injection.[102]

Advantages

Ethanolamine oleate was first reported to be an ideal sclerosing agent by Biegeleisen[103] in the medical literature in 1937. No toxic effects were noted in 500 injections and it is thought to be less likely to cause allergic reactions than either SM or STS.[104] However, pulmonary toxicity has been associated with this sclerosing agent (see Chapter 8).

[a]Sclérémo product information from Laboratories E. Bouteille, 7 Rue des Belges, Limoges 8100, France (1987).

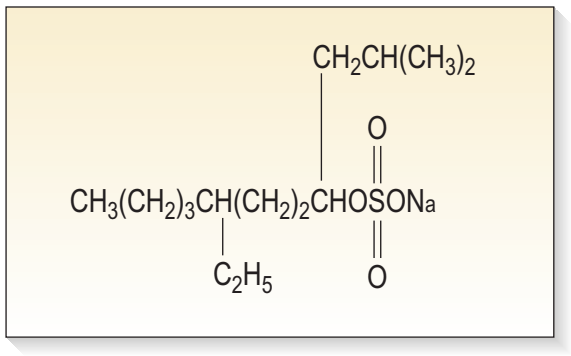


Figure 7.24 Structural formula of sodium tetradecyl sulfate.

The sclerosing action is thought to occur as a dose-dependent, extravascular inflammatory reaction caused by diffusion of EO through the venous wall.[a] Autopsy findings regarding its use in esophageal varix injection demonstrated that variceal obliteration occurred as a result of mural necrosis, followed by fibrosis, and that thrombosis was a transient phenomenon.[105,106]

Disadvantages

Ethanolamine oleate is a viscous solution that can be injected only through a 30-gauge needle with dilution. Some degree of nonspecific RBC hemolysis may occur with its use. A hemolytic reaction occurred in 5 of 900 patients with injection of over 12 mL of EO 0.5% per patient per treatment session.[107] Acute renal failure with spontaneous recovery followed injection of 15 to 20 mL of Ethamolin in two women.[b] The patients were described as 'feeling generally unwell and shivery, with aching in the loins and passage of red-brown urine. All rapidly recovered with bed-rest and were perfectly normal the next day.' One hundred and four injections of less than 12 mL per treatment session did not result in this reaction.

In addition, even a 0.5% solution produces an unacceptable incidence of eschar, ulceration or pigmentation when injecting telangiectasias of less than 1 mm in diameter.[102]

SODIUM TETRADECYL SULFATE

Sodium tetradecyl sulfate (Sotradecol, Mylan Pharma Group, Inverin, Co. Galway, Ireland and Angiodynamics, Latham, NY; Thrombojet, Omega Laboratories, Montreal, Canada; Trombovar, Laboratoires Innothéra, Arcueil, France) is a synthetic, surface-active substance first described by Reiner[45] in 1946 (Fig. 7.24). It is composed of sodium 1-isobutyl-4-ethyloctyl sulfate plus benzoyl alcohol 2% (as an anesthetic agent) and phosphate buffered to a pH of 7.96 to 7.9 depending on the manufacturer. It is recommended that solutions be protected from light. It is a long-chain fatty acid salt of an alkali metal with the properties of soap. The solution is clear, nonviscous, has a low surface tension and is readily miscible with blood, leading to a uniform distribution after injection.[108] It primarily acts on the endothelium of the vein, because, if diluted with blood, the molecules attach to the surface of RBCs, causing hemolysis. The recommended maximum dosage suggested by STD Pharmaceutical Products in a treatment session is 4 mL of a 3% solution or up to 10 mL of lower concentrations (e.g., 1%).[a] Although the recommended maximum dosage from Mylan Pharma Group is 10 mL of a 3% solution, the dosage should be kept small, using 0.5 mL to 2 mL (preferably 1 mL) for each injection.[b] Omega recommends no more than 2 mL of either concentration (1% or 3%) into a single varicosity, respecting a 5-cm interval between two injection sites, with no more than 3 mL of the 3% (30 mg/mL) solution per visit.[c] The recommended interval between treatments is usually 5 to 7 days.

The solution just mentioned should not be mixed with other anesthetic solutions because it will become turbid and form a new compound.[109] In addition, heparin should not be included in the same syringe as STS because the two are incompatible.[b] Yet, a paired comparison study of STS with and without heparin disclosed no difference in the therapeutic effect between the two solutions.[36]

In the United States, STS is available as a 1% or 3% solution that can be diluted with sterile water or normal saline to achieve an appropriate therapeutic concentration. It is also available—with the same pH and preservative—as Fibro-Vein (STD Pharmaceutical Products, Hereford, UK), in 5-mL multiuse vials in concentrations of 0.2% and 3% and in 2-mL ampules in concentrations of 0.5%, 1% and 3%. The manufacturer recommends dilution with sterile water to preserve the original pH level.[a]) It is limpid and does not stick to the syringe cylinder when blood is withdrawn to ensure accurate needle placement. Concentrations of 0.1% to 0.3% are commonly used for the treatment of telangiectatic veins 0.2 to 1.0 mm in diameter; 0.5% to 1% for treatment of uncomplicated varicose veins 2 to 4 mm in diameter; and 1.5% to 3% for the treatment of larger varicose veins, incompetent perforating veins or an incompetent SFJ. Fibro-Vein is a powerful surface active anionic detergent and should be used at half to one third the strength of POL for the same size vein.[a]

Advantages

Sodium tetradecyl sulfate became widely used in the 1950s after its introduction in 1946 by Reiner.[45] Tretbar[110] in 1978 first reported the injection of a 1% solution into spider angiomata. He noted excellent results in virtually all 144 patients treated. He also noted an unspecified number of episodes of epidermal necrosis without significant sequelae and a 30% incidence of postsclerosis pigmentation that resolved within a few months.

Shields and Jansen[111] in 1982 were the first to describe microsclerosis of telangiectasias with STS in the dermatologic literature. They injected STS 1% into 105 patients and reported only one episode of necrosis in more than 600 treatments of vessels less than 5 mm in diameter. There were no systemic reactions and the majority of postsclerosis

[a]Product information from Glaxo Pharmaceuticals, Research Triangle Park, NC (1989).
[b]Ethamolin injection, 5%; product information from Glaxo Pharmaceuticals (December 1988).

[a]STD Pharmaceutical Products, product information, Hereford, UK (website accessed August 11, 2015).
[b]Sotradecol, product insert, Mylan Pharma Group, Inverin, Co. Galway, Ireland (rev 3/13).
[c]Thromboject, product insert, Omega Laboratories, Montreal, Canada (2001).

pigmentary changes resolved in 3 to 4 months. However, as more experience with its use in the treatment of leg telangiectasias occurred, even further dilutions (0.1% to 0.3%) were recommended, both to achieve clinical efficacy and to limit adverse sequelae (see Chapter 12).

Disadvantages

Approved for use by the FDA for vein sclerosis, STS nevertheless has a number of disadvantages. Epidermal necrosis frequently occurs with extravasation of concentrations higher than 1%; however, telangiectasias and spider veins are usually treated with 0.1% to 0.2% and extravasation at this concentration rarely causes a problem. Allergic reactions occur rarely. Postsclerotherapy hyperpigmentation occurs in proportion to its concentration (see Chapter 8), therefore its dilution is critical. The previously mentioned percentages per diameter of treated vein provide only a preliminary guide for effective treatment. In addition, the Canadian and Irish manufacturers recommend that as a precaution against anaphylactic shock, 0.3 mL and 0.5 mL, respectively, of a 1% solution should be injected into a varicosity, and then the patient should be observed for several hours before proceeding with further injections.[b,c] The reason for this recommendation is unclear, impractical and potentially hazardous; it is discussed further in Chapter 8.

The intravenous lethal dose in 50% of the population (LD_{50}) is 90 ± 5 mg/kg in mice and between 72 and 108 mg/kg in rats. When tested in the L5178YTK mouse lymphoma assay, STS did not induce a dose-related increase in the frequency of thymidine kinase-deficient mutants. However, long-term animal carcinogenicity studies have not been performed.[b]

Historical Manufacturing of STS Injections

Historically the commercial STS injections were made from a compound manufactured as a high-grade detergent used to clean optical surfaces by Niacet (Niagara Falls, NY). The product is manufactured in an industrial plant and is called NIAPROOF Anionic Surfactant 4, also known as NAS 4 and NIAPROOF 4. It is manufactured to have between 26% and 28% by weight STS with 20% by weight maximum of diethylene glycol ethyl ether (carbitol) and 1% to 2% by weight sodium chloride. During the manufacture, carbitol is added so that the final product is three parts STS to two parts carbitol. This 27% parent compound is the same compound provided to each manufacturer of STS for injection. Each manufacturer then purifies the active ingredient STS to remove the carbitol. Interestingly, analysis performed by an independent laboratory shows that the four major companies that manufacture STS have different levels of impurities, including carbitol. Fibro-Vein contains 0.02% w/v of carbitol; Sotradecol produced by Elkins Sinn until 2000 contains 0.6% w/v of carbitol, and Trombovar contains 2.6% w/v of carbitol. (Analysis performed 4 January 1989, 20 June 1989 and 8 May 1990 by Butterworth Laboratories, UK, Leberco Testing, Roselle Park, NJ, and County of Avon Scientific Services, Bristol, UK, confirmed these percentages of carbitol content.) Sotradecol produced by Mylan Pharma Group (previously Bioniche) since 2007 contains no carbitol or any other impurities (analysis performed by ChemCon, Freiburg, Germany, 19 November 2007.) What effect the carbitol impurity has on efficacy or toxicity is unknown.

Carbitol has about the same toxicity as ethylene glycol when ingested, which has a mean lethal dose in humans of 3 to 4 oz (90–120 mL).[112] The LD_{50} for intraperitoneal carbitol was 5.39 mL/kg in both rats and mice. The Ames test was very weakly mutagenic for *Salmonella typhimurium* and *Saccharomyces cerevisiae*. Carbitol is reported to be teratogenic in rats and mice.[113] Cutaneous contact with carbitol also can produce a dermatitis with both immediate and delayed hypersensitivity.[114,115]

Many compounding pharmacies supply STS. Various loopholes in Federal and State regulations allow pharmacies to compound a variety of medications for use in humans. The FDA has no regulatory power over this 'branch' of the pharmaceutical industry. Although the compounding pharmacy industry has voluntary standards, no organization exists to test the quality and accuracy of medications provided by the compounding pharmacies. Our analysis found both a discrepancy between the stated concentration and the actual concentration of STS in bottles from all three compounding pharmacies. The concentration of the sclerosing solution should be matched to the size and type of vein treated to produce the minimal sclerosing effect.[116]

The reason for the difference in concentration may be related to the variability of the percentage of the bulk STS industrial solution. At temperatures below 15°C, the product fractionates so that the concentration of STS is greater than 27% at the bottom of the drum and below 27% at the top of the drum. An analysis of this 27% STS solution by the Professional Compounding Centers of America (PCCA; Houston, TX) performed in July 2003 found that the 27% STS contained 27.94% of STS. No analysis of the carbitol component or any other component in the industrial solution was performed. The presence of impurities in any intravenous injection is worrisome (Table 7.4).

Compounding pharmacies manufacture STS from industrial source material. Carbitol is a known contaminant of industrial STS. If a company is going to use an industrial chemical to prepare a pharmaceutical injectable product, then it is duty bound to disclose other chemical compounds present too. However, by far the most important consideration in our opinion is that carbitol, like STS, is a high-molecular-weight organic molecule. The presence of both molecules in an injectable product will increase the risk of unwanted side effects relating to sensitivity and anaphylaxis. It is not a coincidence that Fibro-Vein has displayed a very low incidence of such side effects, but rather that it is a

Table 7.4 Analysis of Sodium Tetradecyl Sulfate (STS) from Four Sources

Batch	pH	STS (%)	Carbitol Content (%)
Fibro-Vein	7.5	3.0	0.045
CAP	7.89	2.59	1.79
McGuff	8.01	3.39	4.18
Kronos	7.99	3.21	0.33

From Goldman MP. Dermatol Surg 2004;30:1454.

result of the very low levels of carbitol that have been present in Fibro-Vein for the last 25 years. We find it very difficult to justify the deliberate administration by intravenous injection of two large-molecule organic compounds when physicians are being led to believe that they are only injecting the one compound, namely STS. In fact, Alemeida and Raines have compared the therapeutic effect of compounded STS with Sotradecol and found that compounded STS was less effective in sclerosing varicose veins.[117]

Current Manufacturing of STS Injections

In recent years the FDA has made it a requirement that all active ingredients in pharmaceutical products are manufactured according to current good manufacturing practices (CGMP). The same ruling came into effect in Europe on 30 October 2005. The legislation means that a pharmaceutical product manufactured and sold in either the United States or the European Union must have the active ingredient manufactured under CGMP conditions. It is no longer acceptable to purify and dilute an industrial-grade concentrate.

To our knowledge, only two brands of STS injection are currently made using an active ingredient manufactured under the rigorous conditions required by the US and EU pharmaceutical regulations: they are Fibro-Vein and Sotradecol.

Fibro-Vein has the active ingredient manufactured in Europe using the same process as the original Niacet molecule but now manufactured in a pharmaceutical plant.

Sotradecol is manufactured by Mylan (previously Bioniche) Pharma Group in an FDA-approved facility at Inverin, County Galway, Ireland. The formulation involves preparation of a solution of the active ingredient, STS, and the inactive ingredients, benzyl alcohol, dibasic sodium phosphate and water for injection. After sampling, testing and approval of the sample, the product is sterile filtered. Aseptic filling occurs in a class 100 clean room with a class 1000 background.

The Mylan active pharmaceutical ingredient (API) was tested for the presence of carbitol by gas chromatography analysis.[a] A carbitol reference standard was sourced from Sigma Aldrich, St Louis, MO. The test results revealed that no carbitol was detected.

Accelerated stability studies of Sotradecol 3% and 1% manufactured by Mylan were performed at 40°C and analyzed for impurities. The results for Sotradecol 3% are shown in Table 7.5.

Pharmaceutical-grade STS is sourced by Mylan under an exclusivity agreement from a supplier who holds a Drug Master File (DMF) for the API. The API is a white to off-white solid and meets the following specifications for chromatographic purity:

7-Ethyl-2-methyl-undec-3-ene/7-Ethyl-2-methyl-undec-4-ene	NMT 0.15%
7-Ethyl-2-methyl-4-undecanol	NMT 0.10%
Individual unknown	NMT 0.10%
Total impurities	NMT 1.0%
Assay	96.0% to 100.0%

[a]Analyses were performed at the Mylan Pharma Group Limited Quality Control Laboratory, Inverin, Co. Galway, Ireland.

Table 7.5 Analysis of Impurities in Sotradecol* 3%

Individual Impurities	1 month	2 months	3 months
7-Ethyl-2-methyl-undec-3-ene/7-Ethyl-2-methyl-undec-4-ene	None detected	None detected	None detected
Benzaldehyde	None detected	None detected	None detected
7-Ethyl-2-methyl-4-undecanol	None detected	None detected	None detected
Single largest unknown	None detected	0.085%	None detected

*Bioniche Pharma Group, Inverin, Co. Galway, Ireland.

Forced degradation of the API at 80°C for 2 hours increased the impurities:

7-Ethyl-2-methyl-4-undecanol	5.0%
7-Ethyl-2-methyl-undec-4-ene	2.1%
7-Ethyl-2-methyl-undec-3-ene	0.4%

If a temperature of 80°C was required to distill out carbitol (which is not the case with the Bioniche product), then there is an increased likelihood that the impurities mentioned earlier would appear.

POLIDOCANOL

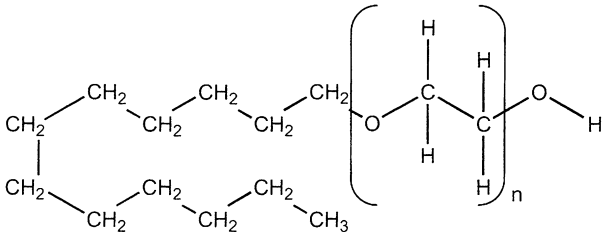
Polidocanol, manufactured by Chemische Fabrik Kreussler (Wiesbaden-Biebrich, Germany) and sold under the names of Aethoxysklerol and Asclera, distributed by Merz Aesthetics (Franksville, WI), is composed of a mixture of hydroxypolyethoxydodecane dissolved in distilled water, to which 96% ethyl alcohol is added to a concentration of 5% to ensure emulsification of POL micelles (which provides a clear solution) and to decrease foaming during the production process. Thus, 1 mL of POL contains 40.5 mg of ethanol, and patients taking disulfiram (Antabuse; Wyeth-Ayerst Laboratories, New York, NY) should be warned about a possible alcohol–disulfiram reaction.

Varying from one country to another, POL is available in 2-mL ampules in concentrations of 0.25%, 0.5%, 1%, 2%, 3% and 4%, as well as multiuse 30-mL vials in 0.5% and 1% concentrations. In the United States, it is available as 2-mL ampules of 0.5% and 1.0%. The other ingredients are disodium hydrogen orthophosphate dihydrate and potassium dihydrogen orthophosphate. Sclerovein (lauromacrogol 400) (Globopharm, Switzerland) contains chlorobutanolum as a preservative, 0.5 g/100 mL. Its pH varies from 4.8 to 6.1. The manufacturer has no stability data on POL when it is diluted with bacteriostatic water or normal saline, but Sadick and Farber[118] have determined that it remains sterile for at least 3 months following dilution. The sterility is confirmed even when used daily through a multiuse vial. Manufactured by Craveri (Buenos Aires, Argentina), AET is

Table 7.6 Maximum Daily Dose of Polidocanol (POL)

Concentration of POL (%)	Dose (mL) According to Body Weight of Patient				
	50 kg	60 kg	70 kg	80 kg	90 kg
0.5%	20	24	28	32	36
1.0%	10	12	14	16	18
2.0%	5	6	7	8	9
3.0%	3.3	4	4.6	5.3	6

From Kreussler & Co. Product insert for Aethoxysklerol, Wiesbaden-Biebrich, Germany, 1985.



$C_{12}H_{25}(OCH_2CH_2)_nOH$ Polyethylene glycol monododecyl ether
Mean extent of polymerization (n) : Approximately 9
Mean molecular weight : Approximately 600

Figure 7.25 Structural formula of polidocanol.

diluted in absolute alcohol and is available in 2-mL ampules of 0.25%, 0.5%, 1%, 1.5%, 2%, 3% and 4%, as well as in 2-mL syringes at concentrations of 0.25%, 0.5% and 1%.

POL was synthesized by BASF and introduced in 1936 as a local and topical anesthetic under the tradename Sch 600. Unlike the two main groups of local anesthetics—esters (procaine, benzocaine and tetracaine) and the amides (lidocaine, prilocaine, mepivacaine, procainamide and dibucaine)—POL has a noncyclic chemical structure. The anesthetic effect is not a direct function of its concentration but is optimum at a concentration between 3% and 4%.[a] Animal trials on its use as a local anesthetic demonstrated the occurrence of obliteration of vessels as a side effect.

Henschel, the former Medical Director of Kreussler Pharma, first started clinical trials of several concentrations of POL to treat varicose veins (correspondence from B. Olesch, 1992). The maximum daily dose recommended by Kreussler Pharma is found in Table 7.6. Blenkinsopp[119] recommended a higher maximum daily dosage of 10 mL of a POL 6% solution for an average person based on toxicity experiments extrapolated from rats. However, rats are much less sensitive to POL. As the LD_{50} in rabbits is approximately 11.7 mg/kg, Blenkinsopp's minimum dose may be toxic (Pfahler B, Kreussler, personal communication, 29 March 1990).

Polidocanol is unique among local anesthetics in its lack of an aromatic ring. As an aliphatic molecule, it is composed of a hydrophilic chain of polyethylene glycolic ether and a lipo-soluble radical of dodecylic alcohol. It is used as a topical anesthetic agent in ointments and lotions for mucous membranes, including hemorrhoidal treatment.[120] It is also used as a local anesthetic for skin irritation, burns and insect bites and as an epidural anesthetic.[121–123] The subcutaneous anesthetic effect of a 0.4% solution is equal to a 2% solution of novocaine.[121] The LD_{50} in rabbits at 2 hours is 0.2 g/kg, which is three to six times greater than the LD_{50} for novocaine.[122] The LD_{50} in mice has been found to vary from 110 mg/kg (personal correspondence from Kreussler Pharma, 1992) to 1.2 g/kg.[121] The systemic toxicity is similar to that of procaine and lidocaine.[124] Thus, POL was considered an ideal local anesthetic. However, it soon became apparent that intravascular and intradermal instillation produced sclerosis of small-diameter blood vessels and 'moderate, clinically unimportant reversible damage to healthy tissue'.[a] Therefore, compound Sch 600 was considered for use as a sclerosing agent. The POL preparation Aethoxysklerol was registered at the German health authority, the Bundesgesundheitsamt (BGA), in 1967.[123]

Experimental evaluation of absorption, distribution, metabolism and excretion of POL has been studied in dogs, rats and humans.[123] It is rapidly distributed throughout the body within minutes of injection.[123] The compound is rapidly metabolized and eliminated, having a terminal elimination half-life of 1.4 to 1.7 hours in dogs. After 72 hours, 97% of the administered compound is excreted (61% in urine, 37% in feces).

In humans, the elimination half-life is 4 hours, with 89% of the dose eliminated from the blood within 12 hours. Amounts excreted in the urine and feces are equal, and almost 80% of the injected compound is excreted via respiration through a breakdown into low-molecular-weight products. Polidocanol is completely eliminated from body organs whether the patient receives one dose or repeated doses. Therefore, no accumulation takes place, nor does POL cross the blood–brain barrier.[123] Sixty-four percent of POL is bound to protein, with a volume of distribution of 24.5 L/hour. The total clearance is 11.7 L/hour, with renal clearance of 2.01 L/hour and biliary clearance of 3.08 L/hour.[b]

The capacity of POL to cross the placental barrier was investigated in rats.[123] Of radioactivity from labeled POL, 15% to 87% was recovered from fetal tissue after 13 days. The striking variations in an earlier differentiation phase may come from weight differences between fetuses. The fetus of day 19 accumulated less activity per gram of tissue than those of day 13 and showed only 18% to 19% of the maternal blood values. From the data obtained, the placenta is evidently only a partial barrier for POL, and its penetration capacity declines on increasing differentiation of the fetus.

Polidocanol belongs to the class of detergent sclerosing solutions that are nonionic compounds. It consists of an apolar hydrophobic (polyethylene oxide) chain and a polar hydrophilic part (dodecyl alcohol) that is esterified (Fig. 7.25). In solution POL is associated as macromolecules

[a]Henschel O. Sclerosing of varicose veins sclerotherapy with Aethoxysklerol-Kreussler (product booklet), Chemische Fabrik Kreussler, Wiesbaden, Germany.

[b]Kreussler Pharma. 'Expert Information on Aethoxysklerol', July 1993.

through electrostatic hydrogen bonding between the H^+ atom of the OH^- group in one molecule, and the free electron-pair of an oxygen atom of a second molecule. This bonding results in the formation of a network (see Fig. 7.4). The sclerotherapeutic activity results from this double hydrophobic and hydrophilic action, and thus POL is a 'detergent'. The optimal efficacy of the compound coincides with the highest concentration that still permits the existence of nonaggregated molecules, 3%.[a] However, Kreussler Pharma states that POL 4% is also optimal and soluble (personal correspondence, 1992).

Telangiectasias are treated with concentrations of 0.25% to 0.75%. A randomized study determined that a 0.5% concentration may be ideal for sclerosis of leg telangiectasias.[125] Varicose veins are treated with concentrations of 1% to 4%. Small vessels and telangiectasias respond well. Efficacy is decreased in the treatment of large or medium-sized varicose veins. Kreussler Pharma[b] recommends the use of POL 4% for treatment of varicosities greater than 8 mm in diameter. A 3% solution is recommended for varicose veins 4 to 8 mm in diameter, 2% is recommended for varicose veins 2 to 4 mm in diameter, 1% for veins 1 to 2 mm in diameter, and lastly, 0.5% for spider veins less than or equal to 1 mm in diameter. The practitioner should take care not to exceed the maximum dose of POL, which is 2 mg/kg per day, with a maximum recommended volume per treatment session of 10 mL.[c]

Advantages

Polidocanol is unique among sclerosing agents in that it is both painless to inject and rarely causes cutaneous ulcerations, even with intradermal injection of concentrations less than 1.0% (see Chapter 8). In fact, Duffy injected 3% POL into the mid-dermis of his forearm without subsequent tissue necrosis.[126] When an equivalent concentration of STS is used (1%), ulcerations may occur. Allergic reactions rarely have been reported with POL. The degree of pigmentation produced may be less than that of other detergent sclerosing agents (see Chapter 8).

The safety and efficacy of this agent is such that in the 1950s the Vick Chemical Company developed a derivative of POL, polyoxyethylene dodecanol, as a mucolytic wetting agent for use in vaporizers.[127] Toxicity studies on rats demonstrated a lack of sensitization to cutaneous application and no toxicity with oral ingestion or with exposure to steaming electric vaporizers. A clinical study carried out on 168 infants and children treated with this compound in vaporizers showed no harmful effects.[128]

Henschel[c] stated that the selective activity on damaged endothelium results from the steric structure of POL: 'The macromolecules retard the individual molecules and thus shield the tissue from their uninhibited action.' This damage is therefore said to be reversible in normal tissue. Henschel goes on to claim that because the surface-active-induced absorption on the varix wall is greatest at the point of injection and falls off rapidly with increasing distance, large quantities can be injected without danger of damage to the deep venous system. He recommends the injection of a maximum of 2 mL of POL 3% at each site, with a maximum of 6 mL of POL 3% injected in one sclerotherapy session. However, Goldman et al[43] have demonstrated that POL sclerosis normal vessels (rabbit ear vein) and that the concentration injected is critical to the final outcome of vein sclerosis. Polidocanol is a weaker detergent-type of sclerosing solution than STS. These experimental studies indicate that its sclerosing power is approximately 50% of the strength of STS.

An open clinical trial comparing POL with STS and HS was conducted in Australia by 120 physicians.[129] The results at 2 years showed that 55 of 65 physicians considered that POL had a better efficacy than STS, with two claiming decreased efficacy and eight seeing no difference. When compared with HS, 49 of 58 claimed better efficacy for POL, with one physician reporting decreased efficacy and eight physicians finding no difference. Pain on injection with POL was less than with STS in the experience of 54 of 65 physicians and was less than with HS as reported by 56 of 58 physicians. Finally, 58 of 65 physicians considered that, overall, POL caused fewer complications (pigmentation, ulceration, phlebitis, telangiectatic matting) than STS, and 43 of 58 considered that it caused fewer complications overall when compared with HS.

A double-blind prospective comparative trial between POL and STS in 129 patients found no therapeutic difference between the two agents.[130] Concentrations of POL were twice that of STS for comparable-sized veins. Adverse effects were also not statistically different. All patients had an average 70% improvement with one treatment. An Italian study which did not mention exact numbers of patients treated or concentrations of solutions also compared POL with STS.[131] This study found an increase in closure from 66% to 89% in favor of POL. The adverse reaction of skin inflammation was also increased with STS compared with POL. Thus, POL may have better efficacy than STS as well as fewer adverse effects. In Japan, a 6-year study of 261 patients treated in 21 centers found a 70% to 100% efficacy of POL in treating variably sized leg veins.[132] No subject developed any treatment-related systemic adverse effect.

In another double-blind prospective comparative trial, 63 subjects were randomized to evaluate the safety and efficacy POL versus HS for treatment of telangiectasias and reticular leg veins.[133] Telangiectasias were treated with POL 0.5% or 11.7% HS and reticular veins with POL 1% or 23.4% HS. Subject satisfaction questionnaires were administered and global clinical improvement assessments performed by an independent, blinded physician. Both agents provided effective treatment, but HS caused 2.35 times as much pain during injections and resulted in two episodes of tissue necrosis. No ulcerations or allergic reactions developed after POL injections.

Disadvantages

There are few disadvantages unique to POL to discuss. Polidocanol is considered one of the most versatile and safest sclerotherapy agents associated with very rare allergic reaction, low risk for necrosis with extravasation and little, if any, injection discomfort.[126] Urtication after injection has been

[a]Dexo SA Pharmaceuticals, France. Product description on hydroxypolyethoxydodecane. Received with correspondence, May 1985.
[b]Product information (July 1993) from Kreussler Pharma, Wiesbaden, D-65203, Germany.
[c]Henschel O. Sclerosing of varicose veins sclerotherapy with Aethoxysklerol-Kreussler (product booklet), Kreussler, Wiesbaden-Biebrich, D-6202, Postfach 9105, Germany.

noted to be worse with POL than other scelrosants.[134] When compared with STS, all injection site reactions are reported to be less common with POL with the exception of injection site thrombosis.[a] Contraindications to its use are having a known allergy to POL and acute thromboembolic disease. Because importation of POL was illegal before its 2010 FDA approval, physicians were required to purchase the product from compounding pharmacies wrought with findings of inconsistencies in concentration and contaminants, such as carbitol, which can pose risks to patients.[134] For these reasons, the use of compounding pharmacies is no longer recommended with the availability of the FDA approved formulation of POL.

SCLEROSING SOLUTION COMBINATIONS

As mentioned in the introduction and previously in this chapter, almost any caustic substance can be or has been used to sclerose blood vessels. Although this chapter has detailed those commonly used commercially available solutions, it is by no means complete.

Another method for sclerosing varicose veins is to combine solutions either together or in a sequential manner. Certainly, diluting PII with HS or SX increases the potency and localizes the sclerosing effect to the point of injection. This technique may be useful when sclerosing junctions between the superficial and deep systems (saphenofemoral–saphenopopliteal junctions and/or perforating veins).[135]

Stemmer (personal communication, 1993) found that a mixture of 0.30 mg of sodium salicylate and 1.80 mg of glycerin in 5 mL of distilled water, giving a final concentration of 6% sodium salicylate and 26% glycerin, is an excellent sclerosing solution for telangiectasias of less than 1 mm in diameter. The author's limited experience with this solution in humans confirms Stemmer's observation. According to the rabbit ear model, this solution has an equivalent clinical and histologic effect to undiluted CG 72% (Goldman MP, unpublished observations, 1994).

Adding 66% glucose as a diluent can modify the viscosity of POL. This increases the sclerosant endothelium contact time, which in turn increases the surfactant action of the detergent. Making the solution thicker lowers the force of injection and minimizes the diffusion of the sclerosing solution. A mixture of one third POL 0.5% with one third glucose 66% and one third sterile water has been found to decrease thrombosis and telangiectatic matting in the treatment of telangiectasias.[136]

SEQUENTIAL INJECTIONS OF DIFFERENT SCLEROSING SOLUTIONS

Sequential injections may be useful to enhance the efficacy of a milder sclerosing solution, either by increasing its potency or by the act of sequentially damaging endothelium. After mechanical trauma, endothelial cells are unable to generate various substances or to respond to circulating or locally produced substances.[137] In this damaged state, further injury may produce irreparable damage. In addition, combining a solution with another may produce an additive effect on its potency.

Sodium tetradecyl sulfate 3% is currently the strongest sclerosant approved by the FDA. When treatment with this alone may prove ineffective, such as in patients with a large varicose vein or an area of high reflux, sequential use of HS produces a stronger, synergistic effect. This technique has been reported recently using ultrasound guidance to sclerose the SFJ.[138] One-year follow-up of 66 patients treated with STS 3% alone under ultrasound guidance at the SFJ demonstrated a recanalization rate of 25%. When a second group of 70 patients with similar pathology were treated with STS 3% immediately followed by HS 23.4%, only 12% demonstrated recanalization at 1-year follow-up. Thus, the sclerosing effect was enhanced. A second report of the identical technique performed on 100 patients reported that a 'small number' of treatment failures have occurred.[139] Unfortunately, when the author reported on the 1- to 2-year follow-up in a response to a 'letter to the editor',[140] he noted that gradual recanalization was the rule on duplex evaluation, even though the clinical outcome was good.

VOLUMES, CONCENTRATIONS AND PROGRESSIVE DILUTION OF SCLEROSING AGENTS

A sclerosing reaction is induced by the contact of a sufficiently concentrated agent with the venous wall for a sufficient period of time. This adequate/effective concentration remains theoretical and ranges between a too strong, 'aggressive' concentration (responsible for transparietal burn and adverse reactions) and a too low, ineffective concentration (not inducing a sclerosing reaction). Contact should be even and homogeneous along the whole length of the vein being treated, and around the complete circumference of the vein. However, injection of liquid in a vein which is full of blood leads to some dilution, and adequate concentrations in situ are difficult to obtain. In veins smaller than 3 mm, a laminar flow of sclerosing agent replaces blood in the vein and no dilution occurs, but in bigger veins, a turbulence occurs and is responsible for dilution of the sclerosant.

The following is a method to compute theoretically how much sclerosing agent is necessary to fill up a vein. The inner volume V of a vein segment is: $V = L \times \pi \times (D/2)^2$, where L is the length and D the inner diameter. It is very simple to calculate that, for example, a length of 10 cm of a vein of 0.7 cm inner diameter has an inner volume of 3.85 cm^3. Other examples are computed in Table 7.7 (Fig. 7.26).

$V = L \times S$, therefore:

$L = V/\pi(D/2)^2$

$0.5\ cm^3$ represents a length of approximately

3 mm	in a	14 mm	Var. Vein
10 mm		8 mm	Var. Vein
25 mm		5 mm	Var. Vein
160 mm		2 mm	Retic. Vein
630 mm		1 mm	Telangiect.

Figure 7.26 Volume and injected length. V = inner volume of vein segment; L = length; D = inner diameter.

[a]Asclera, product insert, Chemische Fabrik Kreussler, (rev 5/13).

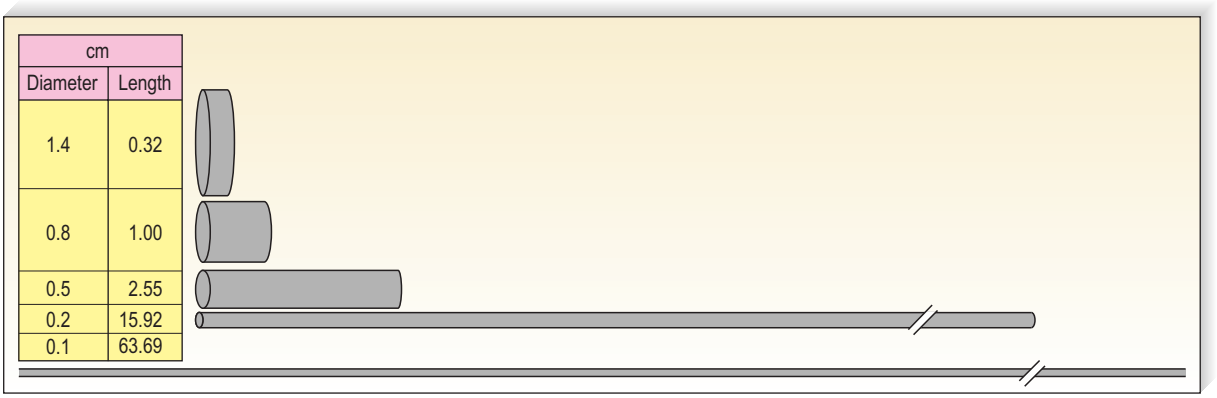


Figure 7.27 Proportional representation of a 0.5-cm^3 injection volume.

Table 7.7 Volume in cm^3 of a Vein Segment According to Venous Diameter and Venous Length

Vein Diameter (cm)	Length (cm)					
	5.00	10.00	15.00	20.00	25.00	30.00
1.00	3.93	7.85	11.78	15.71	19.63	23.56
0.90	3.18	6.36	9.54	12.72	15.90	19.08
0.80	2.51	5.03	7.54	10.05	12.57	15.08
0.70	1.92	3.85	5.77	7.70	9.62	11.55
0.60	1.41	2.83	4.24	5.65	7.07	8.48
0.50	0.98	1.96	2.95	3.93	4.91	5.89
0.40	0.63	1.26	1.88	2.51	3.14	3.77

From Guex J-J: Semin Vasc Surg 2005;18:25.

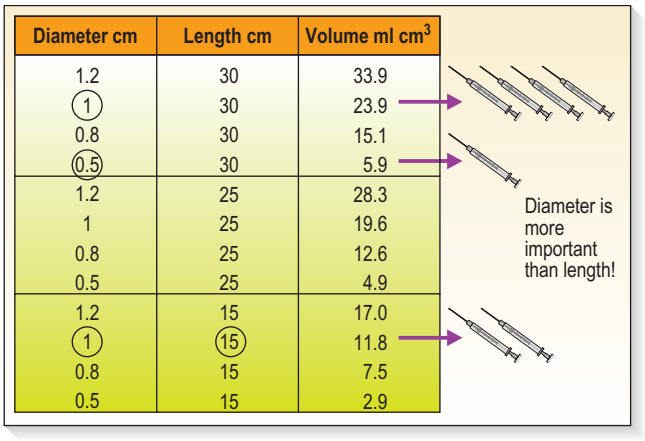


Figure 7.28 How much to inject? (theoretical).

It is interesting to note that because volumes are proportional to the square of the radius, it is possible to inject a very long vein of small diameter with a small volume of liquid. Figure 7.27 emphasizes the fact that the injection of 0.5 cm^3 has very different diffusions in veins of different diameters. This leads us to understand that when deciding the injected volume, the most important reference is the venous diameter (Fig. 7.28).

For all these reasons, we presented a theoretical model that is useful for predicting subsequent sclerosing reactions from a given dilution (Fig. 7.29).[141] The concentration of sclerosing agent decreases progressively when drifting away from the point of injection (Fig. 7.30A). Practically, when the liquid sclerosing agent is injected at a single point, the injected concentration is usually too high (in order to obtain a sufficiently long sclerosed zone, despite some dilution) and can induce side effects. To some extent, the problem can be addressed by injecting a greater volume of a milder solution (Fig. 7.30B) or by injecting small volumes in multiple points close to each other (Fig. 7.30C). If a venous spasm occurs, or if some means allows a reduction in the vein diameter, the laminar flow will further improve the phenomenon (Fig. 7.30D). The ultimate evolution of this thinking is the use of foam, as described later.

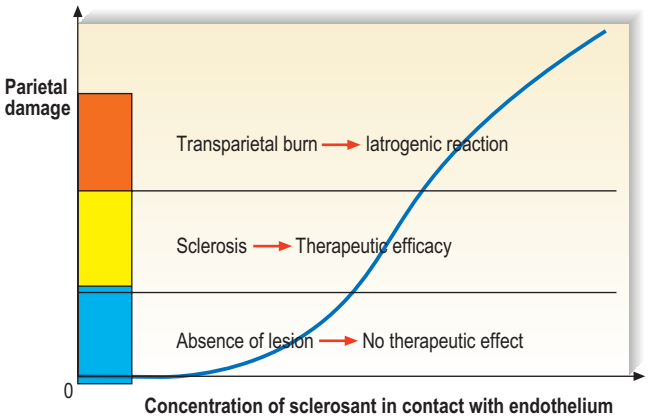


Figure 7.29 Effects of concentration.

FOAM SCLEROTHERAPY (FOAMED SCLEROSING AGENTS, SCLEROFOAM)

The first foam sclerosants were described 80 years ago and Wollmann[142] has demonstrated well that it is hard to tell who really invented the technique. However, it remains obvious that two authors—Cabrera in Spain[143] and Monfreux in France[144]—boosted its use in the 1990s, and today foaming

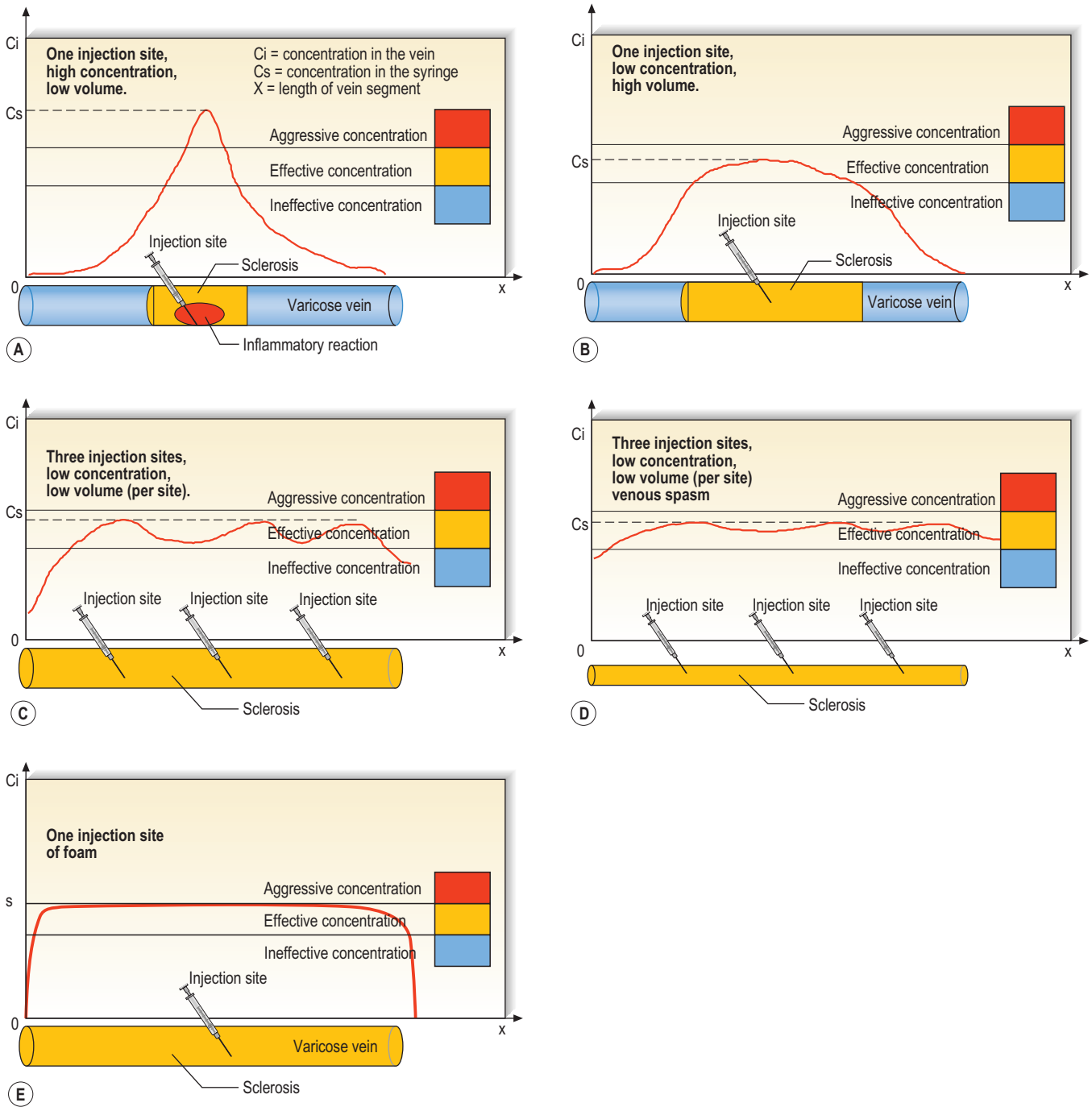


Figure 7.30 **A–E,** Theoretical modeling of dilution of sclerosing agents in several conditions.

STS and POL is the generally accepted injection standard for treatment of reticular veins of the legs. This technique is currently an 'off-label' use of the commonly used STS and POL formulations but has been used widely with successful results and a high degree of safety.[145]

The use of foam offers many advantages in the treatment of larger lower extremity veins. The first advantage of foam is that it completely fills the caliber of the vein, does not mix much with blood and, therefore, is not as rapidly diluted by blood as compared with nonfoamed agents.[134] Provided the diameter is not too large, the foam 'pushes' the blood like liquid does, increasing overall contact with and the time of contact between the vessel wall and sclerosant while ensuring an even effect on the endothelium (Fig. 7.30E). As a result, a greater degree of targeted endothelial damage occurs resulting in the distinct advantage of an improved therapeutic effect using a lower concentration and volume of sclerosant, which has the added benefit of reducing potential local and systemic side effects. However, when diameters of vessels are too large, the foam floats and only the upper wall is in contact. In these cases, additional maneuvers should be undertaken to ensure a full contact (alternative massages, compression, elevation, creation of spasm). Eventually dilution of foam will occur through two

Figure 7.31 Turbofoam. (Courtesy i2m-labs, Caen, France.)

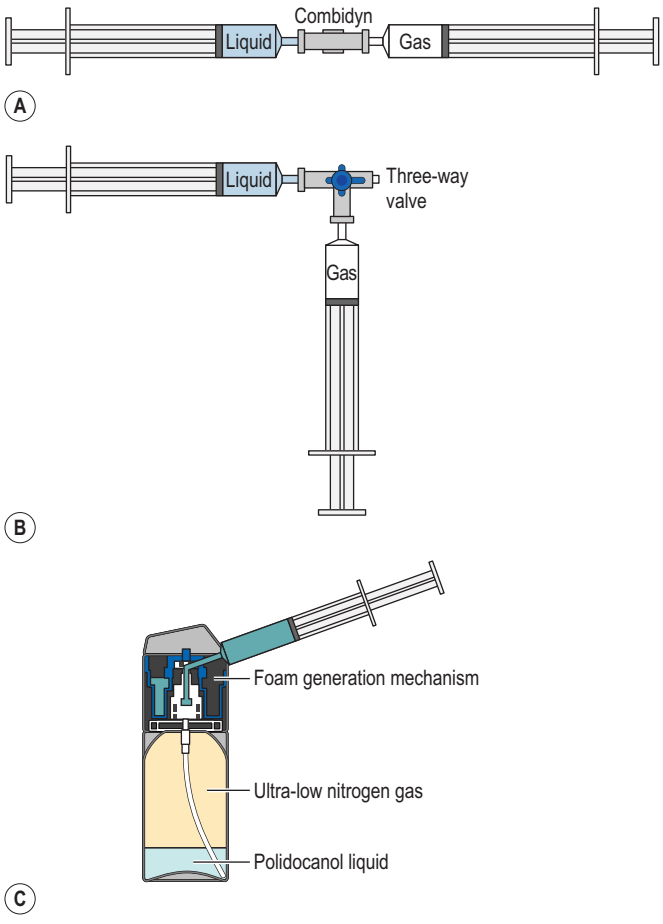


Figure 7.32 Methods for producing physician-compounded foams (PCFs) and the proprietary polidocanol endovenous microfoam (PEM). **A**, DSS method with Combidyn connector. **B**, Tessari method with 3-way valve. **C,** The proprietary canister system for generating PEM (Varithena). (Redrawn from Carugo D, Ankrett DN, Zhao X, et al. Benefits of polidocanol endovenous microfoam (Varithena) compared with physician-compounded foams. Phebology OnlineFirst, published on June 1, 2015 as doi:10.1177/0268355515589063.)

distinct phenomena: dilution of the sclerosing agent bound to the microbubbles—leaving plain gas bubbles—and dispersion of microbubbles after coalescence into larger bubbles. Many different types of foam have been used and presented, using different sclerosing agents (only detergent solutions like STS, POL and SM foam), different gases (room air, sterile air, CO_2, O_2, CO_2 + O_2, N_2O), different gas/liquid ratios, different preparation tools, etc. At present, two techniques are predominant: the Provensis, which has been manufactured and standardized, and the double-syringe technique. The double-syringe method mixes gas and liquid through either a three-way stopcock (Tessari) or a female–female Combidyn/Luer lock connector (DSS technique). The DSS has been mechanized by use of an automated device: Turbofoam (Kreussler France, Paris) (Fig. 7.31). A commercial low nitrogen (<0.8%) foam preparation, Varithena (BTG, London, UK), gained initial FDA approval in 2013 following the VANISH-1 and VANISH-2 trials.[146] Varithena is a drug/device combination intended for intravenous injection using ultrasound guidance, administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities.[a] The various methods for producing physician-compounded foams (PCFs) and the proprietary polidocanol endovenous microfoam (PEM) Varithena device are depicted in Figure 7.32.[147]

Foam sclerosants also offer the advantage of being an excellent contrast medium for B-mode echography because ultrasounds are scattered by the multiple air/liquid interfaces and foam is recognized by its white cloud aspect and dark shade cone. Therefore, in cases involving ultrasound-guided sclerotherapy, foam is more echogenic, and thus, it allows for more accurate administration and imaging.[148–150] Thanks to this property, control of diffusion within the desired vein is simple and accurate.[151] In veins smaller than 3 mm, theoretical advantages of foam sclerosants are less obvious, as experiments have demonstrated that a laminar flow ensures replacement of blood by injected liquid sclerosants. The increased sclerosing power must be taken into account with care, and adverse reactions caused by transparietal burn are common. In addition, foam sclerosants are not currently recommended for small-diameter telangiectasia because of the potential increased incidence of postinflammatory hyperpigmentation.[134] Chapter 9 details the use and Chapter 8 describes side effects related to the use of foam for the treatment of varicose, spider and reticular veins.

A complete discussion on the use of foam in sclerotherapy treatment of varicose veins is found in Chapter 9.

[a]Varithena, product insert, BTG, London, UK (rev 3/15).

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8 Complications and Adverse Sequelae of Sclerotherapy

Mitchel P. Goldman, with contributions by Douglas Wu

When analyzing side effects and complications of sclerotherapy, one should remember that sclerosing agents are drugs that are injected into veins not to cure them but to obliterate them. In terms of safety of use and results, sclerosing agents are more comparable to a surgical tool than to an intravenous (IV) drug. However, their toxicity and allergenicity must be known. Bad results using these methods are usually the consequence of an inappropriate use or indication.

As with any therapeutic technique, sclerotherapy is associated with a number of potential adverse sequelae and complications. Fairly common and often self-limiting side effects include cutaneous pigmentation, edema of the injected extremity, a flare of new telangiectasia, pain with injection, localized urticaria overlying injected sites, blisters or folliculitis caused by postsclerosis compression, and recurrence of previously treated vessels. Relatively rare complications include localized cutaneous necrosis, nerve damage, systemic allergic reactions, thrombophlebitis of the injected vessel, arterial injection with resultant distal necrosis and deep vein thrombosis (DVT). The latter may result in chronic venous insufficiency or pulmonary emboli. This chapter addresses the pathophysiology of these reactions, methods for decreasing their incidence and treatment methodology should they occur.

ADVERSE SEQUELAE

POSTSCLEROTHERAPY HYPERPIGMENTATION

The reported incidence of hyperpigmentation is variable and depends on many factors, including sclerosing solution type and concentration and treatment technique, as well as how *pigmentation* is defined. We believe that the definition of posttreatment–related pigmentation should be 'any brown-black staining of the skin occurring after sclerotherapy', with a subcategory of *persistent* pigmentation further delineated by those patients whose brown staining is still present after 1 year. As discussed later, it is our hypothesis that pigmentation develops because of the extravasation of red blood cells (RBCs) through damaged vessels with consequential inflammation contributing to ineffective digestion of hemosiderin. This results in a hemosiderin tattoo.

Pigmentation is usually temporary. Physicians report a 1% to 2% incidence of pigmentation persisting after 1 year.[1,2] Pigmentation is usually linear along the course of the treated blood vessel. We use the term *ghost of the blood vessel* to explain to patients that it represents a resolving and not a functioning vessel. However, in addition to linear lines of pigmentation, osmotic sclerosing solutions may produce punctate pigmentation at points of injection, which may be related to their mechanism of action through an osmotic gradient that produces maximal osmolality and resultant endothelial destruction at the injection site. In contrast, detergent-type sclerosing solutions destroy the treated vessel for a few centimeters along its length, producing a more linear golden brown color (Figs 8.1 and 8.2). Cutaneous pigmentation is to some degree a relatively common occurrence after sclerotherapy with any sclerosing solution.[3] It has been reported in 11% to 80%[4–6] of patients treated with sodium tetradecyl sulfate (STS). Researchers in one study found that a 0.1% concentration of STS resulted in pigmentation in 11% of patients. The incidence of pigmentation with hypertonic saline (HS) has been reported to range from 10% to 30%.[6–10] Patients treated with polidocanol (POL) have a reported incidence of pigmentation ranging from 6.7%[11,12] to 31%.[8,13,14] A 35% incidence was reported in 7200 patients treated with POL, ethanolamine oleate (EO) or iodine-iodide solution.[15] Postsclerotherapy hyperpigmentation has a reported incidence of 15.7% with dextrose with sodium chloride (Sclerodex; Omega Laboratories, Montreal, QC, Canada),[12] and 32% with iodine and sodium iodide (Sclerodine; Omega Laboratories).[12] A 2% incidence of hyperpigmentation was reported in one series of patients treated with POL, chromated glycerin (CG) and sodium salicylate.[1] A 2% to 4% incidence was reported in another series of 102 patients treated with either STS, POL or CG.[16]

Between 2003 and 2008, 1187 of our patients underwent sclerotherapy. Of this group, 351 had been treated with foam or liquid STS and were available for follow-up. Thirty-five percent of these patients experienced hyperpigmentation following sclerotherapy. However, hyperpigmentation was graded as minimal to mild. Furthermore, no hyperpigmentation was evident in any patient 1 year after treatment. Of note, the 'hyperpigmentation' reported by many patients was actually a posttreatment coagulum.[17]

ETIOLOGIC FACTORS

The cause of postsclerotherapy hyperpigmentation most likely results from a combination of both postinflammatory hyperpigmentation (incontinence of melanin pigment) and hemosiderin deposition.[18–20] However, histologic examination has demonstrated that this pigmentation is caused only by hemosiderin staining of the dermis, regardless of the type of sclerosing solution used, pigmentation of the patient or length of time after injection (Fig. 8.3, Table 8.1).[21–24] Defects in iron storage and/or transport mechanisms have also been found in a significant number of patients who have developed pigmentation after sclerotherapy.[25]

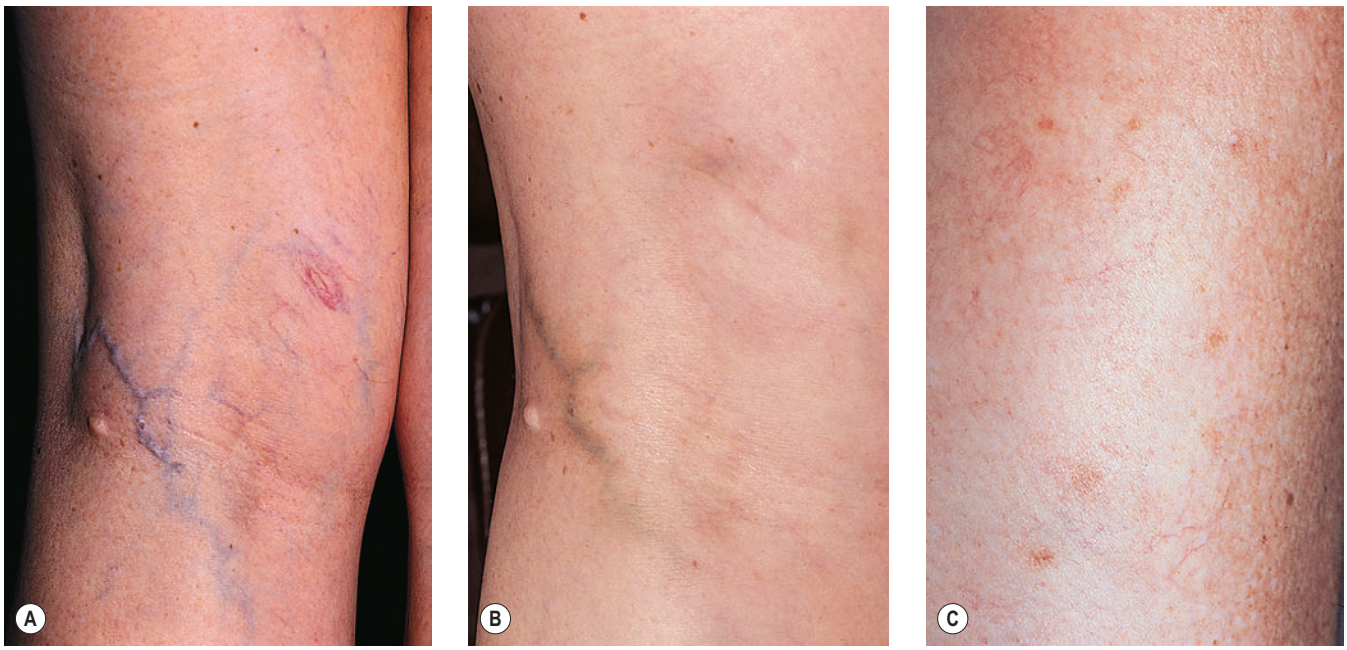


Figure 8.1 Linear pigmentation along the course of a treated blood vessel. **A,** Before treatment. **B,** Eight weeks after treatment with polidocanol 0.5%. **C,** Punctate pigmentation 8 weeks after treatment with Sclerodex. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (C from Goldman MP: Adverse sequelae of sclerotherapy treatment of varicose and telangiectatic leg veins. In: Bergan JJ, Goldman MP, editors. Varicose veins: diagnosis and treatment. St Louis: Quality Medical Publishing; 1993.)

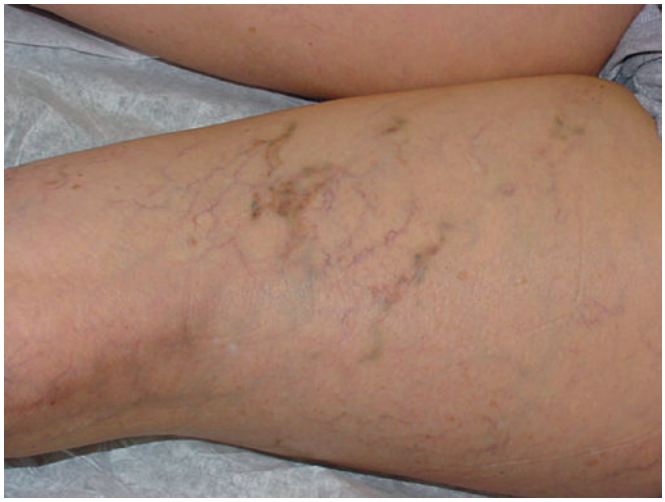


Figure 8.2 Linear pigmentation, no compression, 6 weeks after 0.25% sodium tetradecyl sulfate liquid sclerotherapy.

Hemosiderin deposition occurs predominantly in the superficial dermis, although it may be present in periadnexal and mid-dermal locations, particularly near the ankle. This phenomenon probably occurs when RBCs extravasate into the dermis after the rupture of treated vessels.[26] Erythrocyte diapedesis also may occur after inflammation of the vessel and is commonly seen after thrombophlebitis. Perivascular inflammation is presumed to promote degranulation of perivascular mast cells. Released histamine leads to endothelial cell contraction, which results in widening of endothelial gaps through which extravasation of RBCs can occur.[27–31] Thus, injecting a sclerosing solution dilates the vessel both directly through pressure generated by the syringe and indirectly through histamine-induced endothelial cell contraction.

Perivascular phagocytosis of RBCs occurs either by intact cells or piecemeal after fragmentation by macrophages.[32,33] The intracellular fragments in the macrophage cytoplasm are further compartmentalized into hemoglobin-containing globules. They are referred to as *secondary lysosomes*. Because hemosiderin is an indigestible residue of hemoglobin degradation, it may appear as aggregates up to 100 μm in diameter.[34] Hemosiderin has a variable concentration of these aggregates. Iron concentrations vary from 24% to 36%.[35] Iron hydroxide contained in hemosiderin occurs in different forms, with differing amounts of ferritin.[36] On unstained tissue, it appears golden and is 30% iron by weight. Its elimination from the area through phagocytosis may take years, if it ever occurs.

In addition to being insoluble, hemosiderin may directly affect cellular function. Histologic examination with x-ray fluorescence analysis of patients with varicose ulceration disclosed an elevation of mean iron levels in periulcerated skin.[37] The authors speculate that free radical formation resulting from local iron accumulation may cause melanocytic stimulation, thereby augmenting brown pigmentation. Indeed, multiple authors have demonstrated melanin incontinence in the presence of venous stasis, complicated by extravascular RBCs.[38–40] Whether melanocytic stimulation plays a role in the early appearance of postsclerotherapy pigmentation is unlikely, but it may contribute to the persistence of pigmentation in certain patients, especially in Fitzpatrick skin types V and VI.

Regardless of its cause, the incidence of pigmentation is apparently related to multiple factors, including (1) sclerosing solution type and concentration; (2) sclerotherapy technique; (3) gravitational and other intravascular pressures;

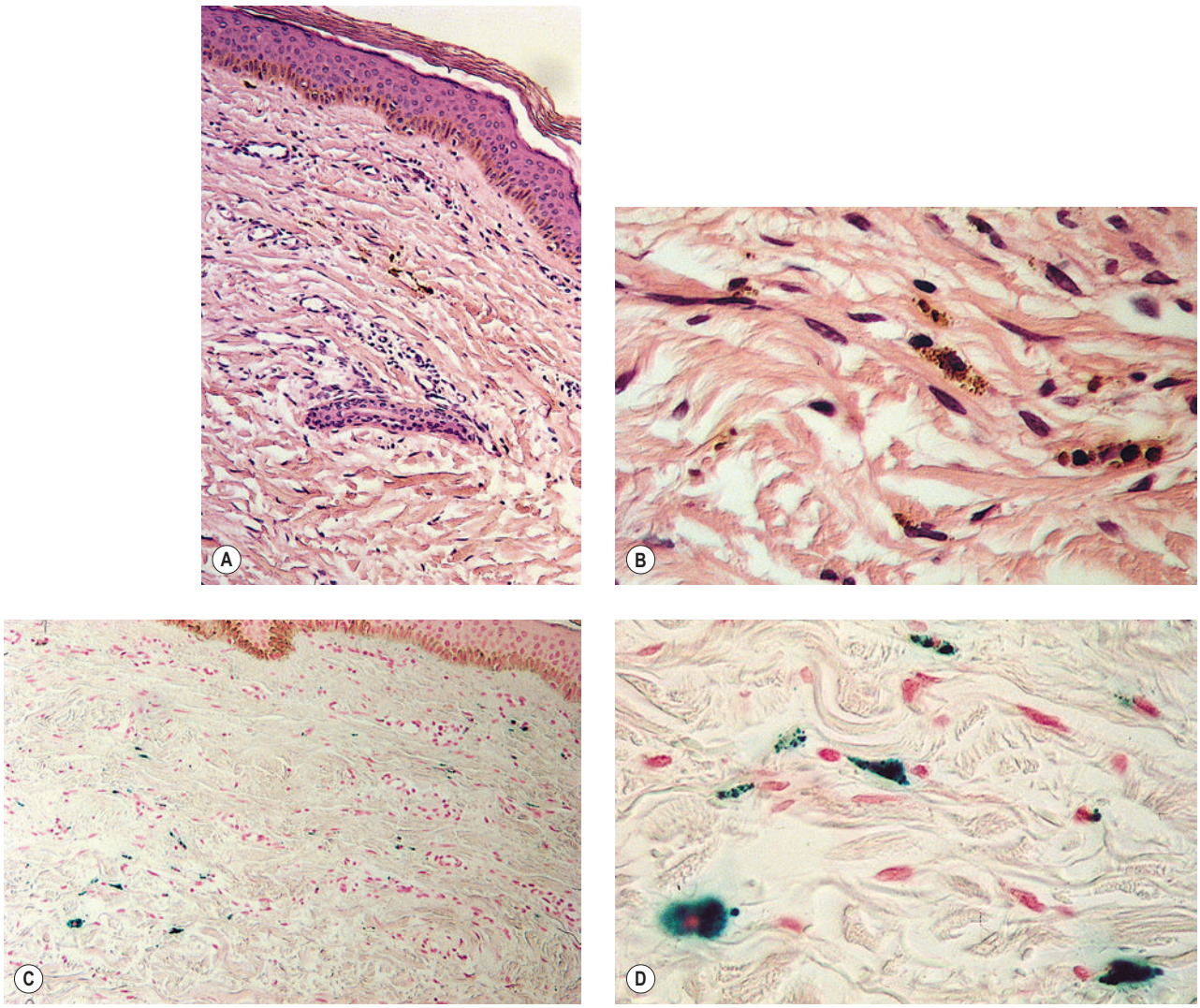


Figure 8.3 Section stained with hematoxylin–eosin taken 6 months after injection with polidocanol 0.75%. Note scattered foci of golden brown pigment. **A,** Original magnification ×50. **B,** Perls-stained section from the same patient shown in Figure 8.1. Note scattered foci of green–blue granules within siderophages. Original magnification ×200. **C,** Original magnification ×350. **D,** Original magnification ×3200. (From Goldman MP, Kaplan RP, Duffy DM. J Dermatol Surg Oncol 1987;13:547.)

Table 8.1 Postsclerotherapy Hyperpigmentation: Treatment Characteristics

Agent	Patient's Race	Time of Biopsy (Period after Injection	Result
POL 0.25%	White	6 weeks	Heme
POL 0.75%	White	6 weeks	Heme
POL 0.75%	Hispanic	6 months	Heme
POL 0.75%	White	2 months	Heme
SM ?	White	7 years	Heme
HS 18%	White	8 months	Heme
HS 20%	White	2 months	Heme
STS 0.5%	White	5 months	Heme
STS 0.25%	Hispanic	3 months	Heme

Heme, Hemosiderin; HS, hypertonic saline; POL, polidocanol; SM, sodium morrhuate; STS, sodium tetradecyl sulfate.

(4) innate tendency toward cutaneous pigmentation (total body iron stores and/or altered iron transport and storage mechanisms, innate enhanced histamine release or hypersensitivity and vessel fragility); (5) postsclerotherapy (graduated compression); (6) susceptibility to postinflammatory hyperpigmentation; (7) vessel diameter; and (8) concomitant medication.

Solution Type and Concentration

The type and concentration of the sclerosing solution affect the degree of endothelial destruction. The extent of endothelial destruction with resulting inflammation and extravasation of RBCs is thought to influence the development of postsclerotherapy hyperpigmentation. The increased incidence of pigmentation with certain concentrations of STS and HS, which produce a greater reaction than POL, confirms this hypothesis.[4,41–43] In fact, when excessive concentrations of POL are used to treat telangiectasias (1%), the pigmentation rate is even higher than with 20%

HS.[44] It is therefore not surprising that sclerosing solutions reported to have the lowest incidence of postsclerotherapy pigmentation—CG,[1,41,45–49] glycerin alone,[50] and sodium salicylate[1,20]—also produce minimal inflammation.

A higher concentration of the same sclerosing solution produces increased inflammation.[51] Thus, the inflammatory response after treatment should be kept to a minimum, and sclerosing solutions and concentrations should be altered for each treatment session so that the minimal effective sclerosant concentration is used.

Foam sclerosants are stronger than liquids for an identical concentration. Therefore, when foam is used, special attention should be directed toward reducing the strength or concentration of the agent. This is especially true for treatment of reticular and spider veins.[52] In analyses of large numbers of patients treated with foam sclerotherapy published in 2007 and 2009, researchers have estimated the incidence of postinflammatory hyperpigmentation to be between 10% and 30%.[53–55] Furthermore, Alos et al noted that although the overall incidence of pain with sclerotherapy using 0.5% POL is rare, foam is more often associated with pain than is liquid.[56]

Technique

Optimal technique consists of limiting pressure into damaged (sclerosed) veins to prevent extravasation of RBCs. To limit the degree of intravascular pressure, larger feeding varices, incompetent varices and points of high pressure reflux should be treated first. A greater incidence of pigmentation occurs if vessels distal to the saphenofemoral junction (SFJ) are treated before successful closure of the junction, with a decreased incidence of pigmentation when treatment is from proximal to distal.[57]

The degree of injection pressure is also important. Because telangiectasias and small venules are composed essentially of endothelial cells with a thin (if any) muscular coat and basement membrane, excessive intravascular pressure from injection may cause vessel rupture. In addition, endothelial pores and spaces between cells in the vascular wall dilate in response to pressure, leading to extravasation of RBCs. It is therefore important to inject intravascularly with minimal pressure. Because injection pressure is inversely proportional to the square of the piston radius, a syringe with a larger radius causes less pressure and theoretically may reduce risks of pigmentation.

The average piston radius is 8 mm for a 2-mL syringe and 5 mm for a 1-mL syringe. The calculated pressure with an implied force of 250 × g is 180 mmHg for a 2-mL syringe and more than 300 mmHg for a 1-mL syringe.[58] This is one reason why we recommend using a 3-mL syringe for sclerotherapy (Fig. 8.4).

Gravitational and Other Intravascular Pressures

Postsclerotherapy pigmentation appears most commonly in vessels treated below the knee[20] but can occur anywhere on the leg, probably as a result of a combination of increased capillary fragility and increased intravascular pressure by gravitational effects in this location. Pigmentation has been observed once in our practice after sclerotherapy of hand veins (Fig. 8.5). Duffy et al[59] noted that pigmentation did not develop after treating 100 patients with dilated hand veins with either 0.5% STS, 1.5% POL or 3% POL.

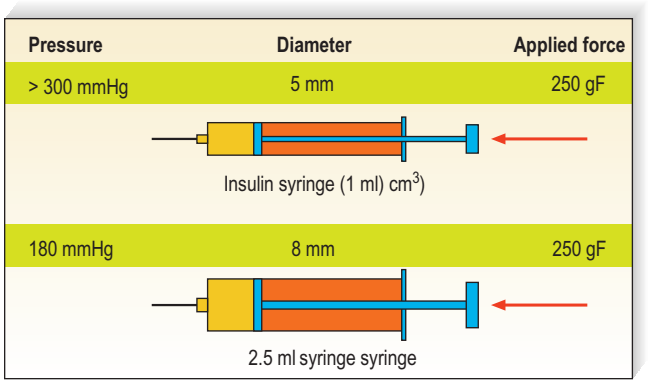


Figure 8.4 Pressure and syringe. Small syringes increase the risk of extravasation and necrosis (microarteriovenous fistulas, backflow injections).

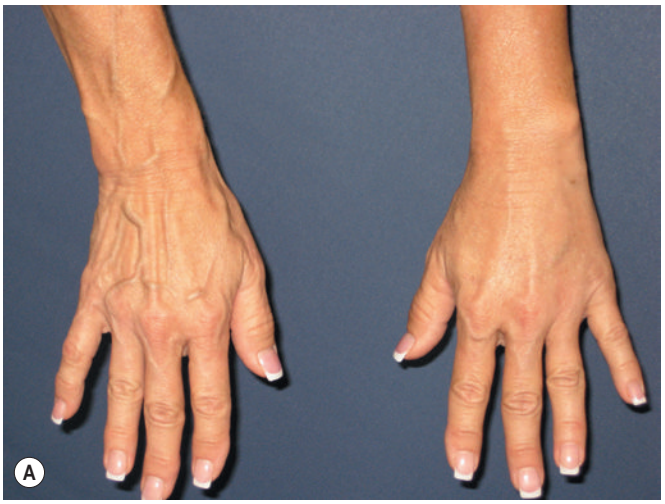
Vessel Diameter

It is commonly observed that telangiectasias that have the maximal incidence of pigmentation are between 0.6 and 1.2 mm in diameter. This could be related to an increased incidence of microthrombi in these vessels. Chatard[20] also observed an increased incidence of pigmentation in the treatment of blue venulectases as opposed to the treatment of red telangiectasias. The reason behind this latter observation is unknown, but it may be related to vessel diameter because blue telangiectasias are usually of larger diameter than red telangiectasias. An evaluation of 113 patients treated with sclerotherapy demonstrated pigmentation only rarely in vessels less than 1 mm in diameter.[60]

Predisposition to Pigmentation

Certain individuals appear to be predisposed to the development of pigmentation through a variety of genetic mechanisms. Pigmentation has been reported as more common and pronounced in patients with dark hair and 'dark-toned' skin.[18] This may be caused by an increased incidence of postinflammatory hyperpigmentation in patients with these colorings. However, Chatard[20] reported that pigmentation is unrelated to skin or hair color. We are not aware of the number of type V and type VI patients Chartard treated, but in our experience (RAW, MPG) it is clear that patients with darker skin coloring and Asian patients do have an increased incidence of postsclerotherapy pigmentation.

Pigmentation resolves from a gradual resorption of ferritin particles from macrophage digestion. It is hypothesized that the patient's iron storage and transport mechanisms may influence the rate of clearance of dermal hemosiderin.[55] A preliminary study of 16 patients with age-matched controls disclosed that pigmentation developed in patients who had higher serum ferritin levels. Serum ferritin levels correlate with total body iron stores.[61] To clarify the relationship between serum ferritin and postsclerotherapy pigmentation, a prospective study of 233 consecutive patients was conducted.[62] A linear relationship between the occurrence of pigmentation and pretreatment serum ferritin levels was found at each posttreatment assessment date. This supports the hypothesis that high total body iron stores increase the susceptibility toward hyperpigmentation. However, serum ferritin levels are not an absolute predictor for the development of hyperpigmentation. In a patient with



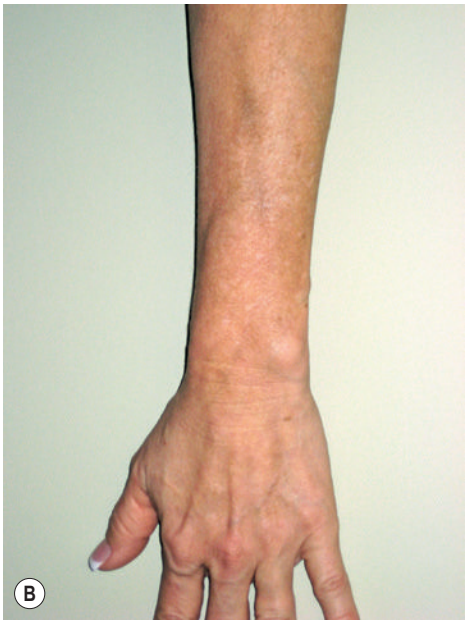


Figure 8.5 **A,** Appearance of dorsal hand veins *(upper)* 2 weeks after treatment with 1 mL of sodium tetradecyl sulfate 0.5% foam mixed 1:4 with room air. Note total resolution of the vein as compared with the untreated hand veins *(below)* and development of minor coagula in the treated dorsal hand vein. **B,** Six months posttreatment there is pigmentation on the dorsal distal arm from the sclerosing effect of the proximal dorsal hand vein.

hemochromatosis having a serum ferritin level of 1200 ng/mL, pigmentation did not develop after sclerotherapy of telangiectasia 0.6 mm in diameter with 0.2% STS.[63] The explanation may be that this patient's physician probably used outstanding technique to avoid extravasation of RBCs.

Therefore, serum ferritin levels may be used to identify patients at risk for this complication. These patients may require special attention with meticulous microthrombectomy, and an increase in time and extent of posttreatment compression is advocated.

If histamine-induced endothelial contraction promotes extravasation of RBCs or hemosiderin, or both, histamine antagonists should prevent or limit its occurrence. The catecholamines norepinephrine (noradrenaline) and isoproterenol antagonize histamine-induced edema in canine brachial artery preparations.[64] Similarly, corticosteroids decrease the size of histamine-induced endothelial gap junctions.[65] Terbutaline also inhibits macromolecular leakage from postcapillary venules in hamster femoral veins.[66] Cimetidine blocks histamine-induced widening of endothelial gaps in rat femoral veins.[67] Therefore, patients who have developed postsclerotherapy pigmentation in past treatments may be pretreated with one or a combination of these medications to block or limit histamine effects.

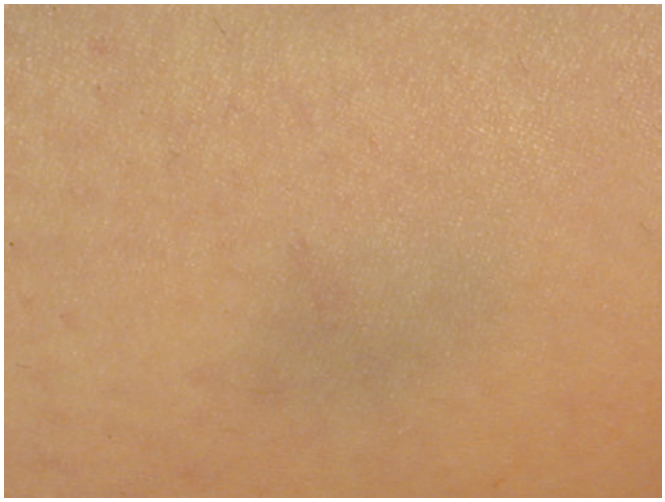


Figure 8.6 Thirty-two-year-old woman who had undergone sclerotherapy for telangiectasia on the thigh with sodium tetradecyl sulfate 0.25% 6 months previously. She presented with a bluish discoloration overlying the treated area, which was devoid of telangiectasia. Her history disclosed that she was taking minocycline 100 mg b.i.d. prescribed by her dermatologist 3 months earlier for acne eruption. Discontinuation of the minocycline resulted in resolution of the pigmentation. No biopsy was taken to confirm the diagnosis of minocycline pigmentation, but the clinical course and history supported the diagnosis.

Vessel fragility may also result in an innate predisposition toward pigmentation. Capillary strength is related to both menstrual cycles and circulating estrogen.[68] Decreased capillary strength occurs 3 to 5 days before and 2 days after menses and during ovulation. Fragility has been found to improve with IV and oral administration of conjugated equine estrogen (Premarin; Pfizer, New York, NY) in postmenopausal women.

Patients taking minocycline may have an increased risk for postsclerotherapy pigmentation.[69,70] This propensity may be related to the inflammatory effects of sclerotherapy. Unlike the golden to deep brown color characteristic of typical sclerotherapy-induced pigmentation, pigmentation associated with minocycline use is most commonly blue–gray (Fig. 8.6). Minocycline, known to have increased tissue distribution because of its lipophilicity, produces pigmentation in a variety of organs and structures.[71,72] The most common form of minocycline-related pigmentation appears as bluish-black or bluish-gray macules within acne scars or at other sites of inflammation.[10,73–77] Other forms of minocycline-related pigmentation on the skin of the lower legs have been described, including that associated with sites of ultraviolet light exposure,[78] as well as with sites of pre-existing capillaritis.[79] The pigment involved in minocycline hyperpigmentation is most likely a drug metabolite–protein complex

chelated with calcium or an insoluble minocycline–melanin complex.[75,78–83] It is hypothesized that minocycline or a metabolite interferes with degradation of hemosiderin through lysosomal disruption, leading to macrophage death and deposition of pigment.[77] In 2007, four cases of minocycline-related hyperpigmentation involving the subcutaneous fat were reported.[84] Histopathologically, tissue exhibited the previously well-described deposition of brown and/or black Fontana-Masson- and Perls-positive granules along elastic fibers in the papillary dermis as well as within dermal macrophages located near vessels and eccrine glands. In addition to these dermal findings, tissue from the four patients also showed green to gray, nonrefractile, flocculent globules within macrophages in the subcutaneous tissue. Also, two of the four patients demonstrated the distinctive finding of pigment-related lipomembranous changes. Although further studies are needed to establish a direct relationship, it may be prudent to withhold minocycline therapy in sclerotherapy patients. Of note, successful lightening of minocycline-induced, posttraumatic pigmentary deposition has been described with successive Q-switched Nd:YAG laser treatments.[85] Often discontinuation of minocycline will result in spontaneous clearing of minocycline pigmentation within 6 to 12 months.

Postsclerotherapy Coagula

Removal of postsclerotherapy coagula may decrease the incidence of pigmentation. Thrombi to some degree are thought to occur after sclerotherapy of all veins, regardless of size, because of the inability to occlude the vascular lumen completely with external pressure. The persistence of a small vascular lumen, even with maximal external pressure, has been predicted with experimental models of vein wall.[86] This has also been directly observed with fiberoptic varicography (Muntlak H, personal communication, 1989).

Persistent thrombi are thought to produce a subacute 'perivenulitis' that can persist for months.[87–89] Perivenulitis favors extravasation of RBCs through a damaged endothelium or by an increase of the permeability of treated endothelium. In addition, intratissue fixation of hemosiderin may occur.[20] This provides a rationale for drainage of all foci of trapped blood 2 to 4 weeks after sclerotherapy. Sometimes blood can be released even 2 months after sclerotherapy.

Thrombi are best removed by gentle expression of the liquefied clot through a small incision made with a 21-gauge needle (Figs 8.7 and 8.8). A number 11 blade or lancet and an 18-gauge no-core needle have also been recommended by some; however, because this results in a larger incision and often requires pretreatment with a local anesthetic, we favor the more conservative 21-gauge needle approach.

The expression of coagula is accomplished through a rocking action applied around the clot to aid in its expulsion. This should be continued until all dark blood is removed. The art of this procedure is to find the right place to puncture, which is best perceived as a hard, subcutaneous nodule. If the thrombosis is in the deep dermis, the area should be marked and lidocaine 1% can be infiltrated around the area to facilitate a less painful removal. Compression pads or stockings are then worn for an additional day or two to prevent further thrombosis formation and

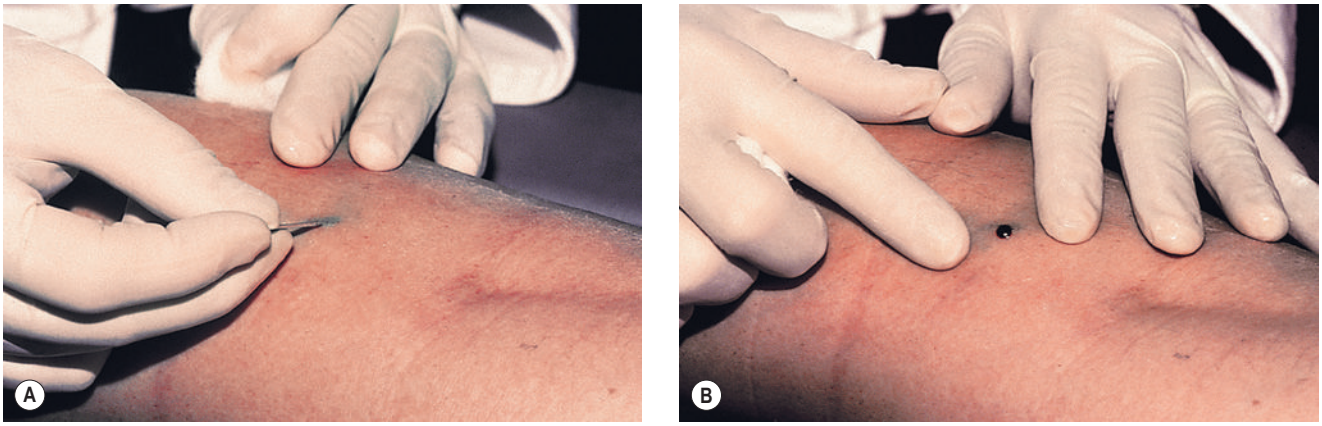


Figure 8.7 Method for evacuation of a thrombosis in a 1-mm diameter reticular varicose vein 2 weeks after sclerotherapy. **A,** Small incision. **B,** Expelling clot (see text for details).

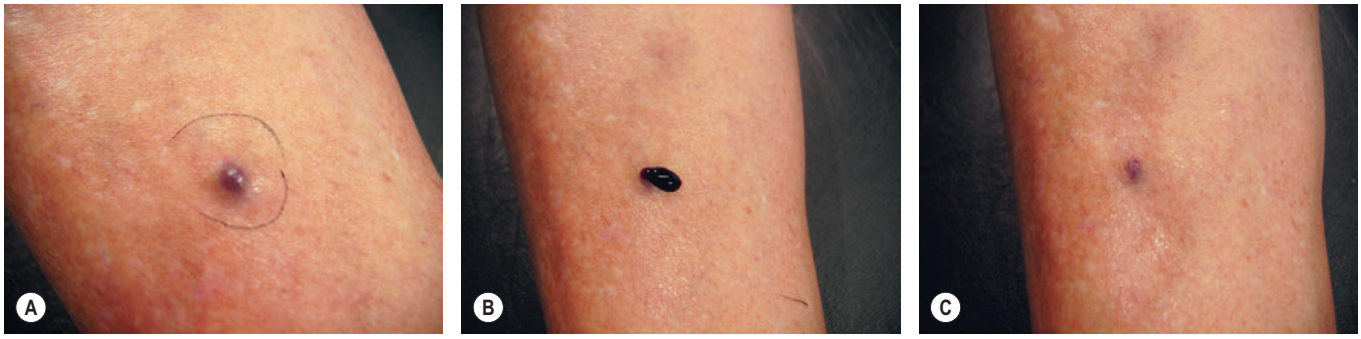


Figure 8.8 Trochard thrombectomy 10 days after injection of a bulging varix of the calf. The content of the vein ('sclerus') is liquid, and little lateral pressure is necessary to empty the vein.

to aid in adherence of the opposing endothelial walls to establish effective endosclerosis.

In a multicenter randomized controlled study, 101 patients with varicose veins were treated at 1 to 3 weeks with microthrombectomy in one half of the treated veins.[90] Photographs of the sclerotherapy-treated areas were evaluated at 16 weeks. Veins up to 1 mm in diameter had less pigmentation when drained, but veins up to 3 mm did not show any benefit from microthrombectomy.

Perchuk[91] raised the possibility of infection occurring from stab incisions. This danger was presumed to be caused by the presence of bacteria in varicose veins—a belief commonly held by physicians 40 to 50 years ago.[92,93] However, there have been no reports in the modern medical literature of infections occurring in patients treated with stab incisions into postsclerotherapy clots. This problem has not occurred in our practice, in which this procedure is used routinely.

DURATION

Despite therapeutic attempts, pigmentation often lasts from 6 to 12 months.[23] Rarely, pigmentation may last more than 1 year. Georgiev[2] estimated that 1% of his patients and Duffy[6] that up to 10% of his patients had pigmentation lasting more than 1 year. Izzo[1] reported a 2% incidence after 1 year. Our experience parallels that of Georgiev.

Persistent telangiectasia may be caused by factors other than sclerotherapy itself. In certain patients, pigmentation may be present over superficial varicosities and telangiectasias before sclerotherapy is performed.[2,20] Hyperpigmentation as a result of 'physiologic' diapedesis of RBCs through fragile vessels is common in patients with venous stasis or over varicose veins. Therefore, preoperative documentation, including photographs, may be beneficial during follow-up patient visits.

PREVENTION AND MINIMIZATION

To minimize the risks of development of pigmentation, sclerotherapy should produce limited endothelial necrosis and not total destruction, with its resulting diapedesis of RBCs. This may be achieved by using meticulous technique, avoiding excessive injection pressures, selecting the appropriate solution concentration and treating areas of venous reflux in a proximal-to-distal manner.

Thibault and Wlodarczyk[62] recommended that patients avoid taking all iron supplements during the course of treatment and for 1 month after treatment. This presumably decreases serum ferritin levels. Alternatively, patients' serum ferritin levels may be assessed before sclerotherapy to determine if iron chelation therapy is warranted. Obviously, this latter recommendation awaits further study. We think it is prudent to ask patients who have developed pigmentation if they are taking iron supplementation and, if so, to discontinue it before future treatments.

Preventing formation of postsclerotherapy-related ecchymoses would theoretically prevent postinflammatory hyperpigmentation through avoidance of dermal hemosiderin deposition. Although *Arnica montana* is routinely used by many surgeons to prevent perioperative bruising, the efficacy of this homeopathic product has not been scientifically proven. In a randomized, prospective, double-blind study from 2006, researchers evaluated the perioperative use of *A. montana* (SinEcch; Alpine Pharmaceuticals, San Rafael, CA) in 29 patients undergoing face-lifts.[94] Interestingly, the amount, duration and degree of bruising did not differ between those treated with 10 days of *A. montana* and those in the placebo group. Although further procedure-specific studies would be necessary, it is likely that this lack of efficacy would be similar if *A. montana* were used in conjunction with sclerotherapy.

Although laser treatment of telangiectatic leg veins is said not to be associated with pigmentation, we have documented numerous patients treated with a variety of lasers who developed prolonged pigmentation (Fig. 8.9).

TREATMENT

Treatment of pigmentation, once it occurs, is often unsuccessful unless one has access to a Q-switched laser. Because

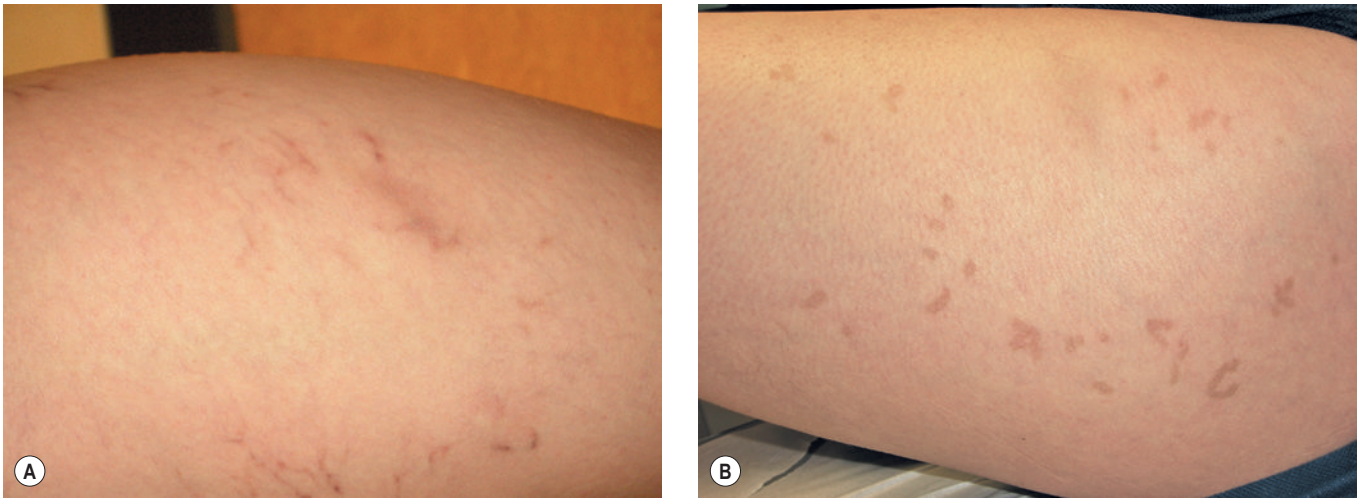


Figure 8.9 **A,** Telangiectasia treated by a nurse not under physician supervision. Treatment was carried out with a DioLite 532 laser (Iridex, Mountain View, CA) at 13 J/cm^2, 3 W and 1000-μm spot size at 5 Hz with a total of 5856 pulses to the leg veins. Note extensive hyperpigmentation over the treated veins 2 months posttreatment. **B,** This pigment failed to resolve over 9 months of topical application of Tri-Luma cream (Galderma Laboratories, Fort Worth, TX), after which the patient was lost to follow-up.

this pigmentation is caused primarily by hemosiderin deposition and not melanin incontinence, bleaching agents that affect melanocytic function are usually ineffective. Exfoliants (trichloroacetic acid) may hasten the apparent resolution of this pigmentation by decreasing the overlying cutaneous pigmentation or promoting the exfoliation of hemosiderin, but they carry a risk of scarring, permanent hypopigmentation and postinflammatory hyperpigmentation. However, some physicians have reported apparent success with this therapeutic method.[1,95] The combination of 20% trichloroacetic acid with retinoic acid and hydroxyquinoline has also been reported to totally fade pigmentation in 76% of patients whose pigmentation persisted for between 6 months and 5 years.[1] Pigmentation decreased in the remaining patients. Treatments were given every 7 to 10 days from 4 to 12 weeks.

Chatard[20] found that using light cryotherapy to exfoliate the epidermis and 'evict the pigment' is helpful. We have not found cryotherapy useful in our practice. Terezakis (personal communication, 1989) found the use of topical retinoic acid to enhance resolution of the pigmentation. She speculated that retinoids enhance fibroblastic removal of hemosiderin. We have treated patients who have had pigmentation for more than 3 months with topical tretinoin (Retin-A 0.1% cream; Valeant Pharmaceuticals, Laval, QC, Canada). Although formal placebo-controlled studies have not been completed, it appears this therapy may be effective. It does not seem to have any adverse sequelae and has the advantage of bringing the patient into active therapy.

A seemingly logical form of treatment would be chelation of the subcutaneous iron deposition. Myers[96] reported the use of a 150 mg/mL ointment of disodium ethylenediaminetetraacetic acid (EDTA) in the treatment of 10 patients with pigmentation after sclerotherapy or vein stripping or with pigmentation in chronic postphlebitic legs. He reported a consistent reduction in the shade of the pigmentation in every patient treated. Unfortunately, this was an uncontrolled study, and there have been no further reports of this form of treatment since its presentation in 1965. In our experience, intradermal injections of deferoxamine in an attempt to cause chelation of the hemosiderin appear to be somewhat effective but are painful and expensive. The timing of injections and the concentration and quantity of deferoxamine injected have not been systematically studied.

The topical iron chelator 2-furildioxime was found to provide a level of photoprotection and theoretically may also be useful in treating cutaneous hemosiderin pigmentation.[97] However, at the time of that research proposal, Procter & Gamble had no interest in providing this agent for clinical testing of postsclerotherapy pigmentation (personal correspondence, October 1994).

Graduated elastic compression with coadministration of the anabolic steroid stanozolol decreases pigmentation in patients with lipodermatosclerosis who also have varicose veins.[98] Skin pigmentation did not change when patients used graduated compression stockings alone. Stanozolol may exert its effect through reduction in perivascular fibrin from fibrinolytic enhancement. In addition, compression alone improves lipodermatosclerotic skin changes, including hyperpigmentation (Partsch H, personal communication, 1992). Although it seems reasonable to promote the wearing of graduated support stockings after treatment, further studies are needed before systemic stanozolol therapy can be recommended.

A study on the use of 20- to 30-mmHg compression stockings after sclerotherapy of telangiectasia and reticular veins 0.4 to 3 mm in diameter found a decreased incidence of pigmentation when compression was used. Compression for 3 days resulted in a 20% decrease in pigmentation; compression for 1 week produced a 60% decrease in pigmentation compared with no compression; and compression for 3 weeks resulted in limited pigmentation in only 2 of 10 patients.[99] This follows the logic of compression reducing vessel lumen size, resulting coagula and hydrostatic pressure. However, Guex found an even lower incidence of residual pigmentation in a prospective study on reticular and spider veins without compression.[100]

Laser treatment has been reported to be efficacious in 45%[24] to 69%[101] of patients with pigmentation of 12 or 6 months' duration, respectively. Hemosiderin has an absorption spectrum that peaks at 410 to 415 nm, followed by a gradually sloping curve throughout the visible spectrum (Fig. 8.10).[102,103] The copper vapor laser (CVL) at 511 nm in a continuous airbrush technique and the flashlamp-excited pulsed dye laser (PDL) at 510 nm should interact relatively specifically with the hemosiderin absorption spectrum. Competition from oxygenated hemoglobin (peak absorption at 577 nm) should be low, but interaction with epidermal melanin, which has a higher absorption rate at these wavelengths, may be significant. These lasers are thought to result in physical fragmentation of pigment granules, which are later removed by phagocytosis. However, penetration of laser energy at 510 and 511 nm is limited to 1 mm below the granular layer. Because hemosiderin may occur up to 2.8 mm below the granular layer, nonthermal effects may result in clinical resolution. An inflammatory reaction from thermal or photoacoustic effects may stimulate hemosiderin absorption. Although CVL-treated pigmentation responded better than that treated with PDL

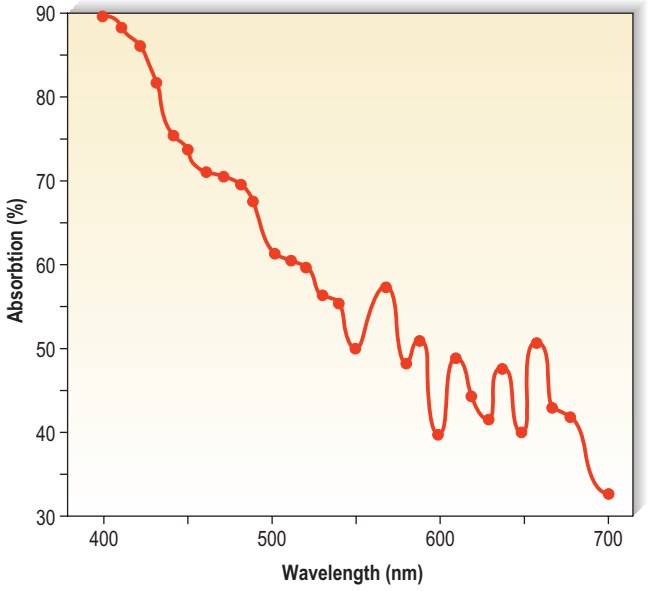


Figure 8.10 Absorption spectra for hemosiderin (freshly frozen, average of two determinations). (From Wells CI, Wolken JJ. Nature 1962;193:977.)

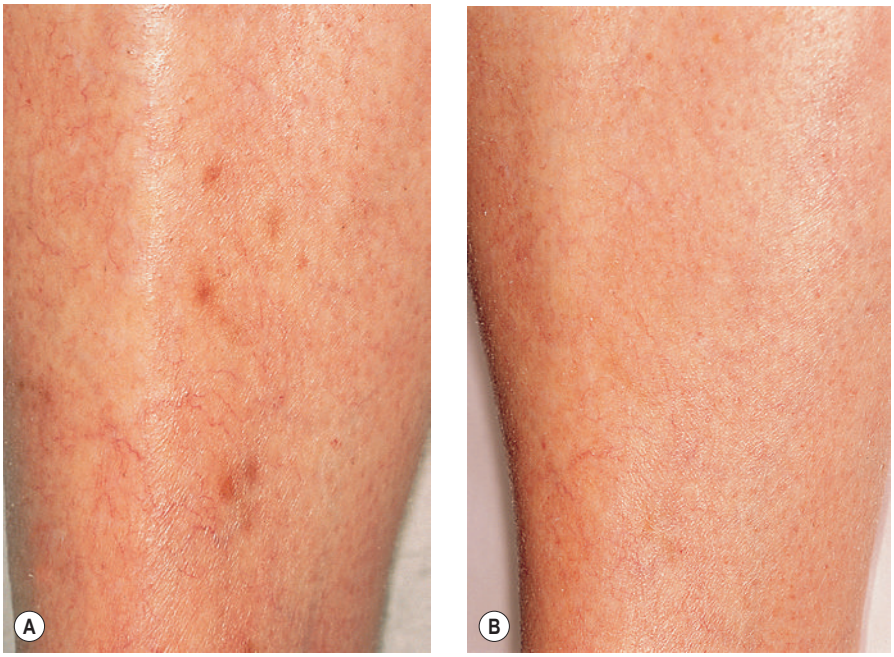


Figure 8.11 **A,** Pigmentation from sclerotherapy lasting over 1 year. **B,** Resolution 2 months after the second of two treatments with the Q-switched ruby laser at 8.0 J/cm^2. (Courtesy David Duffy, MD; from Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishing; 1999.)

therapy, thermal relaxation times used with the latter laser system should be more selective.

The Q-switched ruby laser (694 nm) is also effective in removing recalcitrant pigmentation. Hemosiderin has a peak at 694 nm, and the Q-switching impulse at 20 to 30 ns is effective in removing tattoo granules. In addition, 694 nm is not absorbed to a significant extent by epidermal melanin or hemoglobin and thus has a relative specificity for dermal hemosiderin. An older ruby laser (Laseaway, Walsall, UK) was found to effectively remove or minimize pigmentation in a number of patients (Fig. 8.11).[104] In a study of eight patients with pigmentation still present 1 to 2 years after sclerotherapy, 92% of the lesions lightened with treatment and 58% of lesions demonstrated significant (75–100%) resolution after one to three (average 1.7) treatments. The Laseaway ruby laser was used with a 4-mm beam size and a fluence range of 5.6 to 10.5 J/cm^2. Weiss and Weiss[105] could achieve 90% resolution of pigmentation that had been present for an average duration of 18 months with 3.2 treatments using a Q-switched ruby laser as well (Ruby Star; Asclepion Laser Technologies, Jena, Germany) at 5 to 10 J/cm^2 with a 2-ns pulse and a 4- to 5-mm diameter spot. We now use a Q-switched ruby laser (SINON) from Alma Lasers (Buffalo Grove, IL) at 4 to 7 J/cm^2 with a 20-ns pulse and a 4- to 5-mm diameter spot size. Treatments are performed every 4 weeks until resolution. Care is taken to use the minimal fluence required to produce a whitening of the skin without causing bleeding. Our patients require one or two treatments for complete resolution.

Interestingly, we have not found satisfactory results using a variety of alexandrite lasers in either long-pulse or Q-switched mode, although a case report published in 2015 detailed the successful use of the Q-switched Alexandrite laser for the treatment of cutaneous siderosis secondary to intramuscular (IM) injections of iron dextran.[106] This may be due to the decreased interaction of the 755-nm wavelength with hemosiderin.

Weiss[107] has reported successful clearing with the use of intense pulsed light (IPL) (PhotoDerm PL; Lumenis Aesthetic, San Jose, CA) in 10 patients with pigmentation persisting after 1 to 2 months. He used the IPL at 30 to 40 J/cm^2 given in a single 4-ms pulse with a 590-nm cutoff filter. Significant lightening occurred in 6 of the 10 patients. Similarly, Mlosek et al. used a combination treatment with IPL and radiofrequency (RF) energy to remove postsclerotherapy hyperpigmentation.[108] In their study, they found that increased echogenicity of the dermis (presumably caused by neocollagenesis secondary to IPL plus RF therapy) was associated with improved clearance of hyperpigmentation.

Other Q-switched lasers used to treat hemosiderin-containing hyperpigmentation include a 532-nm/1064-nm Nd:YAG laser (Cynosure, Westford, MA) and a 650-nm Nd:YAG laser. Ten patients who had had persistent pigmentation for an average of 18 months were treated at 2-ns pulse with 75% 1064 nm and 25% 532 nm simultaneously with a 6-mm diameter spot at 2 J/cm^2. There was a 75% resolution in an average of 2.8 treatments.[109] The 650-nm handpiece of the Nd:YAG laser was used in a single case of facial necrobiotic xanthogranuloma with histological evidence of excessive hemosiderin deposition.[110] A total of nine treatments divided by cosmetic subunits were administered, with each subunit receiving two or three treatments at settings of 3.2 J/cm^2, 2-mm spot size and 5- to 20-ns pulse duration. Near-complete resolution of hyperpigmentation was observed and was maintained at 5-month posttreatment follow-up.

The simplest treatment is ‘flashbulb therapy’ or ‘chronotherapy’. Because pigmentation usually resolves within 1 year in the majority of patients, time and photographic documentation to demonstrate resolution are usually all that is necessary for the understanding patient. Persistence of pigmentation beyond 1 year usually indicates untreated reflux from above and should be investigated by duplex ultrasound.

TEMPORARY SWELLING

ETIOLOGIC FACTORS

Multiple factors are responsible for swelling of a treated area. These factors include changes in the pressure differential between the intravascular and perivascular spaces and changes in endothelial permeability. Edema is most common after treatment of varicose veins or telangiectasias below the ankle, because of the increase in gravitational intravascular pressure in this area and the relative scarcity of perivascular fascia at the ankle. Riddock[111] speculates that edema is caused by an unduly prolonged reflex spasm spreading to some of the subfascial (deep) veins.

The extent of edema appears to be related to the strength of the sclerosing solution. This result apparently correlates with the degree of perivascular inflammation produced by the sclerosing solution. The byproducts of inflammation, including release of histamine and various mediators, increase endothelial permeability. In addition to the degree of inflammation induced by sclerotherapy itself, the innate sensitivity of a patient's perivascular mast cells (possibly related to the patient's atopic or asthma history), concomitant medications that may promote or inhibit mast cell degranulation (e.g., corticosteroids, antihistamines, nonsteroidal anti-inflammatory agents) and previous exposure sensitivity to the sclerosing agent may all contribute to edema. Duffy[8] and Goldman[13] estimated that the occurrence of pedal edema ranges from 2% to 5%.

Edema may also occur if compression is not applied gradually. Edema may be produced when localized pressure on the thigh is applied over an injected vein and with the addition of a tape dressing over or under a graduated compression stocking. If patients are informed of the possibility of a tourniquet effect by the extra compression, they can be advised to remove the dressing at the first sign of edema distal to the dressing.

PREVENTION AND TREATMENT

Two techniques may decrease temporary swelling. First, perivascular inflammation must be limited, as previously described (see the sections 'Recommended sclerosing solution amounts and concentrations' and 'Postsclerotherapy compression' in Chapter 9). Ankle edema occurs much less frequently if the quantity of sclerosing solution is limited to 1 mL per ankle.

One method that we have found helpful is topical application of a strong-potency corticosteroid cream, lotion or gel. Methylprednisolone acts both to stabilize mast cell membranes, preventing histamine release and to exert part of its anti-inflammatory action directly on the endothelial cell, rendering it less responsive to various mediators.[112] Ruscus extract inhibits macromolecular permeability, increasing the effect of histamine in the hamster cheek pouch model.[113] This effect is caused by stabilization of endothelial pore size. β-Receptor agonists such as terbutaline and theophylline counteract histamine-induced venular permeability. This effect also occurs with verapamil and glucocorticoids.[114]

A second method for limiting the degree of pedal or ankle edema is application of a graduated pressure stocking routinely after injections in this area.[115] Researchers in one study compared the use of postsclerotherapy graduated compression for 3 days to 3 weeks and reported that none of 10 patients complained of edema when stockings were worn for 3 weeks; 40% of patients who did not wear post-treatment compression stockings had edema; 30% had edema if stockings were worn for only 3 days; and 20% complained of ankle/pedal edema if stockings were worn for 1 week.[99]

TELENIECTATIC MATTING

The new appearance of previously unnoticed, fine red telangiectasias occurs in a number of patients after either sclerotherapy or surgical ligation of varicose veins and leg telangiectasias (Figs 8.12 and 8.13). This occurrence has been termed *flares* by Arenander and Lindhagen,[116] as *distal angioplasia* by Terezakis,[117] *blushing* by many and *telangiectatic matting* (TM) by Duffy.[6] The reported incidence varies from 5%[13] to 75%.[14,43,116] The authors of two retrospective analyses of 2120 and 7200 patients with leg telangiectasia each reported a 16% incidence.[15,118] This incidence has been confirmed in a random sample of 113 female sclerotherapy patients.[42]

Although the average severity was considered minimal, TM was noted in approximately 70% of our patients treated with foam versus 84% of those treated with liquid STS sclerotherapy.[17] Of note, however, all evidence of new vessel formation had resolved completely within several months (on average within 3–6 months). Reasons for the development of TM are multiple. Recovery from an ischemic injury such as closing blood vessels with sclerotherapy may produce hypoxia-induced neovascularization. In addition, injury to endothelial cells may stimulate the release of a variety of growth factors.

These responses are probably a fundamental feedback response, acting to satisfy tissue needs for oxygenation. For example, this response is commonly seen in myocardial collateralization. Circulating endothelial progenitor cells, elevated with estrogen therapy, may also lead to neoangiogenesis.[119] Given these protective factors, it is curious that the incidence of TM after sclerotherapy is not higher; therefore, other innate factors must predispose to the development of TM.

The authors of one report described the incidence of TM increasing with patient age,[116] but this correlation was not observed in another report.[118] Although most authors do not comment on a gender predisposition,[8] we have seen the development of TM in only one male patient with leg telangiectasia. Because fewer men than women seek treatment for leg telangiectasia, an accurate appraisal of the gender incidence of TM cannot be stated.

TM may appear anywhere on the leg, but we have never seen it occur on the face, hand or chest after sclerotherapy. Researchers in one detailed study found that most TM occurred on the medial ankle and the medial and lateral calves.[116] However, TM also has been reported to occur more frequently on the thighs.[120] Duffy reported that in 80% of his patients, TM developed within 10 inches (25 cm) above the knees (Duffy DM, personal communication, October 1994). Our experience is similar to Duffy's. Duffy postulated that relative ischemia occurs in this area from tissue hypoxia that results from the thighs and knees pressing on each other during sleep when persons lie on their side. Hypoxia has been found both in the retina and around

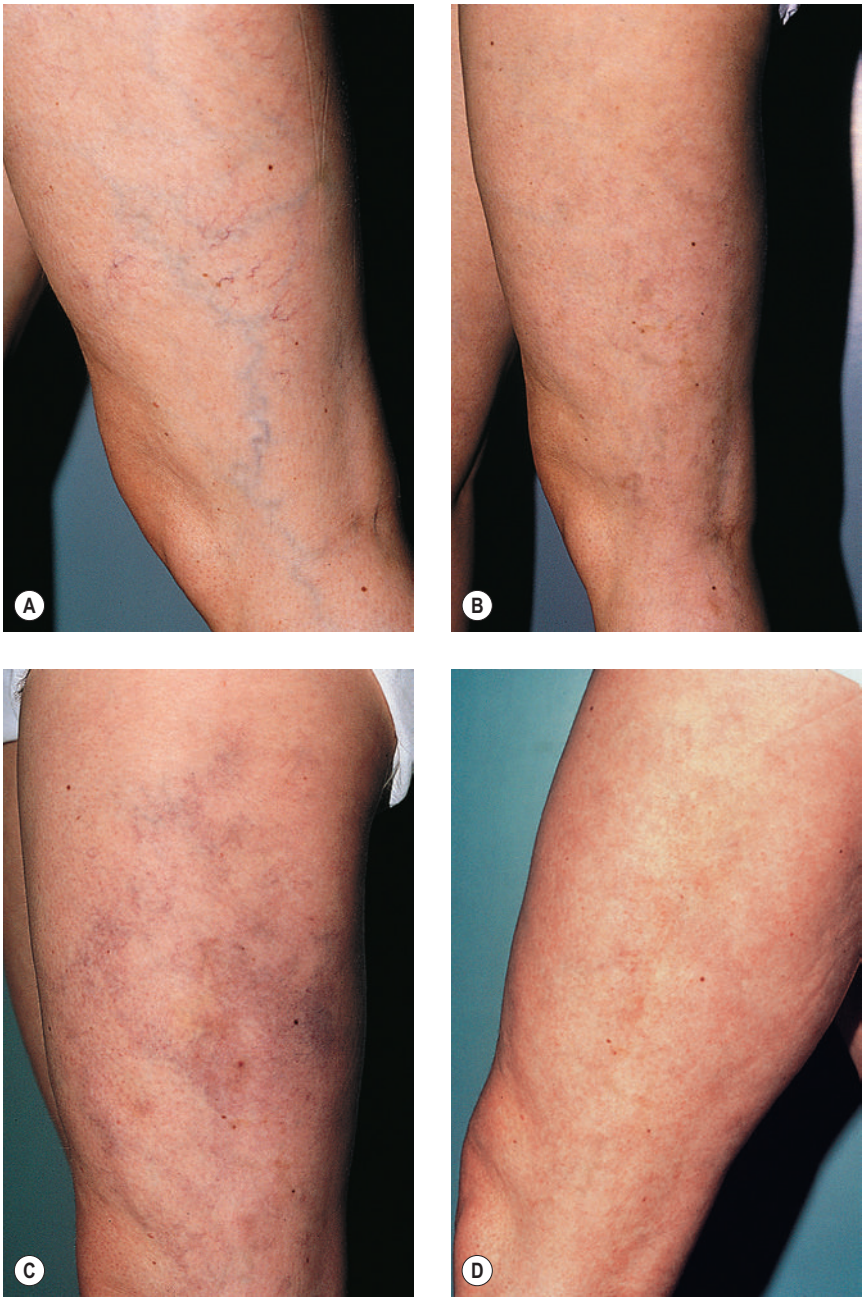


Figure 8.12 Typical telangiectatic matting (TM) in a 36-year-old woman. **A,** Left lateral thigh before sclerotherapy treatment. **B,** Three months after treatment of reticular veins with polidocanol (POL) 0.75%. **C,** Six weeks after treatment of telangiectatic veins with POL 0.5%; note development of extensive TM. **D,** Six weeks later. Note complete resolution of TM without treatment. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Goldman MP. Adverse sequelae of sclerotherapy treatment of varicose and telangiectatic leg veins. In Bergan JJ, Goldman MP, editors. Varicose veins: diagnosis and treatment. St Louis: Quality Medical Publishing; 1993.)

compressive tumors to promote vascular endothelial growth.[121–123] Although a 14.5% incidence of TM has been reported with treatment of hand veins,[59] we have not seen this in hundreds of hand veins treated with sclerotherapy.

ETIOLOGIC FACTORS

Postsclerosis TM was first described in the 1960s by Ouvry and Davy.[124] They observed that the incidence of TM was proportional to the degree of inflammation and thrombus formation. The etiology of TM is probably related either to angiogenesis[8,125] and/or to a dilation of existing subclinical blood vessels by the promotion of collateral flow through arteriovenous (AV) anastomoses.[125,126]

Probable risk factors for the development of TM in patients with leg telangiectasia include obesity, use of estrogen-containing hormones, pregnancy and a family history of telangiectatic veins. Excessive standing does not appear to influence the incidence of TM.[118] Excessive post-sclerotherapy inflammation also may predispose toward development of TM.

After sclerotherapy, the development of TM occurs rapidly; often patients report the development over a few days at 3 to 6 weeks after treatment. Normally, the more than 1 trillion endothelial cells that line blood vessels have a turnover time of more than 1000 days.[127] However, under appropriate conditions, new vessels can develop in 2 to 3 days. In observations of mammalian systems, researchers have demonstrated the development of a vein from a capillary, an artery from a vein, a vein from an artery or from either back to a capillary.[128,129] In coronary vessels, the number of arterioles and capillaries increases within 1 week after injury.[130]

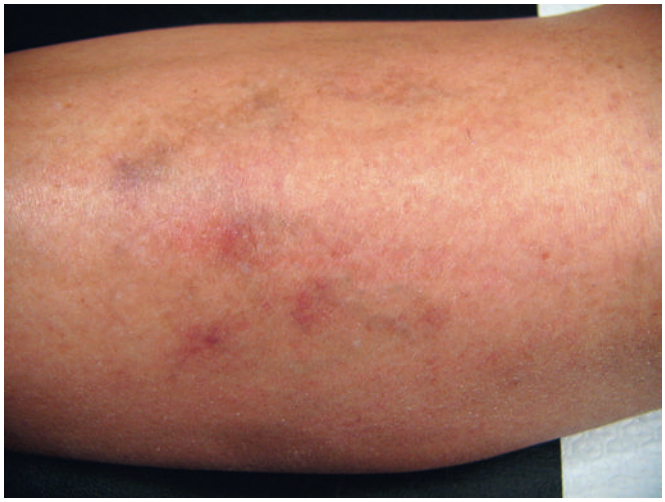


Figure 8.13 Telangiectatic matting after sclerotherapy caused by reflux from above.

Angiogenesis

Angiogenesis is a complex process in which capillary blood vessels grow in an ordered sequence of events. Angiogenic factors act either directly on the endothelium to stimulate locomotion and mitosis or indirectly by mobilization of host helper cells (mast cells and macrophages) with release of endothelial growth factors (see later). When a new capillary sprout grows from the side of a venule, endothelial cells degrade basement membrane, migrate toward an angiogenic source, proliferate, form a lumen, join the tips of two sprouts to generate a capillary loop and manufacture new basement membrane.[131] Obstruction of outflow from a vessel (which is the end result of successful sclerotherapy) is one of the most important factors contributing to angiogenesis.[132] Initiation of angiogenesis also follows disruption of endothelial continuity or intercellular contact. This contact results in endothelial cell sprouting and migration.[133]

Hypoxia with a decrease in the partial pressure of cellular oxygen also is a potent stimulator of neovascularization. With ischemia, one of the first genes upregulated is the gene encoding hypoxia-inducible factor 1.[134] This factor activates genes involved in angiogenesis, glycolysis, modulation of vascular tone and erythropoiesis.[134–136]

In addition, endothelial damage leads to the release of heparin and other mast cell factors that both promote the dilation of existing blood vessels and stimulate angiogenesis.[137–140] Neovascularization may be promoted by numerous other angiogenic factors, including but not limited to heparin-binding fibroblast growth factor (FGF),[2,141,142] tumor necrosis factor (TNF),[138,143,144] platelet-derived endothelial mitogen,[145] endothelial cell growth factor,[146] and other macrophage-derived growth factors.[147,148] These factors and many others are released from perivascular mast cells.[149] FGF is released at cell death and is essential for the stimulation of angiogenesis and wound repair.[150,151] Thus, sclerotherapy, through endothelial damage, promotes the release of both endothelial angiogenic factors and perivascular mast cell angiogenic factors that provide multiple mechanisms for the formation of new blood vessels. Indeed, it is remarkable that postsclerosis TM does not occur more frequently.

Sclerotherapy-induced perivascular inflammation also may promote TM.[26] Inflammation may be considered a hypermetabolic state, with new vessel growth occurring as a result of increased metabolic demand.[152] In addition, mast cells are found in increased numbers in inflammatory states, such as allergic contact dermatitis or delayed hypersensitivity reactions.[153] Because mast cell heparin is one factor responsible for capillary endothelial cell migration,[127] the degree of inflammation should be limited as much as possible to decrease angiogenic stimuli. This is achieved by choosing an appropriate solution concentration for each type of vessel treated, limiting the quantity of solution to the amount that will not produce excessive endothelial damage and limiting the size of postsclerotherapy thrombosis. This was confirmed by Weiss and Weiss,[42] who found in a random sample of 113 sclerotherapy patients that TM developed in 10 patients with injection of POL 1% into vessels less than 1 mm in diameter. When POL 0.5% was used for subsequent treatments in these patients, further areas of TM did not develop. The use of low concentrations of POL was found in a multicenter report of 16,804 legs to have an incidence of TM of 0.04%.[154] However, it is unclear how closely patients in this large prospective clinical trial were followed. A comparison of POL 1% with HS 20% in treating leg telangiectasia showed that the incidence of TM was higher with the more caustic POL (36%) than with HS (31%) (Fig. 8.14).[44]

Another group of investigators reported TM in 12% of patients treated with Sclerodine 0.25%, in 17% treated with Sclerodex and in 15% treated with 0.25% POL.[12] These agents should all be comparatively similar in their sclerosing power despite their different mechanisms of action on endothelial cells. Interestingly, although their effectiveness in eliminating telangiectasia varied from 73% for POL to 44% for Sclerodine and Sclerodex, the incidence of TM was relatively similar.

A study comparing different times of postsclerotherapy compression in treating leg telangiectasia also demonstrated a decrease in TM when compression was maintained for 1 to 3 weeks (5%) versus 3 days (30%) or no compression (40%).[155] This is most likely a reflection of a decrease in intravascular thrombosis with prolonged graduated compression, which results in a decreased phlebitic effect with decreased inflammation.

As noted previously, assuming a role for the perivascular mast cell in the etiology of TM is intriguing. With aging, cutaneous mast cells decrease by 50%, which is associated with a 35% decrease in subepidermal venules.[60] Thus, if TM develops predominantly from mast cell factors, its incidence should be decreased in the elderly; however, this was not observed in two studies.[116,118] Cutaneous mast cells usually occur perivascularly, with a distribution ranging from 7000/mm to 20,000/mm.[7,8,156–159] This represents 0.2% to 0.7% of normal skin. In telangiectatic macules associated with mastocytosis, mast cells account for 3.5% (±1.8 SEM) of cells, whereas telangiectasia not associated with mastocytosis has a mast cell volume of 0.4% (±0.1 SEM).[160] An analysis of mast cell content in TM lesions is needed.

Estrogen may play a role in the development of TM. It appears that the incidence of persistent TM may be increased in patients taking systemic estrogen preparations.[8,42,118] Weiss and Weiss[42] found a relative risk of 3.17

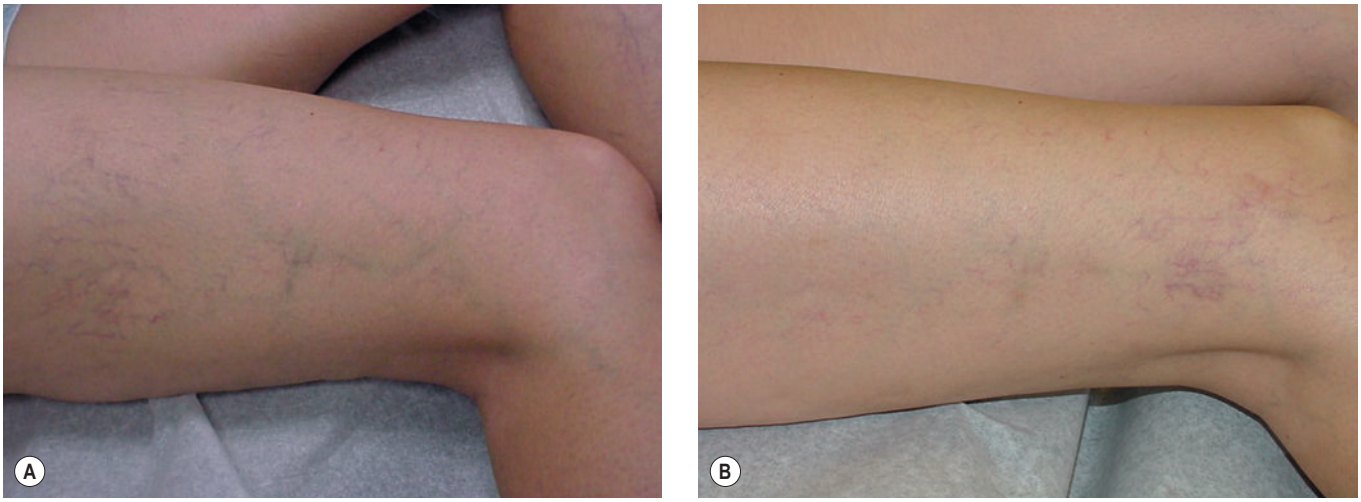


Figure 8.14 **A,** Before treatment. Note reticular vein feeding into telangiectasia on the superior lateral thigh. **B,** Six weeks after sclerotherapy treatment. Note resolution of superior lateral thigh telangiectasia with appearance of 'new' telangiectasia distal to point of injection.

($P < 0.003$) for development of TM while patients were receiving exogenous estrogen. Sadick also found an increased incidence of TM (10% vs 4%) in patients receiving oral contraceptive agents or hormone replacement therapy.[161] The mechanism for promotion of TM by estrogen is speculative but may be the result of its effect on modulating mast cell responses.[162]

Estrogen receptors have been found in a number of tumors, including angioma of the nose, soft tissue sarcoma, breast carcinoma, endometrial carcinoma and unilateral nevoid telangiectasia syndrome. Estrogens also play a role in the development of vascular tissues. In vitro, estrogen and estradiol have promoted endothelial cell migration and proliferation.[163,164] Spider angiomas develop during pregnancy and resolve after delivery.[165,166] Spider nevi also occur in patients with hepatic cirrhosis associated with elevated serum estradiol levels.[167] In addition, Davis and Duffy[105] reported on the virtual disappearance of leg telangiectasia and TM in a 51-year-old woman with estrogen receptor–positive breast carcinoma after initiation of antiestrogen therapy with tamoxifen citrate (Nolvadex; AstraZeneca, Wilmington, DE). This may be caused by the inhibition of angiogenesis by tamoxifen.[168,169] However, although it seems logical that estrogen plays a role in the development of TM, estrogen receptors could not be demonstrated in biopsy specimens from leg telangiectasia.[170] An evaluation of estrogen receptors in 10 patients with TM lesions did not demonstrate estrogen/progesterone receptors as examined by estrogen/progesterone immunocytochemical assay technique.[171] The limiting factors of this study, as stated by the authors, were the small size of the study group and the possibility that the immunocytochemical and radioligand assays may not have been sensitive enough to document a small number of estrogen or progesterone receptors. In addition, a selective estrogen receptor modulator that is specific for blood vessels has yet to be identified.[172] Further, circulating endothelial progenitor cells are also elevated with estrogen therapy and may lead to neoangiogenesis.[119] Because estrogen receptors have been implicated in the promotion of angiogenesis,[173] it may be prudent, albeit premature, to withhold estrogen therapy during sclerotherapy until double-blind controlled studies have been performed.

PREVENTION AND TREATMENT

Regardless of the cause of TM, because patients seek treatment to eliminate leg telangiectasia, it is disconcerting for the sclerotherapist to produce new areas of telangiectasia. Unfortunately, even in the most expert hands, TM occurs in a significant percentage of patients. Fortunately, TM usually resolves spontaneously over 3 to 12 months.[8,42] It has been estimated that 10% to 20% of patients will have persistent TM.[118,174] Our experience is that less than 1% of patients will have TM persisting for 1 year.

Treatment methods for TM are limited. Reinjection with hypertonic solutions or glycerin may be helpful. Because of the extremely small diameter of these vessels, use of a 31- to 33-gauge needle is helpful. Injection of any feeding reticular veins or venulectases into the TM area should also occur.

Various vascular system–specific lasers and IPL sources may be useful in treating these vessels.[175–179] In our practice, at least 75% of patients with persistent TM partially or completely improve after laser or IPL treatment. Interestingly, individual TM lesions may respond better to one laser or IPL than another. Reasons for the variable response are speculative. The 532-nm long-pulse Nd:YAG laser set at the highest fluence and pulse durations available has been found to be most effective on the most recalcitrant lesions. However, persistent and, rarely, permanent hypopigmentation may occur. The use of the PDL may also be effective but result in long-term hyperpigmentation. In 2006, Glaich et al reported successful treatment of postsclerotherapy matted telangiectasias using fractional photothermolysis.[180] Specifically, marked improvement was noted in these telangiectasias, which had been present for longer than 1 year, after five successive treatments with a 1550-nm fractional photothermolysis laser at 4-week intervals. The reason for this reported success is questioned, as in this study resolution required 6 months, which is the time course of spontaneous resolution of TM. In addition, this was a single case report. We therefore cannot recommend fractional photothermolysis as effective at this time. (A complete discussion of

laser treatment is provided in Chapter 13.) Unfortunately, even with the aforementioned therapeutic approaches, rare TM may remain resistant to treatment, possibly because in certain cases TM may have a feeding arteriolar network that prevents persistent vessel elimination.

In patients who demonstrate a propensity for the development of TM, additives to the sclerosing solutions or topical agents may minimize this complication. Protamine blocks the ability of mast cells and heparin to stimulate migration of capillary endothelial cells.[181] Protamine also prevents the neovascularization induced by an inflammatory agent when it is applied locally or given systemically.[182] It has no effect on established capillaries that are not proliferating.[183] In addition, β-cyclodextrin tetradecasulfate administered with cortexolone is a potent inhibitor of angiogenesis.[184]

Systemic treatment before or during sclerotherapy also may be helpful in limiting TM. Through suppression of TNF synthesis, pentoxifylline (Trental; Sanofi-Aventis, Bridgewater, NJ) may minimize angiogenesis.[185,186] Inhibition of mast cell mediators with the cell wall–stabilizing medication ketotifen also may help prevent TM, edema and localized urticaria. Ketotifen, a benzocycloheptathiophene derivative, has H_1 antihistaminic properties in addition to decreasing mast cell mediator release.[187,188] Ketotifen may also exert its effect by depleting mediators in cutaneous mast cells and so requires multiple doses over a few days for maximal effect.[189] Its clinical beneficial effect in patients with chronic idiopathic urticaria, cutaneous mastocytosis and urticaria pigmentosa has been established.[189–193]

PAIN

PREVENTION

Because most patients who seek treatment of leg telangiectasia require multiple treatment sessions, each consisting of numerous injections, an attempt should be made to minimize the unpleasantness of the procedure. Certain areas are slightly more painful, especially the ankles, feet, upper medial thighs and medial knees. We have not found it necessary to use topical anesthetic creams, and indeed a commonly used anesthetic cream, a eutectic mixture of lidocaine and prilocaine (EMLA cream; Akorn Pharmaceuticals, Lake Forest, IL), has been found to produce vessel contraction, making it more difficult to perform treatment (Fig. 8.15). Two variables that can be adjusted to minimize pain are the type and size of the needle and the type of sclerosing solution.

Type and Size of Needle

Using a needle of the smallest possible diameter for injection is the most obvious way to minimize injection pain. Another factor to consider is the shape of the needle bevel. Needles—even those of the same gauge—are shaped differently and may or may not be coated with a layer of silicone. In our experience, acutely tapered needles, especially when tribeveled, and those that are silicone-coated usually are perceived by the patient as less painful.

Technique

With sclerosing solutions that are inherently painful to inject (e.g., hypertonic solutions), slow infusion can minimize pain.[6,8] Slow injection produces a slower distention of tissue and may minimize endothelial cell separation, which may decrease perivascular nerve stimulation.

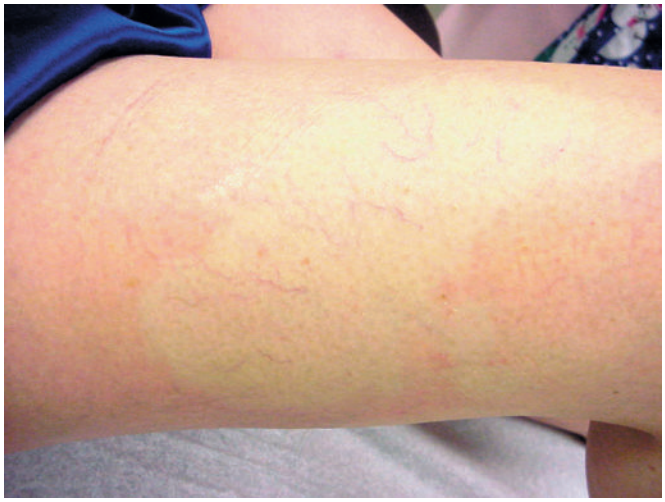


Figure 8.15 EMLA cream (eutectic mixture of lidocaine and prilocaine) applied to the proposed treatment area after 45 minutes of occlusion. Note blanching of target blood vessels.

Type of Sclerosing Solution

Hypertonic solutions are notorious for causing pain upon injection. The cramping pain that may develop after correct IV injection usually occurs a few minutes after injection. Weiss and Weiss[6] reported that 72% of their patients injected with HS 23.4% felt pain that lasted less than 5 minutes; 4.5% of patients had pain that lasted more than 5 minutes. This pain probably occurs at the time the hypertonic solution reaches the nerve fibers of the adventitia, either through the wall of the vein or through the capillaries. Subsequently, because of stimulation of sympathetic perivenous nerve fibers, an active contraction of the muscle occurs that may also produce a cramping pain.[194] In addition, vascular spasm caused by direct effects of the hypertonic solution itself may occur.

Hypertonic solutions also produce muscle cramping after injection. Chou et al[195] noted that with the injection of 5 to 10 mL of heparsal (HS 20% plus heparin, 10 U/mL) per injection site into varicose veins, 16% of 310 patients could not tolerate the pain associated with the procedure. Duffy[8] estimated that 82% of his patients treated with HS reported moderate cramping or aching. This can be limited somewhat by keeping the volumes injected to 0.1 mL or less per injection site and by massaging the area immediately after injection.

Adding lidocaine to the sclerosing solution may lessen muscle cramping and allow placement of additional injections into the same area with less pain.[8,9] A comparison of HS 23.4% with HS 19% diluted from HS 23.4% with a 2% lidocaine solution demonstrated a significant decrease in pain with the lidocaine solution.[14] In the HS 23.4% group, 61.9% of patients rated their pain as none to mild, whereas in the group treated with the HS 19%/lidocaine solution, 90.5% of patients reported no to mild pain. There was no difference in efficacy between the two solutions. However, McCoy et al[44] found that, even with the addition of 2%

lidocaine to HS, patients reported significantly more pain with injection as compared with POL 1%.

The addition of lidocaine to a hypertonic solution is associated with two problems. First, lidocaine, if acidified (in a multidose bottle), is painful during the injection. Therefore, nonacidified lidocaine (found in single-dose 'cardiac' ampules) should be used as an additive. Second, the addition of lidocaine gives the sclerosing solution the potential to produce an allergic reaction (discussed subsequently).

Chromated or plain, glycerin solutions are also painful during injection and may produce mild muscle cramping if more than 1 mL of solution is injected into a single vein.[47] We have found that the addition of lidocaine 1% to the glycerin solution minimizes pain on injection similar to its effect with HS. Two relatively painless solutions are POL and STS. The advantage of STS is that it is painful only when it is injected into perivascular tissues, thereby providing a noticeable check on inadvertent perivascular injection. POL is painless with both intradermal and IV injection. Therefore, one does not have the additional sign of pain to ensure accurate placement of the sclerosing solution. In a double-blind comparison of STS, HS and POL, patients preferred injection with POL.[196] Although relatively painless to inject, STS sometimes produces a dull ache a few minutes after injection. This ache resolves in a few minutes and is most likely related to damaged endothelial cells, which release a variety of factors promoting perivascular edema and inflammation. There is no posttreatment aching with POL.

Despite optimal technique and mild sclerosing agents, posttreatment soreness for 1 or 2 weeks after injection occurs in 20% of patients.[8] With the use of nonosmotic sclerosing solutions and the use of graduated compression stockings after treatment, we have not seen soreness in most patients after treatment. If patients do complain of soreness, the cause usually is secondary to thrombosed or inflamed vessels or even to a poorly fitted graduated compression stocking.

LOCALIZED URTICARIA

Localized urticaria occurs after injection of any sclerosing solution (Fig. 8.16). It is usually transient (lasting approximately 30 minutes) and probably is the result of endothelial irritation with release of perivascular mast cell histamine. Localized urticaria is not an allergic response, because it occurs even after injection of unadulterated HS 23.4%. It is an example of physical urticaria and is frequent in patients demonstrating dermographism.

Urticaria may occur as the earliest manifestation of perivascular inflammation through release of endothelial- or platelet-derived factors that lead to perivascular mast cell degranulation[197] (see previous discussion in sections on pigmentation and edema).

Approximately 40% of patients studied by Norris et al[43] described temporary itching after injections with POL, regardless of drug dosage. Duffy[8] reported an almost 100% occurrence of urticaria with injection of either POL or HS–heparin–lidocaine solutions. The urticaria is usually more intense when more concentrated solutions are used.[8,13] Urticaria also may be more intense with repeat injection sessions, especially when POL or STS is used.

TREATMENT

In our experience, localized urticaria and itching can be diminished by applying topical steroids immediately after injection and by limiting the injection quantity per injection site. This is particularly helpful in patients who will wear a graduated support stocking after treatment. High-potency topical corticosteroids, such as clobetasol propionate, have been shown to rapidly decrease histamine-induced pruritus.[198] Therefore, we recommend application of a nongreasy, fast-absorbing, high-potency corticosteroid to all treated areas after sclerotherapy. A secondary effect of the topical corticosteroid is vasoconstriction, which also may help with vessel resolution, reduction of TM and minimizing posttreatment thrombosis with its sequelae.

TAPE COMPRESSION BLISTER

Tape compression blisters (Fig. 8.17) occur when a tape dressing is applied to an area of tissue movement or to thin, elderly skin. The blister usually appears as a flaccid, fluid-filled sac overlying normal-appearing skin. It usually is not associated with induration or erythema of the adjacent skin. Common sites of occurrence are the posterior calf, medial thigh and popliteal fossa.

Blisters may occur with the use of any tape but appear more commonly with the use of Microfoam tape (3M Medical Surgical Division, St Paul, MN) as opposed to hypoallergenic paper tape (Dermilite II; Johnson & Johnson, New Brunswick, NJ) over foam pads or cotton balls, probably because of the greater adhesiveness of the Microfoam tape. In addition, Microfoam tape usually is placed over the foam dressing with a slight amount of tension, thus increasing the tension on either end of the tape. Blistering is also more common in the summer months, when the weather is hotter, and in elderly patients with thinner, more fragile skin.

The only problem with blistering is that it must be distinguished from early cutaneous necrosis, cutaneous infection or an allergic reaction. Early cutaneous necrosis may appear as a superficial blister. In this situation, the underlying and adjacent tissue usually is indurated and erythematous. Bullous impetigo can also have a similar physical appearance. With it, the blister overlies warm, erythematous skin. If not warned beforehand, patients may think that the blister is the result of an allergy to the sclerosing solution. A detailed explanation of the cause of the blister is usually required before treatment can continue. Thick tape with adhesive is not a recommended method of compression.

PREVENTION

If compression pads will be used under graduated stockings in a patient susceptible to blistering, a tubular support bandage can be used over the pad to hold it in place while the stocking is being applied. Although somewhat costly, this dressing (similar to a net dressing used in burn patients) helps prevent blister formation. (It also can be used in patients with allergies to tape.)

TREATMENT

Resolution of the blister occurs within 1 or 2 weeks without any adverse sequelae. To aid healing and prevent infection of the denuded skin, the use of an occlusive hydroactive

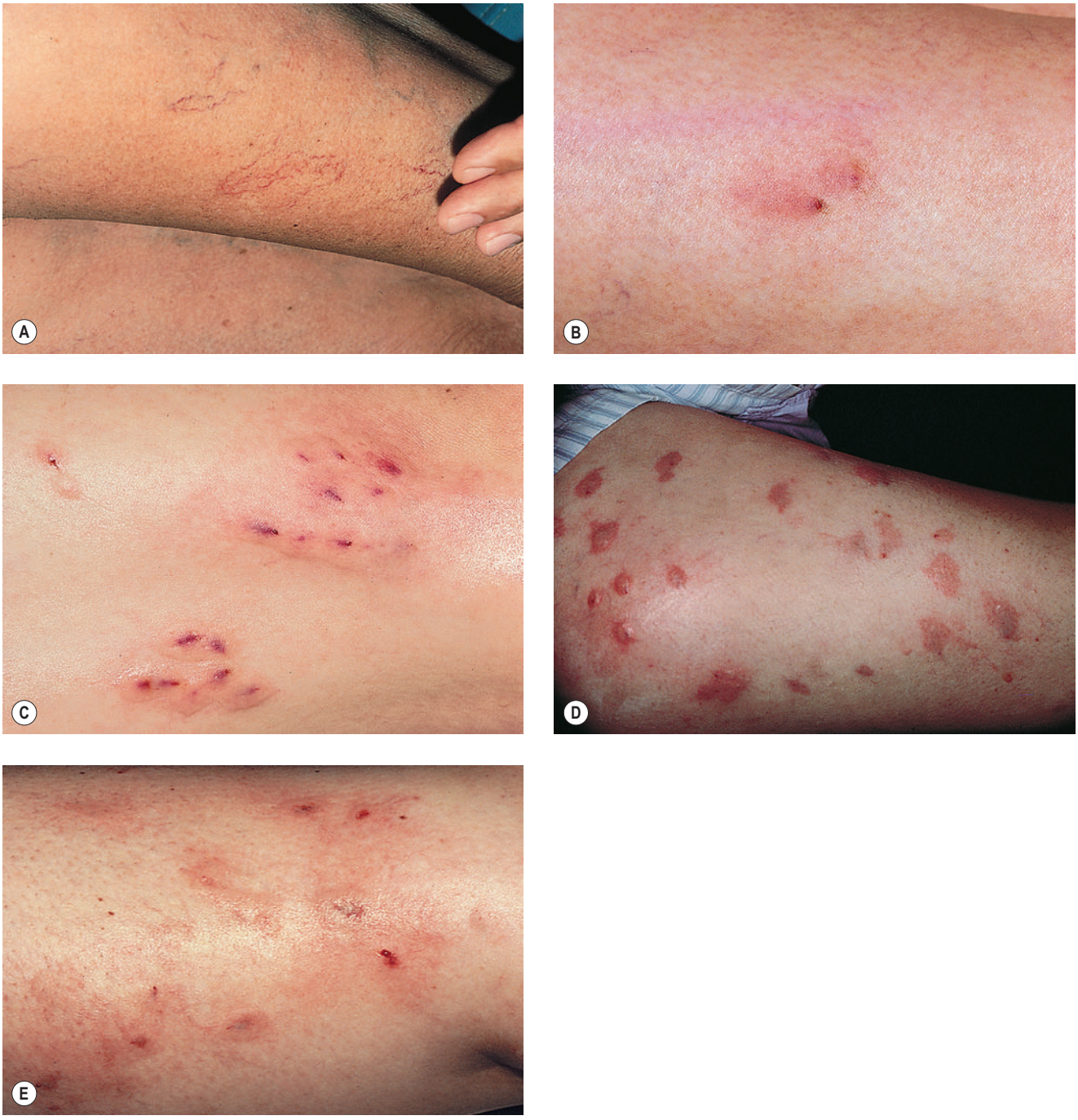


Figure 8.16 Urtication immediately after sclerotherapy with hypertonic saline 23.4% **(A),** sodium tetradecyl sulfate 0.1% **(B),** polidocanol 0.5% **(C),** chromated glycerin **(D)** and Sclerodex **(E).**

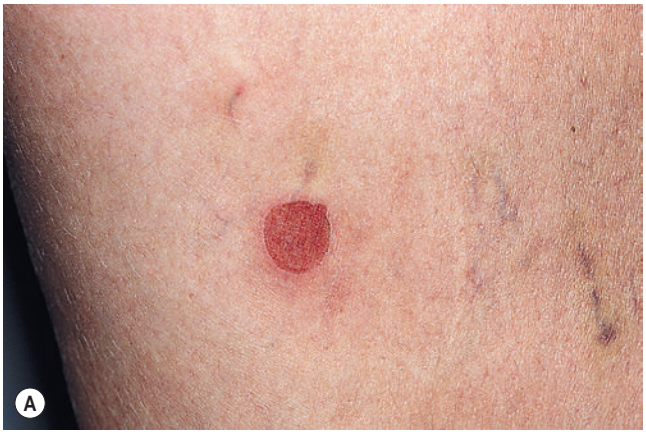
dressing is helpful. Occlusive dressings may also help alleviate any pain associated with the blister.

TAPE COMPRESSION FOLLICULITIS

Occlusion of any hairy area can promote the development of folliculitis (Fig. 8.18). Some patients have secondary alopecia associated with chronic venous insufficiency; however, men seeking treatment for varicose veins usually have hairy legs. If a tape dressing is placed over foam or cotton ball pads under a graduated compression stocking, a follicular inflammation or infection may occur. Folliculitis is more likely to occur in the summer months or when patients are active and perspire under the dressing.

TREATMENT

Treatment consists of removal of the occlusive dressing and application of topical treatment with an antibacterial soap such as chlorhexidine gluconate, or a topical antibiotic gel such as erythromycin 2% or clindamycin phosphate topical solution 1%. The folliculitis usually resolves within a few days. Systemic antibiotics are rarely necessary.



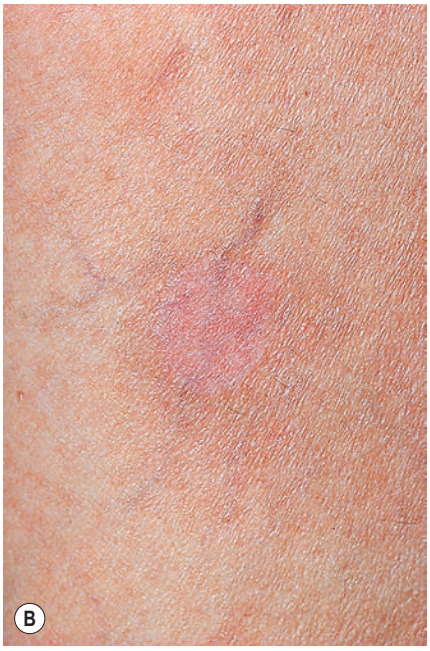


Figure 8.17 **A,** Superficial blister that developed 1 week after sclerotherapy treatment. Compression of the treated area was produced with an STD pad (STD Pharmaceutical Products, Hereford, UK) overlaid with Microfoam tape (3M, Minneapolis, MN) and a 30- to 40-mmHg graduated, thigh-length compression stocking (seen pulled down below the knee). **B,** Complete resolution 3 weeks later.

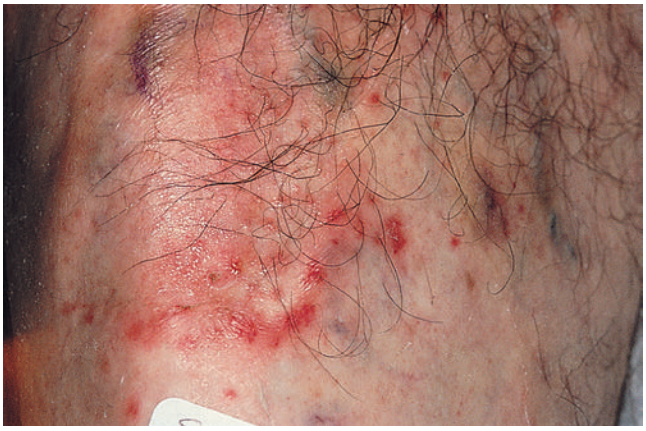


Figure 8.18 Folliculitis apparent 7 days after sclerotherapy. Compression of the treated area was produced with STD foam pads overlaid with Microfoam tape.

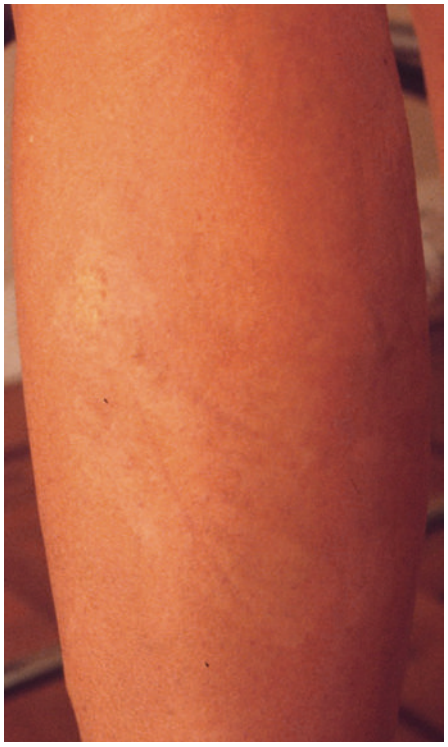


Figure 8.19 Skin tan fading after removal of adhesive tape and consecutive removal of superficial skin layers. Skin color gradient will disappear when suntan fades.

OTHER SKIN DISORDERS

More benign than blisters is skin suntan fading (Fig. 8.19), which is caused by the removal of more superficial skin layers of tanned skin. Although completely harmless, these little inconveniences can be misinterpreted by certain patients; fortunately, their duration is limited to a couple of weeks. In some cases, the tape can cause a dehydration of superficial skin layers and be responsible for an allergic-like reaction (Fig. 8.20).

MORPHEAS

Presenting like morphea observed in scleroderma, this can appear after injection of subcutaneous varicose veins. The etiology is unknown and the incidence is rare. Some patients with scleroderma have been treated by sclerotherapy without presenting morphea; conversely, patients without scleroderma have developed morphea (Fig. 8.21).

RECURRENCE

Although we believe that recurrence is really the formation of new vessels in the same region that was previously treated, recurrence of sclerotherapy-treated vessels has been estimated to occur in 3% to nearly 100% of leg telangiectasias at 5-year follow-up (Figs 8.22–8.24).[199,200] Recanalization of initially thrombosed leg veins is procedure-dependent. The larger the extent of intravascular thrombosis, the greater the likelihood of recanalization of the thrombosis during organization.[201,202] The recanalization of injected varices

without subsequent compression or with inadequate compression is caused by the following:

- Clot contraction and the formation of sinuses that may become lined with endothelium
- Central clot liquefaction and the formation of vascular tunnels through the thrombosis
- Formation of vascular organization of the thrombosis and collateral vessel formation of the newly formed capillaries
- Formation of peripheral sinuses filled with sludged blood (Figs 8.25–8.27)[202,203]

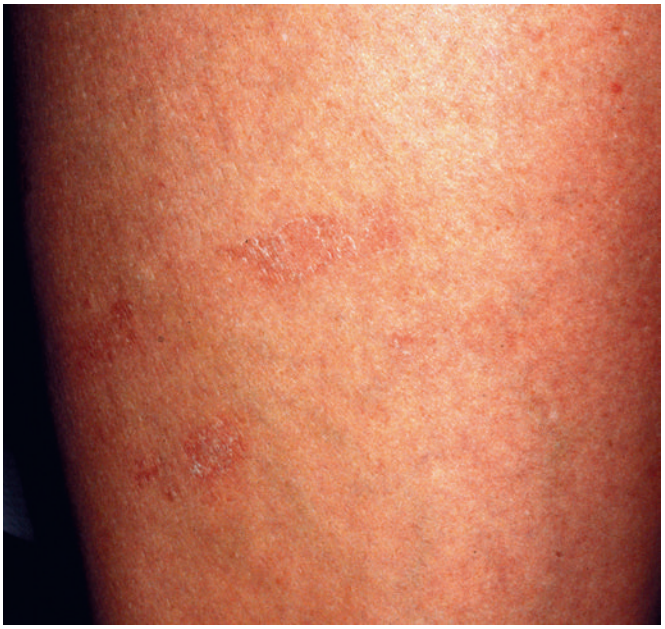


Figure 8.20 Epidermal dehydration by adhesive tape. Not to be considered as an allergy.

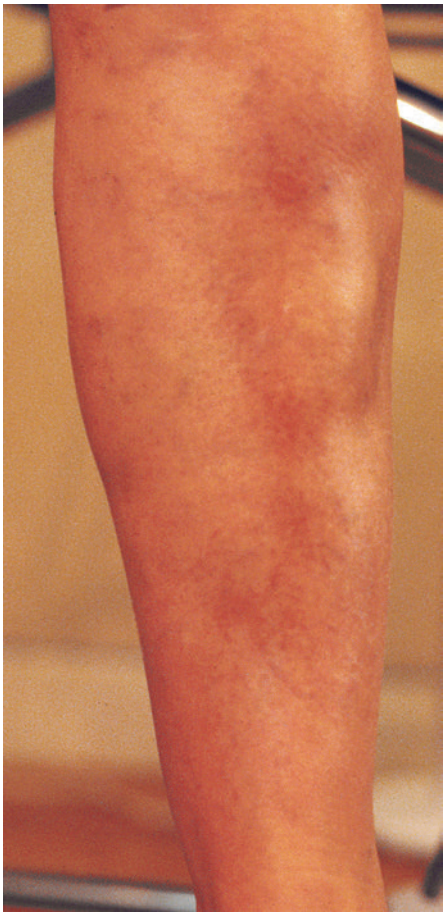


Figure 8.21 Morpheas: subcutaneous and cutaneous retraction following sclerotherapy of subcutaneous varices. The patient (a 67-year-old woman) did not have scleroderma (either clinical or biological). A type of localized scleroderma can be suspected.

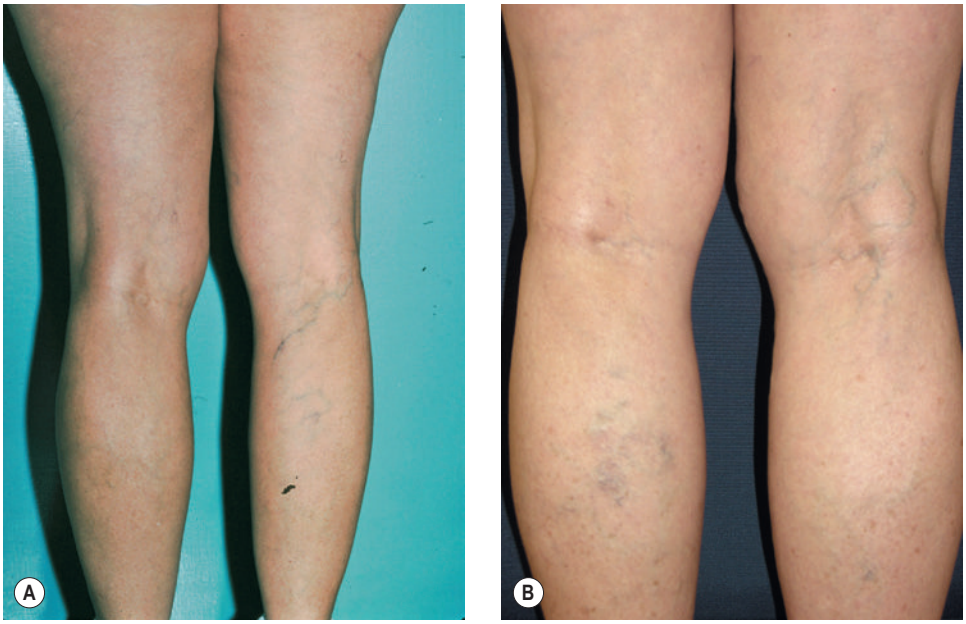


Figure 8.22 **A,** Original photograph of reticular and telangiectatic veins treated with sodium tetradecyl sulfate 0.25% with complete resolution. **B,** A 53-year-old woman 12 years after treatment of reticular and telangiectatic leg veins on the right posterior thigh. Note persistent resolution of originally treated veins with development of new reticular and telangiectatic leg veins bilateral posterior legs.

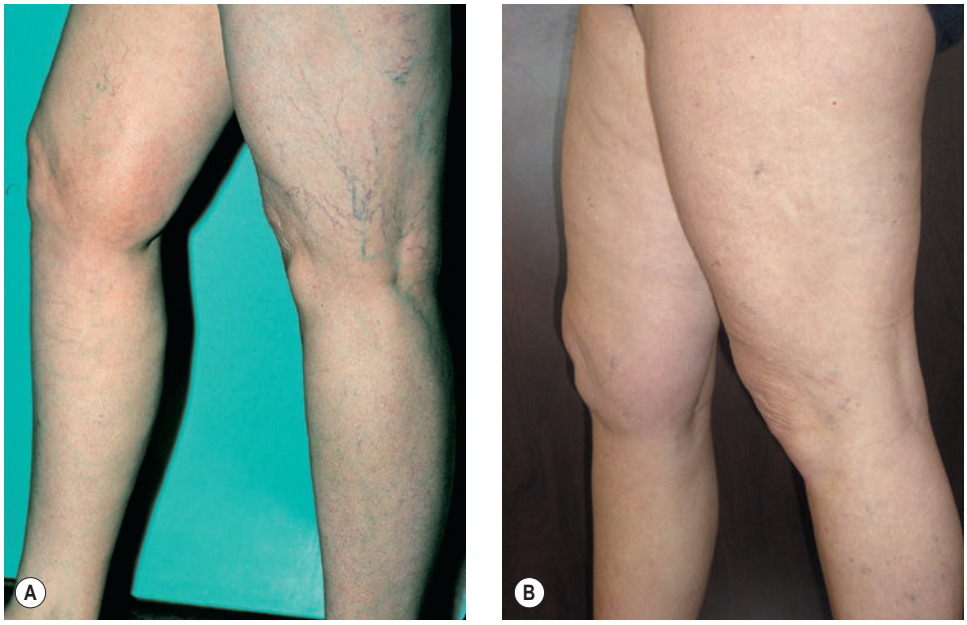


Figure 8.23 **A,** Marked telangiectasia and reticular veins left lateral thigh. **B,** Seventeen years after sclerotherapy treatment with sodium tetradecyl sulfate 0.25%. Note complete resolution of the treated veins with appearance of some new reticular veins.

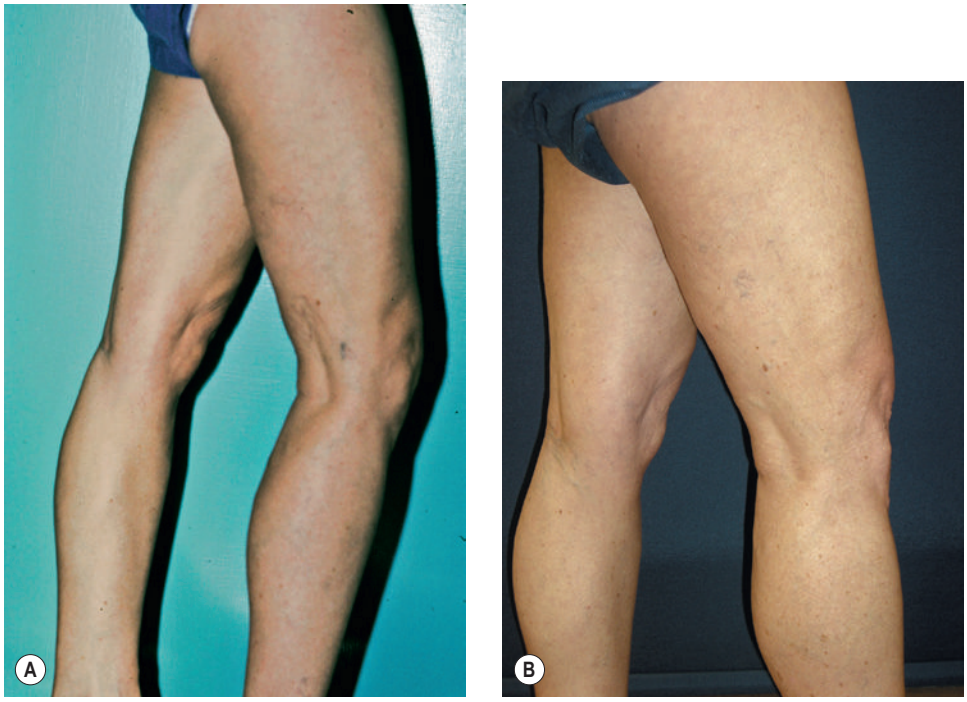


Figure 8.24 **A,** A 48-year-old woman with multiple reticular and telangiectatic leg veins at the right lateral knee treated with sodium tetradecyl sulfate 0.25%. **B,** Twelve years after sclerotherapy. Note total resolution of the treated veins with some new telangiectasia in other locations.

Therefore, the most important factor in preventing recurrence is limiting intravascular thrombosis. Another consideration is the possibility of deeper perforator vessels that feed the recurrent or resistant telangiectasia. Schuller-Petrovic et al. studied 26 patients and observed that 65% of telangiectasias resistant to sclerotherapy were in direct communication with feeding or perforating segments of the deep and saphenous veins.[204] Treatment of these underlying vessels with 0.5% POL foam resulted in complete clearance of the telangiectasias.

TREATMENT

Tournay[205] was the first physician to stress the importance of postinjection removal of blood clots, in 1938. The importance of draining these postsclerotherapy thrombi has since been emphasized by Sigg,[206] Pratt,[207] Hobbs,[208] and Orbach.[201]

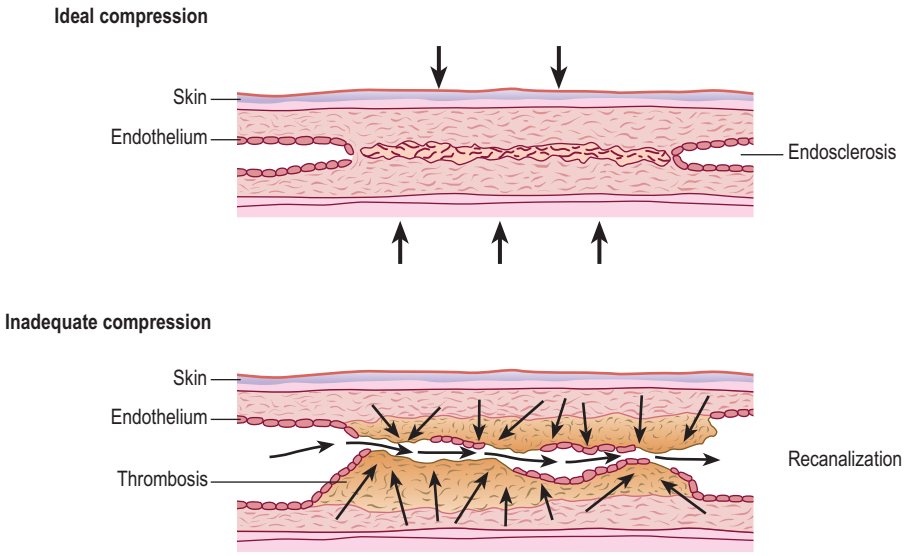


Figure 8.25 Diagrammatic representation of recanalization of a varicose vein through a sclerotherapy-induced thrombosis. (Redrawn from Wenner L. Vasa 1986;15:180.)

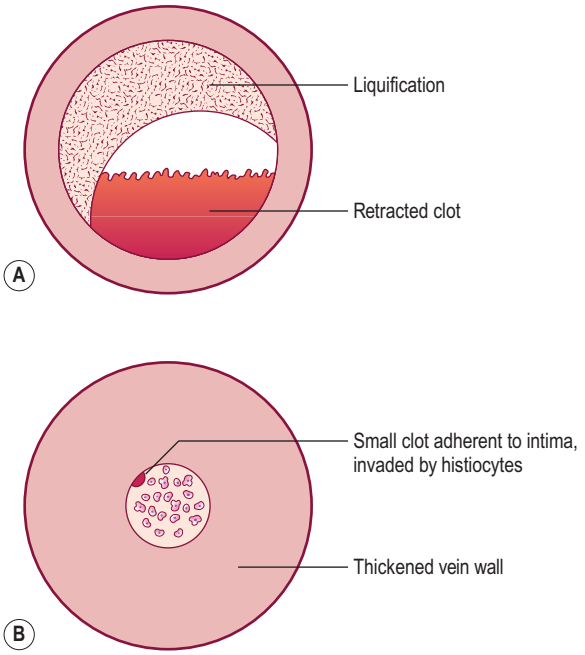


Figure 8.26 Diagrammatic representation of a histologic study from Fegan demonstrating the appearance of a varicose vein after sclerotherapy treatment. **A,** Without compression. **B,** With continuous compression for 6 weeks. (From Orbach EJ. Vasa 1974;3:475.)

With proper technique, varicose veins only rarely recur. A biopsy study of six patients with 'recurrence' of previously treated veins demonstrated that the veins thought to have recurred were in reality new varicose veins.[209] Raymond-Martimbeau and Dupuis[200] reported a 3.6% recurrence rate with 2-year follow-up of 884 sites of telangiectasia in 525 patients. When high recurrence rates have been reported, the patients have usually been treated with minimal compression.[201] For example, in one study of 310 patients, 83% required reinjection of a treated varicosity. These patients received only 48 hours of compression with elastic bandages.[195]

Unlike recanalization through a varicose vein cord, recanalization is not common through a sclerosed telangiectasia. Posttreatment histologic studies have demonstrated only fibrosis in an area treated with sclerotherapy.[7] Researchers in one study of telangiectasia found a 'recurrence rate' of 56% when patients were evaluated 5 years after sclerotherapy. In 48% of patients affected by a recurrence, the additional telangiectasias were of minimal extent, requiring little if any treatment.[210] Examination of telangiectasia present 1 year after treatment most likely indicated either untreated telangiectasia or new telangiectasia, and not recurrent veins. Our experience in observing before-and-after images on thousands of patients with multiple treatments over two decades confirms that telangiectasias are typically not recurrent but new.

STRESS-RELATED SYMPTOMS

VASOVAGAL REFLEX

The vasovagal reflex (neurocardiogenic syncope) is a common adverse sequela of any surgical or invasive procedure. A survey conducted in an ambulatory care center revealed an incidence of 10.6% during vein cannulation in 1500 patients.[211] It has been estimated to occur in 1% of patients during sclerotherapy[212] and is more frequent when using the technique of Fegan or Sigg, which requires patients to stand on insertion of needles.[213] Duffy,[8] who performs sclerotherapy with 30-gauge needles in reclining patients, estimates the incidence of vasovagal reactions at 0.001%. Interestingly, the percentage of men who have this response far exceeds the percentage of women. We (MPG, RAW) have seen a patient with a vasovagal reaction only twice in over 20 years of performing sclerotherapy in reclining patients and, interestingly, we have seen vasovagal reactions many times in male patients just being examined with duplex ultrasound or hearing the Doppler flow sound.

Vasovagal reactions have typical clinical findings. The usual symptoms include light-headedness, nausea and sweating. The patient also may have shortness of breath and palpitations. Syncope may occur and usually provokes the most concern in the physician and staff. With progression

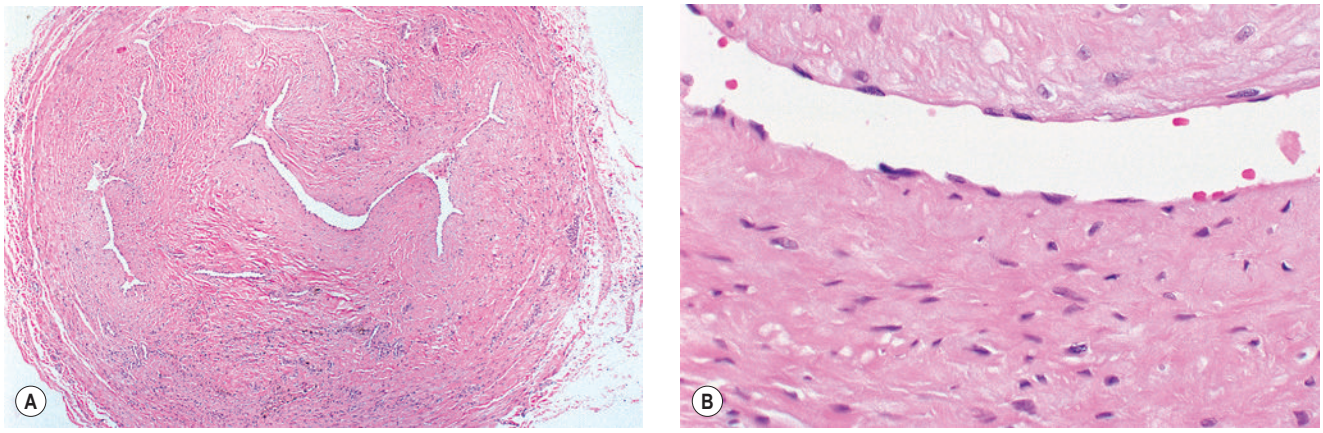


Figure 8.27 A 50-year-old man with a varicose great saphenous vein fed by an incompetent midthigh perforator vein without evidence of saphenofemoral junction reflux. The vein recurred 1 year after successful closure with 2 mL of sodium tetradecyl sulfate 3% and was subsequently removed with ambulatory phlebectomy. **A,** Appearance of recanalized sclerosed vein (hematoxylin–eosin stain; original magnification ×10). **B,** At ×400 original magnification, endothelial slits are lining a newly recanalized channel.

of the reaction, a seizure may occur, as well as cardiac arrhythmia with a rapid decrease in cardiac output and even cardiac arrest.[214] Vasovagal reactions most often are preceded by painful injection but may even occur from the patient seeing the needle or smelling the topical isopropyl alcohol or sclerosing solution.

Prevention

The main concern with a vasovagal reaction is that the patient will fall and be injured. Therefore, both the nurse and physician should watch the patient closely for signs of restlessness, paleness and excessive perspiration. All patients should be warned to sit down if they become dizzy. It is also helpful when needle placement is performed on a standing patient for the patient to hold on to an arm rail or other support, although treatment while the patient is standing is not a technique we advocate. All such reactions are easily reversible when the patient assumes the supine or Trendelenburg position. Preventive measures consist of recommending that the patient eat a light meal before the appointment, maintaining good ventilation in the treatment room and maintaining constant communication with the patient during the procedure.

The physician must recognize the vasovagal response in a patient and not assume that an anaphylactic reaction is occurring. If subcutaneous epinephrine (adrenaline) is given in the mistaken belief that an anaphylactic reaction is occurring, the symptoms will become both exaggerated and obscured. This only further confuses the clinical situation and adds to patient apprehension about further treatment sessions.

Treatment

The patient should be placed in the Trendelenburg position and observed. If the reaction persists or intensifies, consider a subcutaneous injection of 1 mL of atropine 0.4 mg/mL.[215] This safe and effective treatment rapidly reverses the vasovagal reaction and prevents its progression. Although a medical workup is rarely necessary, the reader is referred to an excellent review article on this subject.[216]

UNDERLYING MEDICAL DISEASE

More serious stress-induced problems include exacerbation of certain underlying medical diseases. Patients with a history of asthma may start wheezing, which can be treated with bronchodilator therapy such as metaproterenol sulfate (Alupent from Zydus Pharmaceuticals, Pennington, NJ; Proventil from Merck, Whitehouse Station, NJ) or over-the-counter epinephrine bitartrate or metered-dose inhalers (Primatene; Armstrong Pharmaceuticals, Rancho Cucamonga, CA).

Angina may develop in patients with cardiovascular disease and can be treated with sublingual nitroglycerin (NTG) tablets. As discussed in detail later, POL is a negative inotropic agent and slows cardiac contractility in a dose-dependent manner. Chest pain has also been reported with the use of STS, but this is not cardiac in nature. In our practice, one 65-year-old patient without a history of cardiac disease and treated with STS had acute chest pain on two separate occasions when using 2 to 4 mL of 0.5% STS. An electrocardiogram (ECG) taken immediately while the patient was having chest pain was normal and sublingual NTG was ineffective in resolving the pain, which lasted approximately 5 minutes. This may have been an idiosyncratic reaction.

URTICARIA

Urticaria is easily treated with an oral antihistamine but may be a sign of systemic allergy. Therefore, the use of the sclerosing agent in future treatment sessions should be carefully evaluated. The incidence of urticaria with various sclerosing agents is detailed later. Urticaria has occurred in only one of our patients treated with STS, in over 20 years. It lasted less than 1 hour and resolved with oral diphenhydramine. Subsequent treatment with POL was unremarkable. One of us (RAW) had one patient who developed urticaria secondary to a latex-containing syringe with injection of 3 mL of STS 0.5% liquid. This urticarial reaction also lasted 1 hour, was not accompanied by respiratory symptoms, and resolved with IM epinephrine and oral diphenhydramine.

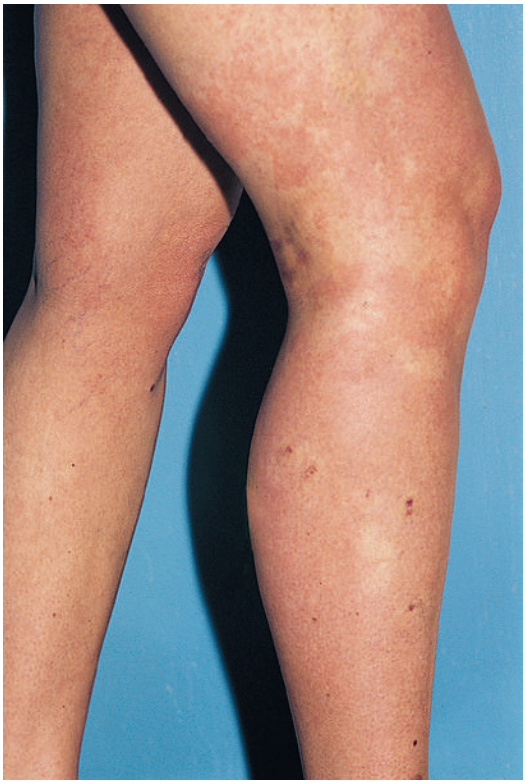


Figure 8.28 One day after sclerotherapy treatment of telangiectasia with application of a 30- to 40-mmHg graduated compression stocking. Note generalized urticarial reaction on the leg treated with the compression stocking. The nontreated leg appears normal.

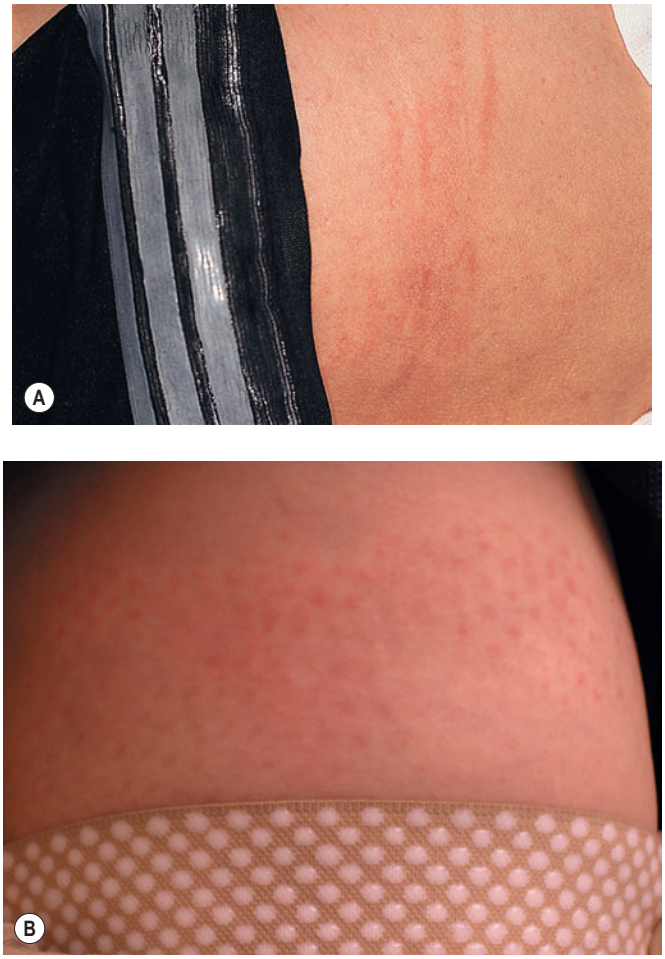


Figure 8.29 **A,** Localized linear erythematous urticarial reaction in similar pattern to the silicone banding on the compression stocking 1 day after application. **B,** Forty-eight hours after application. Note urticarial pattern of silicone beads on the thigh secondary to the compression stocking.

It is intriguing that urticaria and periorbital edema have occurred even with injection of unadulterated HS solution (Duffy DM, personal communication, 1989). This may be related to histamine release from irritated perivascular mast cells.

Rarely, an urticarial reaction has been noted with use of graduated compression stockings. In one patient, a diffuse urticarial eruption occurred under the compression stocking only on the leg treated with sclerotherapy that was compressed with the stocking (Fig. 8.28). This ruled out a systemic reaction from the sclerosing solution, making the most probable cause the compression stocking itself. In another patient, a dermatopathic urticarial reaction was observed in the skin under contact with the silicone band of the compression stocking (Fig. 8.29). Both of these patients did well when a different brand of compression stocking was used. Detailed communication with the stocking company whose product caused the reaction failed to disclose a definite etiologic factor.

LOCALIZED HYPERTRICHOSIS

Localized hypertrichosis developing after sclerotherapy with the use of multiple sclerosing agents has been described. The cause may be multifactorial. The most logical explanation of increased hair growth appears to be improved cutaneous oxygen content. Other factors may also stimulate increased hair growth. A long-standing, low-grade inflammatory reaction may increase vascularity as well as release various cytokines and growth factors. Vascular endothelial growth factor serves as a growth factor for hair follicle dermal papilla cells.[217] Mast cell histamine release is associated with the release of various neuropeptides that may also have a direct effect on the isthmus and bulge region of the hair follicle.[218] Clinically, patients with chronic venous insufficiency have been reported to develop localized hair growth after surgical treatment.[219]

Localized hair growth has been reported from a variety of sclerosing solutions has been reported. Hair growth at the site of injection has been described in three patients treated with STS.[220] All patients were given injections of 1 to 6 mL of STS over 5 to 10 sessions. Localized hair growth developed 4 to 7 months after the last injection. The site of hair growth was related to the area of skin most damaged by venous incompetence. Another report of localized hypertrichosis occurring 9 months after a patient's (second) STS sclerotherapy session was notable in that it is the first published case to our knowledge of this phenomenon occurring after use of the foam technique.[221] Weissberg[222] also reported the development of localized hypertrichosis in 1 of 62 patients treated with STS. The hair growth occurred at the

site of injection 1 month after treatment. It lasted for 4 months and then subsided. A 44-year-old Korean woman also developed localized hypertrichosis on the shin 1 month after sclerotherapy with 3% STS for recurrent varicose veins.[223] Sclerotherapy with polyiodinated iodine has also been associated with hypertrichosis at the injection site in three cases.[209] Two cases of hypertrichosis after sclerotherapy with POL have been noted.[224] Duplex-guided sclerotherapy of the SFJ, as well as sclerotherapy of the posterior arch vein, has also produced temporary hypertrichosis in two patients.[225] Therefore, the sclerosing solution itself is most likely not the cause of localized hypertrichosis; its stimulation of the surrounding microcirculation and/or induction of inflammation produces this effect. Although there are multiple case reports of hypertrichosis, this effect must be very rare because we have seen it in only two patients despite having performed thousands of sclerotherapy treatments over the past 30 years.

COMPLICATIONS

Complications have been observed and described since the very beginning of use of the technique, but their precise incidence remained unclear until.[226–228] The actual number of complications in a collective of sessions including all types of sclerotherapy (liquid, foam, with ultrasound guidance or not; varicose, reticular and spider veins) is presented in Table 8.2. Interestingly, certain complications previously presented as frequent, such as allergy or skin necrosis, have not been observed in this study. This might demonstrate the progress of the technique: improvement in quality of sclerosing agents, improvement in phlebologists' training and subsequent skill, impact of ultrasound guidance and foam sclerosants, better knowledge of indications, and so forth. Regardless, analysis and knowledge of complications is an important part of sclerotherapy.

Table 8.2 Complications Observed in a Prospective French Registry of 12,173 Sclerotherapy Sessions*

	Liquid (*T* = 12)	Foam (*T* = 28)
Immediate Complications		
Anaphylactic shock	–	–
Intra-arterial injections	–	–
Vasovagal fainting (VVF) alone	4	6
Headaches alone	–	–
Paresthesias alone	2	1
Nausea, vomiting alone	1	0
Visual disturbances alone	4	8
Visual disturbances associated with one or more of headache, nausea, VVF	–	8
Others	1	5
	Liquid (*T* = 0)	**Foam (*T* = 9)**
Delayed Complications		
Deep vein thrombosis	–	1
Muscular vein thrombosis	–	1
Muscular vein extension	–	1
Perforating vein thrombosis	–	3
Intense superficial thrombophlebitis	–	3
Skin necrosis	–	–

Adapted from Guex JJ, Allaert FA, Gillet JL, Chleir F. Dermatol Surg 2005;31:123.
*5434 (44.6%) with liquid, 6395 (52.5%) with foam and 344 (2.8%) using both.
T, total number of complications per type of agent form (liquid or foam).

CUTANEOUS NECROSIS

ETIOLOGY

Cutaneous necrosis may occur with the injection of any sclerosing agent, even under ideal circumstances and does not necessarily represent physician error (Fig. 8.30). Fortunately, its occurrence is both rare and usually of limited sequelae. Its cause may be the result of any of the following:

1. Extravasation of a sclerosing solution into the perivascular tissues
2. Injection into a dermal arteriole or an arteriole feeding into a telangiectatic or varicose vein
3. A reactive vasospasm of the vessel
4. Excessive cutaneous pressure created by use of compression techniques

Extravasation

Extravasation of caustic sclerosing solutions may directly destroy tissue. The extent of tissue injury is directly related to both the concentration of the sclerosing solution and the quantity extravasated. As discussed subsequently, different sclerosing solutions have a greater or lesser ability to destroy tissue. Because the final clinical appearance of the skin may not be apparent for several days, therapeutic intervention must be undertaken as soon as possible in all cases.

Clinically, bright erythema is present in the skin overlying the extravasated solution (Fig. 8.31). With certain extravasation injuries, the formation of epidermal blistering may occur but does not predict a partial thickness injury, although it may precede eventual full-thickness necrosis.[229]

During injection of an abnormal vein or telangiectasia, even the most adept physician may inadvertently inject a small quantity of sclerosing solution into the perivascular tissue (Fig. 8.32). A tiny amount of sclerosing solution may be left in the tissue when the needle is withdrawn, and sclerosing solution may leak out of the injected vessel, which has been traumatized by multiple or through-and-through needle punctures. Rarely, the injection of a strong sclerosing solution into a fragile vessel may lead to endothelial necrosis and rupture, producing a 'blowout' of the vessel and perivascular extravasation of sclerosing solution (Fig. 8.33). Therefore, injection technique is an important but not foolproof factor in avoiding this complication, even under optimal circumstances.

Sclerosing solutions vary in the degree of cellular necrosis they produce. If a sclerosing agent causes minimal tissue necrosis, it may perhaps be suitable for perivascular

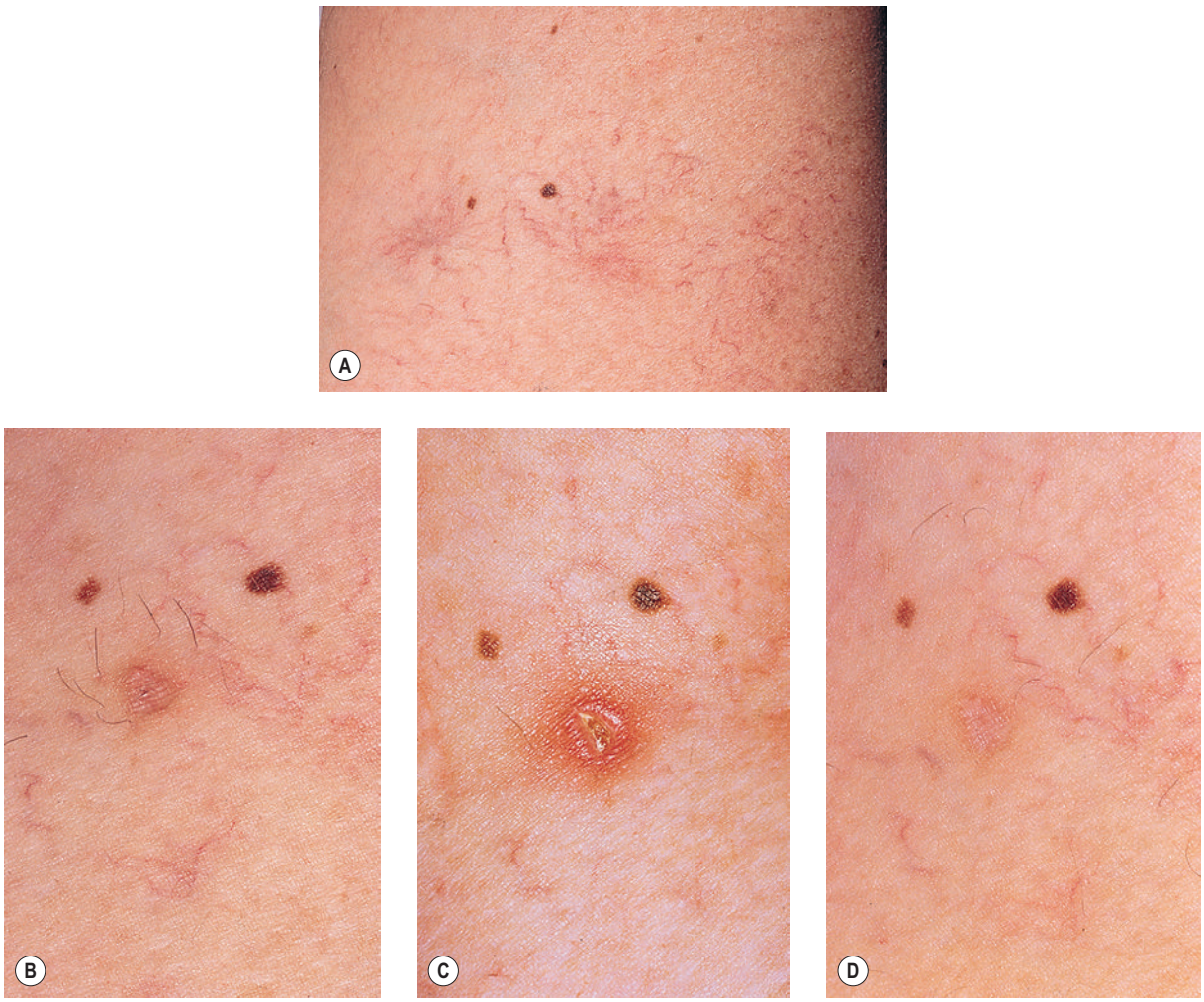


Figure 8.30 Cutaneous necrosis after injection with polidocanol 0.5% into telangiectasia. **A,** Preinjection. **B,** Early atrophie blanche 10 days after injection. **C,** Superficial ulceration is present 5 weeks after injection. **D,** Clinical appearance 24 weeks after injection; complete resolution had occurred in 12 weeks.

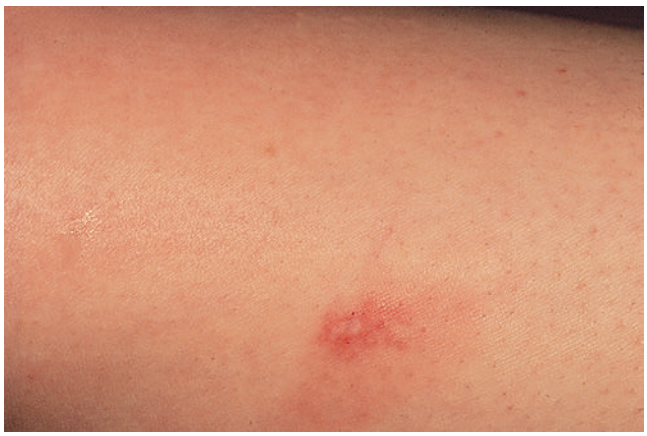


Figure 8.31 Erythema overlying an area of extravasation from injection of a telangiectasia with sodium tetradecyl sulfate 0.25%.

injection in the treatment of telangiectatic mats whose vessels cannot be cannulated even with a 33-gauge needle.

With an osmolality greater than that of serum (281–289 mOsm/L), hyperosmotic agents can cause tissue damage as a result of the osmotic gradient. Epidermal necrosis has even occurred from extravasation of solutions containing 10% dextrose.[230] HS 23.4% is a caustic sclerosing agent, as demonstrated in intradermal injection experiments. Clinically, small punctate spots of superficial epidermal damage occur at points of injection, especially when a small bleb of the solution escapes from the vein. However, subcutaneous injection of up to 1 mL of HS 23.4% (by mistake) in lieu of lidocaine into the neck or cheek has been reported to result in no adverse sequelae.[231] In this situation, cutaneous necrosis was most likely avoided by rapid physiologic dilution of the HS. Alternatively, dermal tissue may be more resistant to the caustic effects of hypertonic solutions. However, the increasing frequency of cutaneous necrosis occurring after extravasation of inadvertent subcutaneous injection of HS moved the U.S. Department of Health and Human Services and the product manufacturer (American Regent, Inc., Shirley, NY) to recommend that HS be stored only in pharmacies where all dilutions would be performed before dispensing. This would eliminate the possibility of an iatrogenic medication error outside the pharmacy (Mary Helenek, American Regent, written communication, May 1990). It is recommended that HS be stored in a location separate from other injectable solutions to prevent this potential complication.

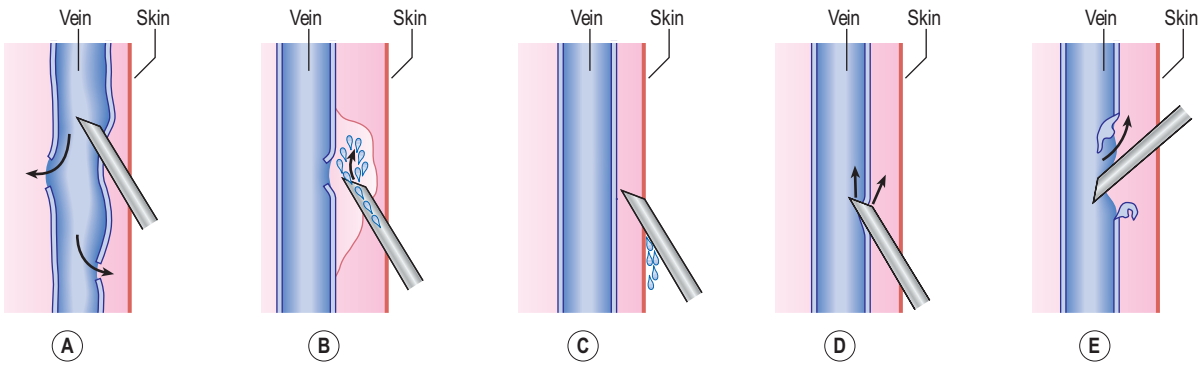


Figure 8.32 Mechanism for extravasation of sclerosing solution. **A,** Extravasation through multiple needle puncture holes. **B,** Extravasation from injection of sclerosing solution after slight withdrawal of the needle. **C,** Extravasation of sclerosing solution along needle shaft. **D,** Extravasation from injection with needle bevel partially in the vein. **E,** Extravasation through excessive destruction of the vein wall. (Redrawn from Biegeleisen HI. Varicose veins, related diseases, and sclerotherapy: a guide for practitioners. Montreal, QC, Canada: Eden Press; 1984.)

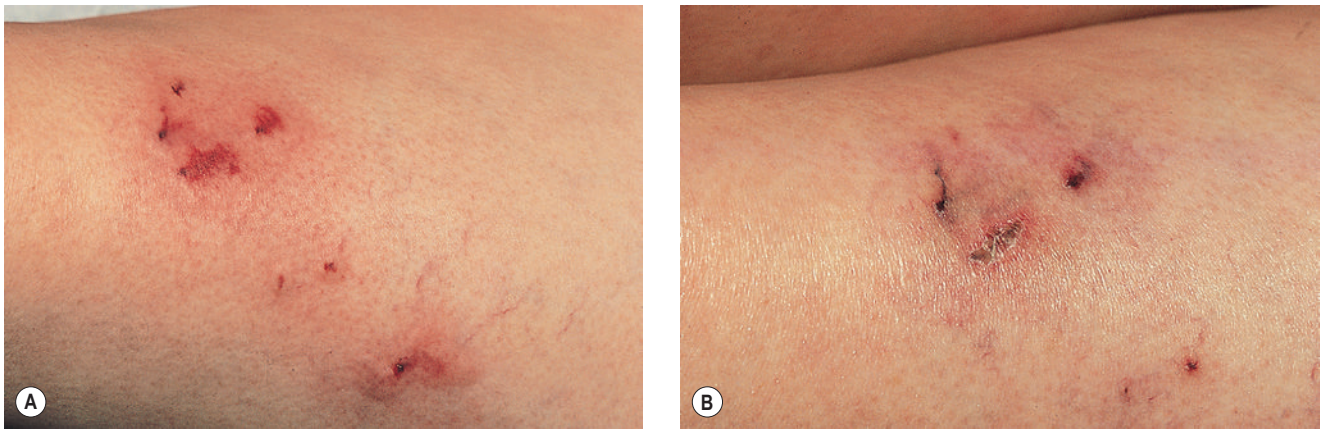


Figure 8.33 Cutaneous necrosis after injection of sodium tetradecyl sulfate 0.5%. **A,** Immediately after injection. Note 'hyperemic burn reaction'. **B,** Necrotic epidermis 2 weeks after injection.

Experimentally, POL apparently is minimally toxic to subcutaneous tissue. Duffy[232,233] reported injecting 0.5 mL of a 3% solution of POL directly into his own forearm skin without the development of an ulceration. Additionally, experimentation on Sprague-Dawley rats revealed that cutaneous necrosis could not be observed with subcutaneous injection of 0.5%, 1%, 2% or 3% POL foam or liquid at volumes less than 0.5 mL.[234] At higher volumes, a minimum concentration of 2% POL foam was required to provoke visible skin necrosis, whereas liquid POL could demonstrate this adverse event at 1% concentration. Although some physicians advocate the use of intradermal POL 0.5% to treat tiny telangiectatic leg veins,[235,236] POL in sufficient concentration causes cutaneous necrosis. Solutions of POL greater than 1.0% may produce superficial necrosis with intradermal injection.[235] This unfortunately occurred in our practice with the mistaken injection of 0.1 mL of POL 5% solution into a leg telangiectasia 0.2 mm in diameter. This injection resulted in extensive overlying cutaneous necrosis that took 8 weeks to heal. Therefore, POL is not without risk of cutaneous necrosis if a strong enough concentration is injected.

Although STS is more toxic to tissue than is POL, with extravasation, concentrations above 0.25% usually are necessary to produce ulceration. Banning[237] reported on the development of ulcerations in 5 of 4860 consecutive patients after telangiectasias were injected with STS 0.1%. As discussed later, this probably represents injection into an arteriole.

Of note, several cases of Nicolau livedoid dermatitis (NLD) following sclerotherapy have been reported.[238–241] Although most commonly seen after IM injections, NLD manifests as pain at the injection site followed by the development of a livedoid plaque, often progressing to cutaneous necrosis. One case of delayed NLD following ultrasound-guided sclerotherapy with POL 2% foam was described in 2010.[241] This particular case was unique in that it not only followed an IV injection but also did not manifest until 4 days after the procedure, when the patient first experienced acute pain followed by subsequent cutaneous ischemia. Interestingly, in each reported case of NLD following sclerotherapy, duplex scans failed to show evidence of thromboses in major arteries or deep veins. The author hypothesized that NLD most likely occurred via perivascular spreading of the sclerosant, after leakage from a site of IV injection. Subsequently, POL probably acted as a local irritant, inducing arterial or arteriolar vasospasm. Concentrations of POL associated with sclerotherapy-induced NLD ranged from 0.5% to 3%, thus not supporting a concentration-dependent phenomenon. One unifying theme among these isolated cases of NLD is that each occurred after injection into veins known to be in close proximity to rich arterial or arteriolar networks. Examples of these at-risk sites include the

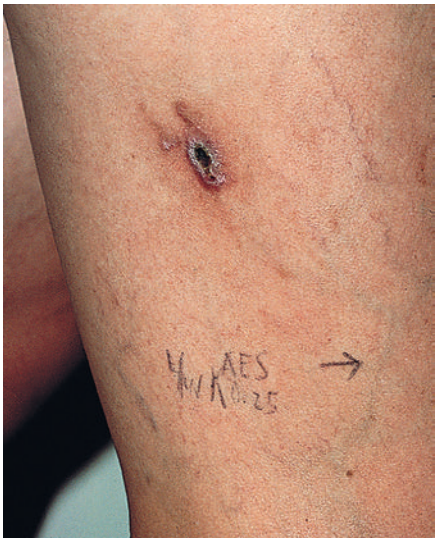


Figure 8.34 Cutaneous necrosis 6 weeks after sclerotherapy with polidocanol 0.25%. Note that 2 mL of solution was injected into a feeder vein approximately 10 cm distal to the necrotic area.

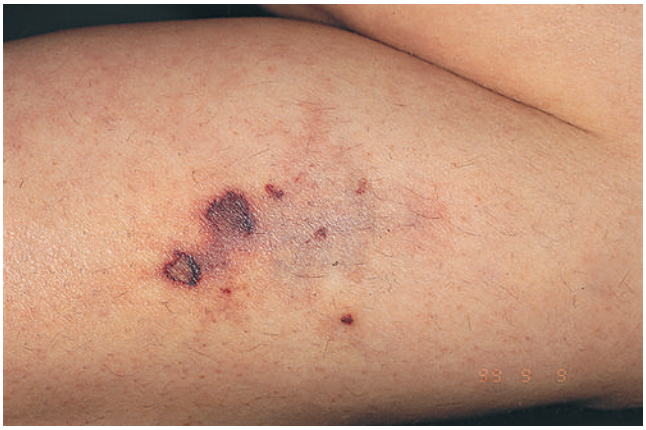


Figure 8.35 A 38-year-old woman who had undergone numerous sclerotherapy treatments with and without ultrasound guidance. The last ultrasound-guided sclerotherapy treatment with sodium tetradecyl sulfate 2% into a perforating vein resulted in immediate blanching of the overlying skin. Nitroglycerin paste was rubbed into the affected area. A 7 × 5–cm dusky blue patch developed 1 week later when the compression stocking was removed, with areas of superficial skin necrosis 2 × 5 mm in diameter. In this instance, the injection was clearly intravenous, even though the effects were those of arterial ischemia. (From Bergan JJ, Weiss RA, Goldman MP. Dermatol Surg 2000;26:535.)

inguinal fold, medial knee and medial ankle. Although the limited number of cases of NLD following sclerotherapy reflects its rarity, the clinician is encouraged to remain aware of this potential complication.

Glycerin or CG solutions have not been reported to produce cutaneous necrosis with extravasation. Duffy (personal communication, 1992) showed that injection of 'full-strength' CG will not produce cutaneous necrosis when it is injected into the mid-dermis. Histologic examination of his patient showed no evidence of dermal or epidermal damage.

Even when sclerotherapy is performed with expert technique using the safest sclerosing solutions and concentrations, cutaneous ulceration may occur (Figs 8.30, 8.34 and 8.35). Therefore, it appears that extravasation of caustic sclerosing solutions alone is not totally responsible for this complication.

Arteriolar Injection

De Faria and Moraes[242] observed that 1 in 26 leg telangiectasias is associated with a dermal arteriole. Bihari and Magyar[243] found pulsatile flow in 68.9% of patients in 16 of 18 biopsies (2.5 × 1.5 cm) taken from pulse-positive telangiectasias in patients demonstrating AV microshunts. This gives a 61% incidence of AV microshunts in patients with leg telangiectasia. An expanded study of 155 patients with leg telangiectasia by the same group demonstrated a 72.2% incidence of pulsatile flow.[244] We believe that the incidence seen in our patients is considerably lower and may represent only 10% or less, and that it might be attributed to a different age or subset of patients or perhaps to the more physiologic conditions seen with Duplex ultrasound rather than biopsy. The higher incidence found in the latter two studies[243,244] is probably caused by the larger biopsy specimens taken. Of the 22 Doppler-positive telangiectasias, 19 demonstrated AV microshunts on biopsy. Thus, it is likely that rapid injection or large-volume injection into leg telangiectasias that are associated with microshunts will force the sclerosing solution into the arterial circulation. It is our opinion that inadvertent injection into or near this communication is the most common cause of cutaneous ulcerations.

It has been shown by Duffy and by our experience that when POL is injected intradermally to effect sclerosis of TM, cutaneous ulceration does not occur, even with the injection of 0.5 mL of a 0.75% solution. However, we have noted the development of 3- to 6-mm diameter ulcerations in approximately 0.0001% of injections with POL 0.5%. Five consecutive ulcerations that appeared over the course of 12 months were excised. In these patients, each cutaneous ulceration developed as a result of occlusion of the feeding dermal arteriole. This produced a classic wedge-shaped arterial ulceration (Fig. 8.36). In the Australian Polidocanol Open Clinical Trial, researchers reported 43 ulcers on 32 legs at 2 years after sclerotherapy of varicose and telangiectatic leg veins on 12,544 legs, for an incidence of 0.23%.[245] Therefore, it appears that rare cases of small ulcerations may be unavoidable to some extent, especially in the pretibial and malleolar areas.

Interestingly, since we started using glycerin solution in a 72% concentration mixed 2:1 with lidocaine 1% with or without epinephrine 1:100,000, we have not seen ulcerations at all. The safety of glycerin may be its high viscosity, which prevents the solution from flowing into arteriole connections. Alternatively, the epinephrine mixed into the solution may put the arteriolar portion of the AV anastomosis into spasm and/or the lidocaine portion may vasodilate and protect the arteriolar portion of the AV anastomosis, or the actual incidence of AV anastomosis may be much lower than estimated.

Vasospasm

Rarely, after injection of the sclerosing solution, an immediate porcelain white appearance is noted at the site of injection (Fig. 8.37). A hemorrhagic bulla usually forms over this

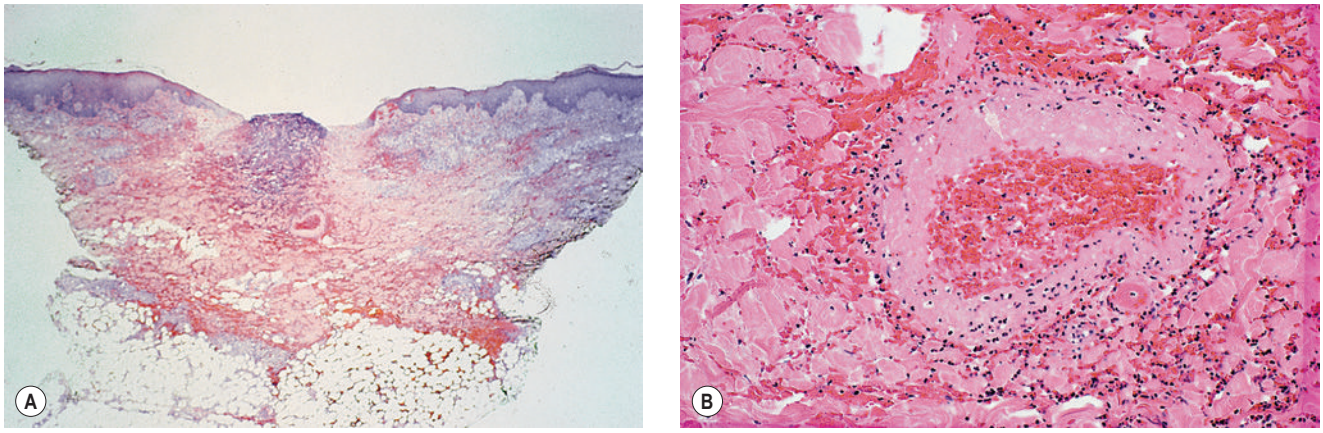


Figure 8.36 **A,** Low-power view showing skin ulceration and focal inflammation extending into the subcutaneous fat. A thrombosed vessel, most likely an artery, is present directly under the area of necrosis (hematoxylin–eosin stain; original magnification ×25). **B,** Higher magnification of the same area shown in **A,** depicting a thrombosed artery that caused the infarct. The arterial lumen is completely occluded by fresh thrombus (hematoxylin–eosin stain; original magnification ×200).

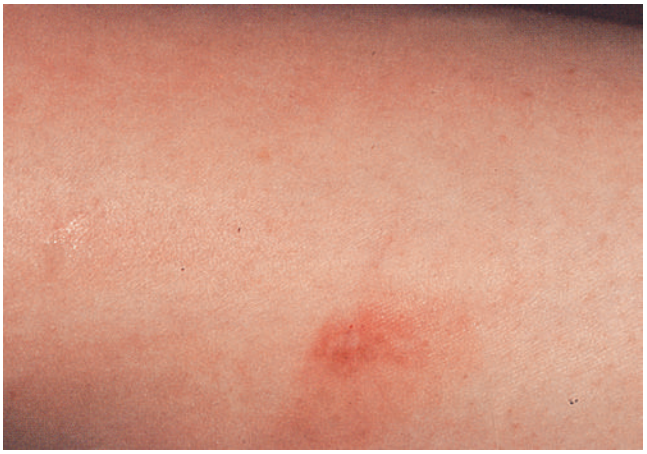


Figure 8.37 Porcelain white cutaneous reaction immediately after injection with polidocanol 0.25%. This area progressed into a punctate cutaneous ulceration.

area within 2 to 48 hours (Fig. 8.38) and progresses to an ulcer.[87] This cutaneous reaction might represent an arterial spasm. Duffy[234] reported this effect when injecting facial telangiectasia.

Vasospastic reactions of arteries occur in predisposed individuals for unknown reasons.[246–248] This may occur even with puncture of the artery without injection of sclerosing solution.[248] Thus, small vessels, when irritated in susceptible patients, may spasm.

In an attempt to reverse the spasm, vigorous massage when the white macule appears usually prevents the development of ulceration. However, prevention of the ulceration with massage alone is not always successful. Massaging in a NTG ointment 2% is more likely to prevent the development of ulcerations in this setting.

The major systemic action of nitrates is a direct reduction in venous smooth muscle tone.[249] Nitrates also relieve spasm of angiographically normal and diseased arteries.[250] Topical NTG ointment has been reported as beneficial in treating both dopamine extravasation and vasoconstriction necrosis.[251,252] Although more experience needs to be reported by other investigators, it seems prudent to use this technique.

Another technique that may help in reversing vasospasm is the topical application of nitric oxide–generating gel. This gel has been found to increase baseline blood flow in the fingers of patients with Raynaud's syndrome.[253] Because patients with Raynaud's syndrome have abnormal digital vasoconstriction, the improvement found in application of this gel may cross over to potential improvement in sclerotherapy-induced vasospasm. The gel is prepared by mixing a solution of K-Y jelly (Reckitt Benckiser, Parsippany, NJ) and sodium nitrate (5% weight per volume [wt/vol]) with a solution of K-Y jelly and ascorbic acid (55% wt/vol).

Arterial spasm also may explain the development of cutaneous ulceration upstream from the injection site (see Fig. 8.34). In this latter case, 2 mL of POL 0.25% was injected into a feeding reticular vein (*arrow,* Fig. 8.34). That was the only injection given to the patient in that sclerotherapy session. This has also been reported by Rabe and termed *embolia cutis medicamentosa.*[254]

Lymphatic Injection

Injection into a lymphatic vessel also may lead to cutaneous necrosis. Histologic studies have disclosed evidence of lymphovenous anastomoses in humans.[255] It is possible that injection into such an anastomosis could result in necrosis of the associated lymphatic vessel and infiltration of the sclerosing solution extravascularly. If the sclerosing solution is caustic to extravascular tissues, tissue necrosis may result.

Subcutaneous Injection

Parmentier observed a case of necrotizing panniculitis after an accidental, large-volume subcutaneous injection of 0.5% POL.[241] We have seen a similar patient develop a small necrotizing panniculitis after injection with HS (Fig. 8.39).

Excessive Localized Compression

Excessive compression of the skin overlying the treated vein may produce tissue anoxia with the development of localized cutaneous ulceration (Fig. 8.40). Subcutaneous tissue flow in the leg is decreased when cutaneous pressure exceeds 20 mmHg.[256] In addition, external pressure greater than 30 mmHg reduces muscle blood flow in some patients.[257] Therefore, excessive compression may produce

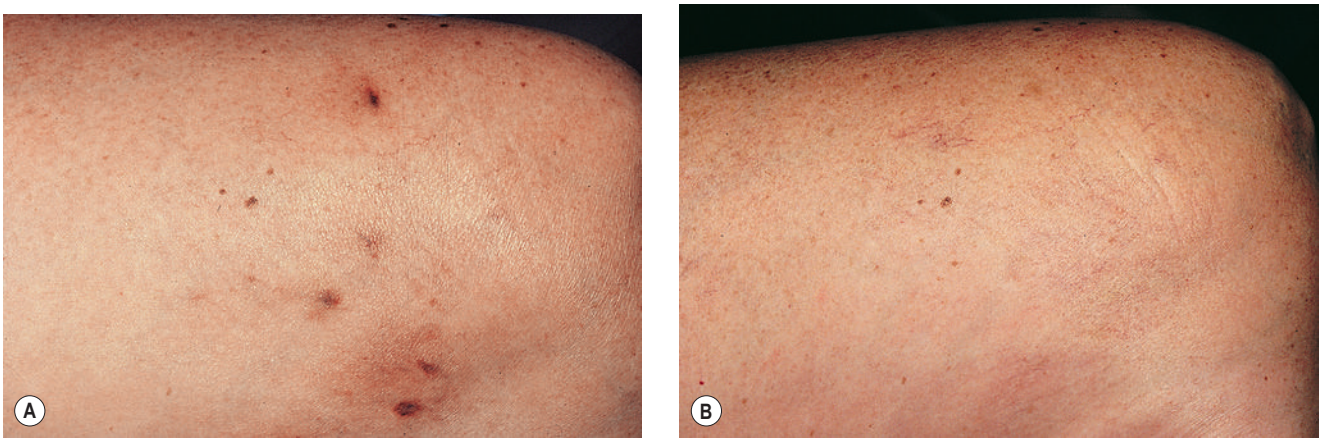


Figure 8.38 **A,** Hemorrhagic macular reaction 1 week after injection with polidocanol 0.5%. **B,** Appearance after 2 months. This area healed without any complication.

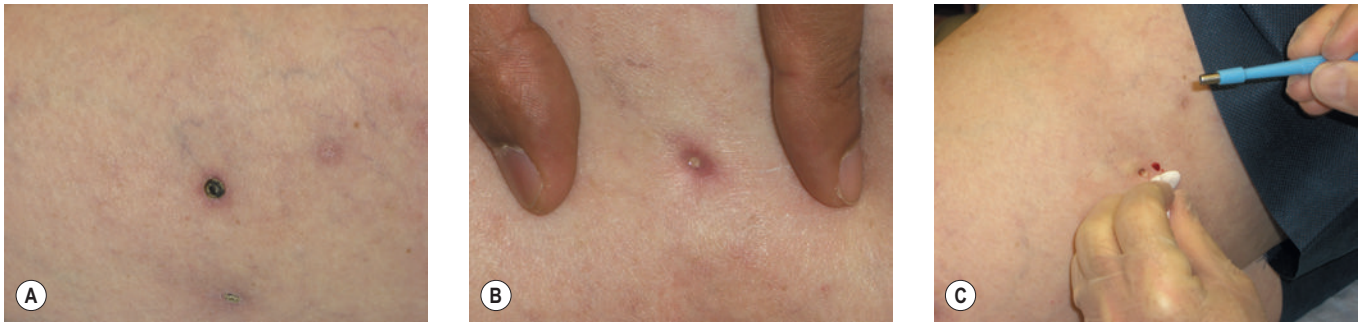


Figure 8.39 **A,** A 55-year-old woman who developed a nonhealing ulceration 6 months after treatment by a nonsupervised cardiac catheterization nurse with hypertonic saline for leg telangiectasia. There is necrotic debris within the ulceration. **B,** Removal of the necrotic debris shows extrusion of adipose tissue. **C,** Excision of the necrotic area with a 4-mm surgical punch closed with a 5-0 nylon suture resulted in rapid healing over 2 weeks with minimal scarring. Pathologic examination was remarkable only for necrotic adipose tissue with a mixed inflammatory infiltrate.

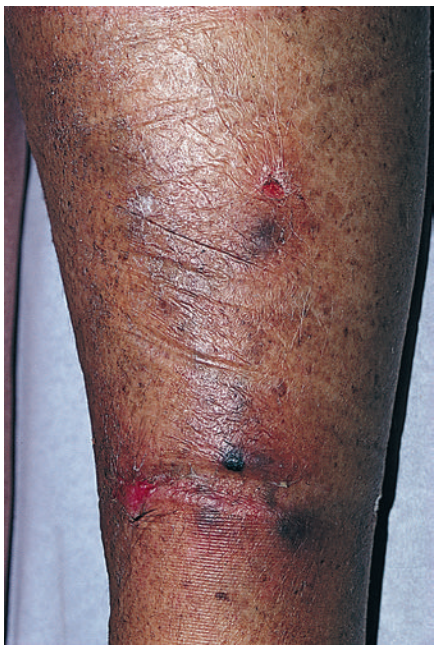


Figure 8.40 Cutaneous ulceration developed 2 days after application of a compression bandage in a nongraduated manner.

tissue ischemia. However, two studies[256,257] used indirect measurements of subcutaneous tissue flow and calf muscle blood flow and thus must be interpreted with caution. A more physiologic method for measuring the effect of compression on blood flow was performed through determination of femoral blood flow.[258] The authors who reported using this method demonstrated that in the recumbent patient, static, graduated external compression of approximately 20 mmHg at the ankle, reduced to approximately 10 mmHg in the upper thigh, produces an increase in femoral flow of up to 75%. However, if calf pressures exceed 30 mmHg when the patient is recumbent, a progressive decrease in subcutaneous tissue flow and deep venous velocity occurs. Therefore, it is recommended that patients not wear a graduated compression stocking of greater than 30 to 40 mmHg when lying down for prolonged periods.

One method for applying compression to treated veins that could be varied with patient position consists of a double layer of graduated compression stockings. This ensures that maximal pressure over the vein is maintained while the patient is ambulatory. When the patient is recumbent, the outer stocking is removed, thereby decreasing the cutaneous pressure to 20 to 30 mmHg at the ankle, which should prevent a reduction in cutaneous and subcutaneous

blood flow. Another method described in Chapter 6 is to use foam or rolled cotton wool directly over the treated varicose vein, which increases the pressure applied by the foam by over 50%.

Hypercoagulable State

Two separate case reports of ulceration following sclerotherapy with appropriate concentrations and amounts of STS and POL into leg telangiectasias have been reported, with both patients having an underlying hypercoagulable state.[259,260] In the first patient, a mutation in factor V Leiden was uncovered and in the second, a primary antiphospholipid syndrome. Interestingly, these patients, 45 and 49 years old, had no previous history of ulcerations until undergoing sclerotherapy. The hypercoagulable states in these women promoted excessive thrombosis in perivenous arterioles, causing cutaneous ulcerations.

Although we are not recommending that all patients be screened for hypercoagulable states before sclerotherapy, this should be looked for in the rare patient who develops unexplained ulceration after treatment.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an inflammatory skin condition that results in the development of an ulcer at sites of minor trauma and in surgical wounds. It is usually associated with autoimmune conditions, such as inflammatory bowel disease and hematologic malignancies, but it may also be idiopathic. There is one report of the development of a 1.5-cm painful ulceration 4 weeks after ultrasound-guided sclerotherapy to the great saphenous vein (GSV) and anterior thigh circumflex vein in a patient with a past history of PG.[261] This resolved after treatment with systemic prednisone as well as a topical steroid. Therefore, sclerotherapy should be undertaken carefully in patients with a history of PG, and nonhealing ulcerations after sclerotherapy should be evaluated by a dermatologist to rule out other etiologies.

PREVENTION

If extravasation of sclerosing solution occurs, the solution must be diluted as soon as possible. Hypertonic solutions should be diluted with copious amounts of normal saline solution. At least 10 times the volume of extravasated solution should be injected to limit osmotic damage.

Detergent sclerosing solutions of adequate strength also may be toxic to tissues. Dilution is again of paramount importance. Dilution with hyaluronidase in normal saline solution limits the extent and prevents development of cutaneous necrosis from STS 3%.[262] Hyaluronidase (Wydase, lyophilized, 150 USP U/mL) enzymatically breaks down hyaluronic acid in connective tissue. This is hypothesized to disrupt the normal interstitial fluid barrier to allow rapid diffusion of solution through tissues, thereby increasing the effective absorption.[263,264] This beneficial effect has been demonstrated in limited IV extravasation injuries from 10% dextrose, calcium and potassium salts, contrast media, sodium bicarbonate, aminophylline, hyperalimentation solution and doxorubicin.[263,265–268] In addition to its enhanced dilutional ability, hyaluronidase may have an independent cellular preservation function.

Hyaluronidase injection improves skin flap survival[269] and reduces myocardial infarction.[270] This has been postulated to occur through enhanced nutritive flow. Enhanced healing with resolution of painful induration was observed when 250 U of hyaluronidase was injected in an area where neoarsphenamine and oxophenarsine (mapharsen) were extravasated subcutaneously.[271] Hyaluronidase also promotes wound repair in fetal skin, contributing to scarless repair of wounds by as-of-yet unclear mechanisms.[272] In summary, accelerated dilution, cellular stabilization and wound repair properties of hyaluronidase appear useful in preventing cutaneous necrosis from inadvertent sclerosing solution extravasation.

Side effects from hyaluronidase use are rare and generally of the urticarial type.[273,274] Because of its limited stability, it should be reconstituted with 0.9% sodium chloride solution immediately before use. The ideal concentration and quantity to inject after extravasation have been reported to be 75 U in a volume of 3 mL. Higher doses did not appear to improve clinical outcome after intradermal infiltration of 0.25 mL of HS 23.4%.[275] For maximum effectiveness, we recommend injecting the diluted solution into multiple sites around the extravasated area. Studies have demonstrated that hyaluronidase solution must be injected within 60 minutes of extravasation to be effective.[276]

TREATMENT

Whatever the cause of the ulceration, it must be dealt with when it occurs. Fortunately, ulcerations, when they do occur, are usually fairly small, averaging 4 mm in diameter in our practice. At this size, primary healing usually leaves an acceptable scar (Fig. 8.41). In addition to various topical therapies applied directly to the ulcer, elevation of the affected extremity and systemic pentoxifylline may be helpful in minimizing the ulcer size. In a series of 26 extravasation sloughs, less tissue damage occurred when limbs were elevated.[276]

Pentoxifylline may decrease tissue injury of ischemia–reperfusion by inhibiting the production of platelet-activating factor during reperfusion.[278] Pentoxifylline should improve microcirculatory dysfunction observed during reperfusion of ischemic tissues. Pentoxifylline causes increased deformability of RBCs and decreased blood viscosity.[279–281] From experimental studies in the canine gracilis muscle model, the optimal dose for protective effects appears to be 25 mg/kg. However, the dose that produces maximal protective effects in humans is unknown.

Bodian,[120] who uses HS 23.4%, notes that ulceration usually takes 3½ months to heal, even when judicious wound care is provided. He advocates treatment with a daily application of 20% benzoyl peroxide powder (Vanoxide Acne Lotion; Summers Laboratories, Hatfield, PA) under moist dressings cut to fit snugly over the ulcer. However, benzoyl peroxide is cytotoxic for newly growing epidermis and therefore cannot be recommended by us. We have found that the use of occlusive or hydrocolloid dressings results in an apparent decrease in wound healing time. Occlusive dressings do not speed healing of full-thickness ulcers until granulation tissue has formed. Hydrocolloid gel dressings enhance debridement of wounds, possibly through their pectin-gelatin base. Nongelatin, nonpectin hydrocolloid dressings act only to stimulate fibrin lysis. Thus, hydrocolloid dressings enhanced efficacy may be related to wound debridement, which should always be used either medically

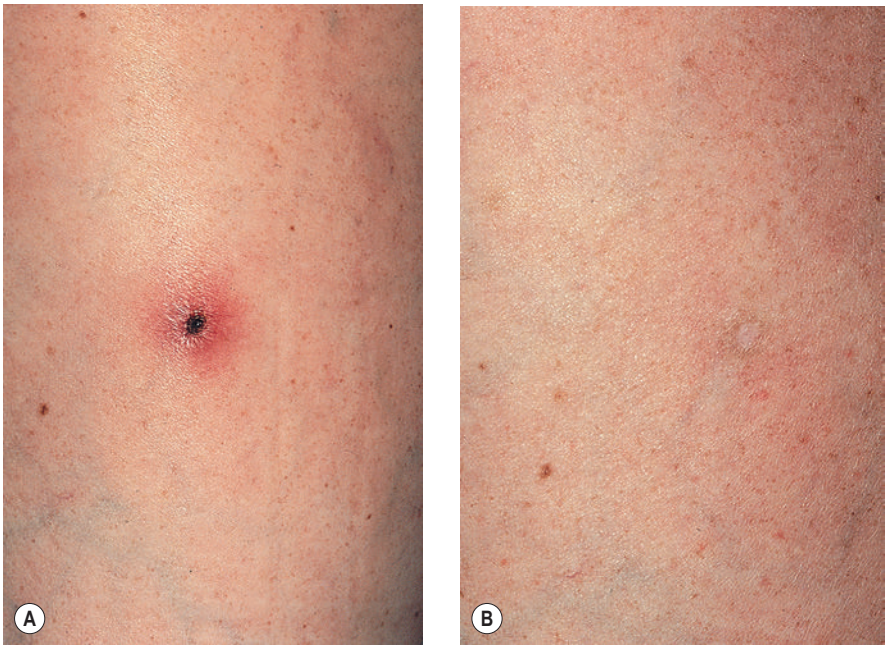


Figure 8.41 Cutaneous ulceration on the posterolateral thigh. **A,** Three weeks after treatment with polidocanol 0.5%. **B,** After 6 months. Treatment consisted of a duoderm dressing that was changed every 4 days until complete healing occurred in 5 weeks. Note the cosmetically acceptable stellate scar.

or surgically to promote granulation tissue formation. More important, the use of occlusive dressings decreases the pain associated with an open ulcer. Dressings must be changed every 3 to 4 days, and necrotic tissue should be sharply debrided every week or two, as needed, to promote granulation tissue.

However, because an ulcer may take 4 to 6 weeks to heal completely, even under ideal conditions, excision and closure of these lesions, if possible, are recommended at the earliest possible time. This affords the patient the fastest healing and an acceptable scar.

SYSTEMIC ALLERGIC REACTION OR TOXICITY

Systemic reactions caused by sclerotherapy occur very rarely.

MINOR REACTIONS

Minor reactions such as urticaria are easily treated with an oral antihistamine such as diphenhydramine (Benadryl; McNeil Consumer Healthcare, Fort Washington, PA), 25 to 50 mg by mouth or hydroxyzine (Atarax; Pfizer, New York, NY), 10 to 25 mg by mouth. Rarely, the addition of corticosteroids is needed if the reaction does not subside readily. A short course of prednisone, 40 to 60 mg/day for 1 week, in conjunction with systemic antihistamine every 6 to 8 hours is helpful. Suppression of the adrenal axis is not a problem with this short course, so a tapering schedule is not necessary.

Because of the possibility of angioedema or bronchospasm, each patient with evidence of an allergic reaction should be examined for stridor and wheezing by auscultating over the neck and chest while the patient breathes normally. Supine and sitting blood pressure and pulse should be checked to rule out orthostatic changes, hypotension or tachycardia that might result from the vasodilation that precedes anaphylactic shock.

Minor degrees of angioedema can be treated with oral antihistamines; however, if stridor is present, an IM injection of diphenhydramine and IV corticosteroids should be administered and a laryngoscope and endotracheal tube should be available.

Bronchospasm has been estimated to occur after sclerotherapy in 0.001% of patients.[8] It usually responds to the addition of an inhaled bronchodilator or IV aminophylline, 6 mg/kg over 20 minutes or to the antihistamine and corticosteroid regimen already noted.

Wheezing has been reported to occur in up to 5% of patients treated with HS solution (Michael Coverman, personal communication, 1991). Coverman reported wheezing that occurs 15 minutes after the completion of sclerotherapy and resolves spontaneously. He found that wheezing ceases if treatment sessions are performed with the patient sitting at a 45-degree angle. This probably is not an allergic reaction but an irritant phenomenon on the airways. Alternatively, it may be related to rapid infusion of histamine from perivascular mast cell degranulation with damage from the hyperosmotic solution.

MAJOR REACTIONS

Four types of potentially serious systemic reactions specific to the type of sclerosing agent have been noted: anaphylaxis, pulmonary toxicity, cardiac toxicity and renal toxicity. These reactions are discussed both in general and separately for each sclerosing solution.

Anaphylaxis is a systemic hypersensitivity response caused by exposure or, more commonly, re-exposure to a sensitizing substance. Anaphylaxis is usually an immunoglobulin E (IgE)–mediated, mast cell–activated reaction that occurs most often within minutes of antigen exposure. Other classes of immunoglobulin, such as IgG, may also produce anaphylaxis.[282] Because the risk of anaphylaxis increases with repeated exposures to the antigen, one should always be prepared for this reaction in every patient.[283]

The principal manifestations of anaphylaxis occur in areas where mast cell concentrations are highest: skin, lungs and gastrointestinal (GI) tract. Histamine release is

responsible for the clinical manifestations of this reaction. Although urticaria and abdominal pain are common, the three principal manifestations of anaphylaxis are airway edema, bronchospasm and vascular collapse. Urticaria alone does not constitute anaphylaxis and should not be treated as such because of the potential side effects of treatment with epinephrine, especially in older patients.

The signs and symptoms of anaphylaxis initially may be subtle and often include anxiety, itching, sneezing, coughing, urticaria and angioedema. Wheezing may be accompanied by hoarseness of the voice and vomiting. Shortly after these presenting signs, breathing becomes more difficult and the patient usually collapses from cardiovascular failure resulting from systemic vasodilation. One helpful clue in distinguishing between anaphylaxis and vasovagal reactions is heart rate. Sinus tachycardia is almost always present in a patient with anaphylaxis, whereas bradycardia or cardiac rhythm disturbances are commonplace in vasovagal reactions.

The recommended treatment is epinephrine (adrenaline), 0.2 to 0.5 mL at 1:1000 subcutaneously. This can be repeated three or four times at 5- to 15-minute intervals to maintain a systolic blood pressure above 90 to 100 mmHg. This should be followed with establishment of an IV line of 0.9% sodium chloride solution. Diphenhydramine hydrochloride 50 mg is given next, along with cimetidine 300 mg; both the IV solution and oxygen are given at 4 to 6 L/min. An endotracheal tube or tracheotomy is necessary for laryngeal obstruction. For asthma or wheezing, IV theophylline 4 to 6 mg/kg is infused over 15 minutes. At this point, it is appropriate to transfer the patient to the hospital. Methylprednisolone sodium succinate 60 mg is given intravenously and repeated every 6 hours for four doses. Corticosteroids are not an emergency medication, because their effect appears only after 1 to 3 hours. They are given to prevent the recurrence of symptoms 3 to 8 hours after the initial event. The patient should be hospitalized overnight for observation.

ALLERGIC REACTIONS TO SCLEROSING AGENTS

SODIUM MORRHUATE

Although promoted by the manufacturer as 'the natural sclerosing agent', sodium morrhuate causes a variety of allergic reactions, ranging from mild erythema with pruritus[284–286] to generalized urticaria[286–288] to GI disturbances with abdominal pain and diarrhea[284,285] to anaphylaxis. It has been estimated that 'unfavorable reactions' from treatment of varicose leg veins occur in 3% of patients.[289] The incidence of allergic reactions in the treatment of esophageal varices ranges from 11% to 48%.[290] The reason for the high number of allergic reactions associated with use of this product may be related to the inability to remove all the fish proteins present in sodium morrhuate. In fact, 20.8% of the fatty acid composition of the solution is unknown.[291]

Many cases of anaphylaxis have occurred within a few minutes after injection or, more commonly, when therapy is reinstituted after a few weeks.[286,292–294] Most of these cases occurred before 1950. Rarely, anaphylaxis has resulted in fatalities,[288,289,295] many of which have not been reported in the medical literature.[284]

Bronchospasm developed in one patient while being treated with a twelfth injection under anesthesia. This responded readily to antihistamine and epinephrine. The patient was subsequently treated with STS without an adverse reaction.[296]

Pleural effusions with pulmonary edema and acute respiratory failure appearing as acute respiratory distress syndrome (ARDS) are common with esophageal injection.[291] It has been estimated that pleural effusions occur in 46% of patients with an esophageal injection.[297] With injection into esophageal varices, the sclerosing solution rapidly enters the pulmonary circulation, causing increased permeability of the pulmonary microvasculature.[291] There have been no reports of pleural effusions with injection into varicose veins of the legs.

Prolonged dysrhythmia requiring placement of a permanent pacemaker has been reported in two cases.[298] This complication has been attributed to a direct cardiotoxic effect of sodium morrhuate.

ETHANOLAMINE OLEATE

EO (Ethamolin; QOL Medical, Vero Beach, FL) is a synthetic mixture of ethanolamine and oleic acid with an empirical formula of $C_{20}H_{41}NO_3$. It is a salt of an unsaturated fatty acid that acts as a sclerosant when administered intravenously.[299] The minimal lethal IV dose in rabbits is 130 mg/kg.[282] The oleic acid component is responsible for the inflammatory action. Oleic acid may also activate coagulation in vitro by release of tissue factor and Hageman factor. Biegeleisen[300] observed no toxic effects in 500 injections, and EO is thought to have a lesser risk than sodium morrhuate or STS of causing allergic reactions.[301] However, pulmonary toxicity and allergic reactions have been associated with this sclerosing agent.

Pleural effusion, edema and infiltration and pneumonitis have been demonstrated in human trials with the injection of esophageal varices. Pleural effusion or infiltration has been estimated by the product manufacturer to occur in 2.1% of patients and pneumonia in 1.2% of patients. One study of 75 patients treated for esophageal varices disclosed abnormal chest x-ray films showing infiltration or effusion in 45 patients, for an incidence of 60%.[302] These conditions usually resolve spontaneously within 48 hours.[302]

Glaxo reported anaphylactic shock after ethanolamine oleate injection in three cases.[303] Another case of a nearly fatal anaphylactic reaction during a fourth treatment of varicose leg veins with 1 mL of solution has also been reported.[304] In one additional case, a fatal reaction occurred in a man with a known allergic disposition.[303] Another episode of a fatal anaphylactic reaction occurred in a woman having her third series of injections.[284] This represented one reaction in 200 patients in that author's practice. Generalized urticaria occurred in approximately 1 in 400 patients; this symptom responded rapidly to an antihistamine.[305]

Acute renal failure with spontaneous recovery occurred after injection of 15 to 20 mL of EO in two women.[306] A hemolytic reaction occurred in five patients in a series of over 900 patients, with injection of over 12 mL of 0.5% EO per patient per treatment session.[305] The patients were described as 'having pain in the loins and passing red–brown urine. All rapidly recovered with bed rest and were

perfectly normal the next day.' Injections of less than 12 mL per treatment session have not caused this reaction.

Transient chest pain also has been reported in 13 of 23 patients treated for esophageal varices.[307] However, pyrexia and substernal chest pain are considered common sequelae of esophageal varices injection with any sclerosing agent.[301]

The EO mixture has also been tested for carcinogenic activity in the albino rat by intradermal injection without induction of tumors.[307] In 2010, EO was found to be a successful sclerosing agent in 21 patients treated for reactive vascular lesions.[308] Interestingly, the authors of that study found that pain developed when the sclerosant permeated the normal dermis before leaking out through the epidermis, and thus they stopped the injections at the first sign of pain development.

SODIUM TETRADECYL SULFATE

A synthetic detergent developed in the 1940s, STS has been used throughout the world as a sclerosing solution. In a comprehensive review of the medical literature (in multiple specialties and languages) through 1987, researchers found a total of 47 cases of nonfatal allergic reactions in a review of 14,404 treated patients; this included six case reports.[310] The authors of a separate review of treatment in 187 patients with 2249 injections reported no evidence of allergic or systemic reactions.[311] In an additional report of 5341 injections given to an unknown number of patients, researchers found 'no unfavorable reaction'.[312] Fegan[313] reviewed his experience with STS in 16,000 patients. He reported 15 cases of 'serum sickness, with hot, stinging pain in the skin and an erythematous rash developing 30 to 90 minutes after injection'. These patients subsequently underwent additional uneventful treatment with STS after premedication with antihistamines. In 10 additional patients, 'mild anaphylaxis' developed that required treatment with an injection of epinephrine. If one were to combine only those reviews of over 1000 patients, the incidence of nonfatal allergic reactions would be approximately 0.3%.[9,305,314–316]

Mylan Pharma Group (Canonsburg, PA), the manufacturer of Sotradecol, notes at least six fatalities associated with the use of Sotradecol, two from the sclerotherapy procedure itself and not specifically related to STS. One fatality occurred in a patient who was receiving an antiovulatory agent. Another death (fatal pulmonary embolism) was reported in a 36-year-old woman who was not taking oral contraceptives. Bioniche Pharma Group, as Mylan was formerly known, was also required through a warning letter issued by the Food and Drug Administration (FDA) to disseminate information to providers regarding four of the six fatalities related to Sotradecol administration, which resulted from anaphylactic shock after sclerotherapy with STS.[317] One of the four patients had an underlying history of asthma, which is a contraindication to the administration of Sotradecol. Similarly, four deaths attributed to anaphylactoid reactions were reported to the Committee on Safety of Medicines for the United Kingdom between 1963 and 1988, with 22 nonfatal allergic reactions such as urticaria noted over the same period.[318]

A fatality was reported after a test dose of 0.5 mL of STS 0.5% was given to a 64-year-old woman.[319] An autopsy performed by the Hennipin County, Minnesota, Coroner's Office revealed no obvious cause of death. Subsequently, mast cell tryptase studies were performed on blood collected approximately 1 hour after the reaction while the patient was receiving life support. A normal tryptase level is less than 5 ng/mL; in experimental anaphylactic reactions induced in the laboratory, levels up to 80 ng/mL have been observed. In this patient, the levels were extremely high at 6000 ng/mL, suggesting that an anaphylactoid reaction caused her death. Because all reported cases of allergic reactions are of the IgE-mediated immediate hypersensitivity type, it is recommended that patients remain in or near the office for 30 minutes after sclerotherapy when STS is used. However, allergic reactions also may develop hours or days after the procedure.[316,320] For example, urticaria occurred 8 hours after treatment in one patient[320] and 2 weeks after treatment in two other patients.[316] Therefore, patients should be warned about the possibility of allergic reactions and how to obtain care should a reaction occur. In a review of 2300 patients treated over 16 years, four cases of allergic reactions were reported (0.17% incidence).[321] Reactions in that study were described as periorbital swelling in one patient and urticaria in three. All reactions were easily treated with oral antihistamines. It is of interest that French phlebologists have advocated a 3-days-before and 3-days-after treatment course with an antihistamine. P. Flurie noted no episodes of allergic reactions in 500 patients treated in this manner.[322]

In a 2-year prospective study of 2665 patients treated with STS by Thibault,[323] there were four cases of anaphylactoid reactions (0.15%). These occurred 10 to 30 minutes after injection of 3% solution, with patients having facial flushing; urticaria; dizziness; tachycardia; shortness of breath; and, finally, GI symptoms of nausea, vomiting and abdominal pain. All four patients responded well to a subcutaneous injection of 0.5 mL of 1:1000 epinephrine followed by IM promethazine HCl 25 to 50 mg. Urticaria occurred in an additional two patients (0.07%).

Between August 1985 and January 1990, 37 reports of adverse reactions to STS, including five cases of suspected anaphylaxis and two cases of asthma induced by injection, were reported to the Drug Experience Monitoring Program of the FDA. One of the cases of anaphylaxis resulted in a death previously discussed. After a detailed review, it is unclear to us whether anaphylaxis indeed occurred in every reported case.

The reports of the Clinical Drug Safety Surveillance Group of Wyeth-Ayerst Laboratories (Collegeville, PA), the prior manufacturer of Sotradecol are compiled from voluntary reporting to the manufacturer or the FDA, or both. The following are summaries of those reports. In the period from January to July 1991, disclosures were one episode of erythema multiforme; one episode of ARDS; one episode of fever, lymphadenopathy and rash; and three episodes of abdominal pain, nausea, vomiting and diarrhea. The case report of erythema multiforme was reported in a woman after her 13th sclerotherapy treatment.[324] Pruritus developed the morning after the last injection, with a generalized eruption beginning on the legs 4 days later. This was followed by fever the following day. A rapid tapering course of oral prednisone was given, with complete resolution of the rash in 2 weeks. From September 1991 to November 1992, there were five reports of urticaria and one episode of ARDS. From December 1992 to September 1993, there was

only one case of a maculopapular rash. From September 1993 through October 1994, there was one case of angioedema, and generalized weakness was reported in one patient after receiving 10 mL of 3% STS. From November 1994 through January 1996, there was one case of anaphylaxis. From January 1996 through December 1996, there was one case of allergic vasculitis. From November 1997 through October 1999, there were three cases of urticaria and four cases of nonspecific hypersensitivity reactions. These reactions voluntarily reported to Wyeth-Ayerst occurred with approximately 500,000 units of 2-mL ampules of 1% and 3% being sold yearly within the United States. Thus, the incidence of adverse reactions is rare. (Most information regarding adverse reactions to Sotradecol was provided by Paul Minicozzi, Ph.D., Wyeth-Ayerst Laboratories, through yearly correspondence.)

A similar low experience with adverse reactions was reported by STD Pharmaceutical Products (Hereford, UK), the manufacturer of Fibrovein (correspondence from Robert Gardiner, Hereford, UK, March 1995, and the Adverse Drug Reaction Information Tracking Product Analysis from the Medicines Control Agency of Great Britain). The adverse drug reactions reported in the United Kingdom between 1963 and 1993 were one nonspecific allergic reaction, two cases of anaphylactic shock, six cases of GI disorder, two cases of bronchospasm, four patients with a nonspecific cutaneous eruption and two patients with urticaria. This summary comprised 30 years, during which time an estimated 7.2 million mL of STD 1% and 3% was sold within the United Kingdom. In the French registry of 12,173 sessions of sclerotherapy, no allergic reaction has been reported.[228] In France, sclerosing agents used are STS, POL and CG.

The most common systemic reaction consists of transient low-grade fever and chills lasting up to 24 hours after treatment.[325] This has also been seen in one of our patients. Of note is that three patients with allergic systemic reactions to monoethanolamine oleate had no evidence of allergy to STS.[325]

An interesting dilemma arises with patients who have a history of allergy to sulfa medication. STS contains a sulfate; therefore, one can assume that these patients are at increased risk for an allergic reaction. However, a review of all reported cases of allergic reactions to STS did not reveal an independent allergic history to sulfa-containing medications (correspondence from Tom Udicious, R.Ph., Wyeth-Ayerst Laboratories, November 1993). We have used STS to treat many patients with a history of sulfa allergy and have observed no adverse sequelae. This experience is shared by Drs. Robert and Margaret Weiss as well (personal communication, 1998).

Reactions can occur with any sclerosing solution; they are not allergic in nature but represent the effect of the sclerosing solution on the vascular system. One such reaction is hemolysis that occurs through lysis of RBCs that are present in the treated vein. A hemolytic reaction occurred in 5 patients in a series of more than 900 patients with injection of more than 8 mL of STS 3%.[305] With a similar reaction that occurred with EO, patients were described as 'feeling generally unwell and shivery, with aching in the loins and passage of red-brown urine. All rapidly recovered with bed rest and were perfectly normal the next day.' Injections of less than 8 mL per treatment session did not result in this reaction. Intravascular hemolysis was also reported to the FDA after injection of STS into a hepatic artery feeding a hepatic tumor.

Although the lethal dose in humans has never been reported, the IV median lethal dose (LD_{50}) in mice is 90 mg/kg.[326] The lethal volume after IV injection in the rat is approximately four to six times as high for STS as for POL in equivalent concentrations.[327] In our practice, it is not uncommon for patients to be treated with up to 30 mL of 0.5% STS. We have not observed an adverse reaction to this dose of STS.

The experience of two of the authors (MPG, RAW) over 20 years in an estimated 40,000 patients is that no patient has developed a serious allergic reaction to STS. Because STS from various sources may have variable purity (see Chapter 7), it appears possible that allergic reactions may occur from the impurities, such as carbitol, and not to STS itself.[328] This may explain the decreased reported incidence of allergic reactions with the use of Fibrovein as compared with Sotradecol and/or Trombovar (Laboratoires Innothéra, Arcueil, France).

POLIDOCANOL

Kreussler Pharma (Wiesbaden, Germany) sold over 250 million mL of POL (brand name: Aethoxysklerol) for sclerotherapy from 1987 to 2010 and estimates that this translates to between 40 million and 45 million treatments (Christian Freyberg, International Sales and Marketing Director, personal communication, January 2010). Allergic reactions to POL are quite rare and had been reported in only four patients in a review of the world's literature up to 1987, with an estimated incidence of 0.01%.[310] Amblard[329] reported no allergic reactions in over 250 patients, including no allergic reactions in 2 patients who were intolerant to STS. Hoffer[236] reported no allergic reactions in over 19,000 cases. In addition, patients who are allergic to STS or iodine have no allergic manifestations after injections of POL.[329–331] However, rare allergic reactions have been reported, including a case of nonfatal anaphylactic shock to 1 mL of POL 2% injected into a varicose vein during a fourth treatment session.[321,332–334] Also, Ouvry et al[335] reported generalized urticaria with cough and dyspnea in a patient after receiving 2 mL of POL 2%; the condition resolved within 30 minutes with IV corticosteroid therapy.

Since the previous review, additional cases of allergic reaction have been reported. Guex[58] reported 7 cases of minor general urticaria in nearly 11,000 patients treated over 12 years. These patients cleared completely in 1 to 2 days with antihistamine and topical corticosteroid therapy, with one patient requiring systemic corticosteroids. Guex more recently reported only one possible case of benign allergy and no cases of anaphylaxis in 3357 patients treated.[336]

Kreussler & Co. GmbH, the product manufacturer in Germany, has documented 35 cases of suspected sensitivity from 1987 to 1993 (personal correspondence, January 1994). Of these reports, most were either vasovagal events or unproved allergic reactions. Nine patients were given repeat challenges with POL, with only three demonstrating an allergic reaction (urticaria or erythematous dermatitis). One patient died as a result of anaphylactic shock 5 minutes after injection with 1 mL, despite maximal intervention. In

1994, Kreussler reported two patients with urticaria. In 1995, two additional patients with urticaria, two with bronchospasm and one with angioedema were reported. In 1996, there were four reports of urticaria, two of anaphylactoid reactions, one with angioedema, one with pruritus and one with contact allergy. Therefore, POL is not free from allergy, and, as with all sclerosing solutions, physicians must be prepared to evaluate and treat patients who have an allergic reaction to the sclerosing solution.

A detailed account of three serious cases of anaphylaxis was reported from the Netherlands.[337] These patients were anaphylactic within 15 minutes after injection of POL. Two of them had received the drug for the first time. One patient, a 70-year-old woman with a complicated medical history of two heart operations, two cerebrovascular accidents and hyperthyroidism, was successfully resuscitated after cardiac arrest. She was receiving multiple medications, including digoxin, carbimazole, captopril, furosemide, mebeverine and acenocoumarol. She had been treated with POL without complications on four previous occasions. The second patient showed signs of ARDS after being treated with epinephrine and systemic methylprednisolone for 'shock'. The third patient developed urticaria, dyspnea, paresthesia, headache and chest pain with ECG findings of cardiac ischemia. No further studies were performed on these patients.

The Australian Polidocanol Open Clinical Trial researchers, reporting at 2 years and with over 8000 treated patients, described nine local urticarial reactions and three generalized reactions, with 2 patients developing a rash, for an incidence of approximately 0.2%. There were no cases of anaphylaxis.[245] After a further 8804 patients were evaluated, an additional 3 patients developed urticaria, again without any additional significant adverse sequelae.[154] A 5-year experience in 500 patients treated with POL 3% reported five cases of allergic reaction (1% incidence); one patient had nonfatal anaphylactic shock, and the other patients experienced urticaria.[338]

Two of 689 sequential patients were reported who developed an immediate-type hypersensitivity reaction with systemic pruritus and urticaria,[339] representing an incidence of 0.3% in this patient population and 0.91% for the 'true' population. These two reactions occurred without prior exposure to POL as a sclerosing agent. Because POL is used as an emulsifying agent in preprocessed foods, patients may have been exposed previously through ingestion. Both patients responded easily to either a single dose of oral diphenhydramine 50 mg or 0.3 mL of subcutaneous epinephrine plus 50 mg of IM diphenhydramine.

Jaquier and Loretan[235] believe that the decrease in antigenicity is the result of the absence of a benzene nucleus and a paramine group and the presence of a lone free alcohol group. Dexo S.A. (St Cloud, France), the product manufacturer in France, recommends that this substance not be used in patients with an allergic diathesis (e.g., asthma).[340] Thus, allergic reactions to POL are similar to those reported with STS.

An interesting adverse effect may be noticed in patients in whom a near-maximal dosage of POL is used. These patients report paresthesia or tingling of the tongue or a strange sensation in taste that resolves within 5 minutes. This effect was reported to Kreussler five times between 1986 and 1993 (personal correspondence, January 1994) and has been noted in our practice as well. Particular effects of the anesthetic properties of POL may explain this sensation.

Other unusual reactions reported to Kreussler (personal correspondence, January 1994) include rare episodes of short, convulsive coughing; acute pressure sensation in the chest; acute difficulty with breathing; and one case of stabbing chest pain without demonstrable ECG changes or myoglobin band creatine phosphokinase fluctuations. The authors of one specific case report described a 30-year-old woman who underwent four separate sclerotherapy sessions with POL. In the fourth session, 3 mL of POL 1.5% and 12 mL of POL 0.5% were administered. The patient complained of chest heaviness and constriction, which had also appeared after two of her other sessions but had not been brought to the attention of the medical staff. During the fourth episode, she lost consciousness and was found without a pulse or blood pressure, with dilated pupils. Spontaneous respiration occurred after 2 to 3 minutes; she began to vomit and complained of headache and earache. She recovered and was discharged well after 10 hours, but she returned the next day with dysosmia, which lasted 6 weeks. Although a brain computed tomographic scan was normal, the presumed cause was cerebral.[341]

Like EO and sodium morrhuate, POL has demonstrated a dose-dependent cardiac toxicity when injected into esophageal varices. POL has a negative inotropic, chronotropic and dromotropic effect, reducing atrioventricular and intraventricular conduction as well as lowering blood pressure. Animal studies have demonstrated a reversible, dose-dependent decrease in myocardial contractility, blood pressure and pulse rate and a prolongation of the PQ interval.[342] This effect may explain the cause of heart failure in three elderly patients with severe liver failure who were given massive quantities of POL during esophageal sclerotherapy (760 mg in a 74-year-old woman, 600 mg in a 70-year-old woman and 750 mg in a 76-year-old woman).[343,344] In addition, a case of sinus bradycardia with eventual asystolic cardiac arrest occurred after administration of 4 mL of 1% POL in a 5-year-old girl with Klippel-Trénaunay syndrome under general anesthesia with sevoflurane 2%. After appropriate emergency care, cardiac function was restored without adverse sequelae.[345]

POL, being a local anesthetic, demonstrates a systemic toxicity level similar to that of lidocaine and procaine; when combined with other anesthetics, an additive risk to the cardiovascular system occurs.[346,347] Specifically, when administered concomitantly with other local anesthetics, additional proarrhythmic effects were observed. The LD_{50} in rabbits at 2 hours is 0.2g/kg, which is three to six times greater than the LD_{50} for procaine hydrochloride.[348] The LD_{50} in mice is 110 mg/kg.[349]

The teratogenicity was evaluated by Fournier in rabbits and rats.[350] The pregnant animals received 2.7 to 4.5 mg/kg per day and did not demonstrate a significant increase in the number of abnormal fetuses.[351] One severe malformation was seen in a rat pup out of 530 normal pups (0.08%) whose mother received 4.5 mg/kg per day. This is far in excess of the recommended doses of POL in humans. Kreussler has reported that POL does cross the placental barrier in rats, but that perinatal and postnatal development and

behavior were not impaired in rats whose mothers received IV POL every other day during late gestation as well as in the lactation period.[347] However, no formal studies in pregnant women have been reported. Sigg[352] reported treating 3600 pregnant women with 34,000 injections without fetal injury or abortion.

CHROMATED GLYCERIN/GLYCERIN

Chromated glycerin 72% (Sclérémo; Laboratoires Bailleul, Bailleul, France) is a sclerosing solution with a very low incidence of side effects.[21,86,353,354] Hypersensitivity is a very rare complication and can be of a delayed type.[355–357] Contact sensitivity to chromium occurs in approximately 5% of the population.[358] IV potassium dichromate leads to complete desensitization in chromium-sensitized guinea pigs. This effect occurs because chromium needs to bind to skin proteins to become an effective antigen.[359] This may be related to the necessity for epidermal Langerhans cells to produce an allergic response, whereas T-lymphocyte accessory cooperation is not optimal with IV injection and its resulting endothelial necrosis. Thus, it is more common for a sclerotherapist to develop an allergic contact dermatitis to CG than it is for a patient to have an allergic reaction to IV use of CG. Indeed, Ouvry (personal communication, 1995) developed an allergic contact dermatitis from CG injected without the use of protective gloves.

Ramelet et al[360] reported seven patients who developed an allergic reaction to CG. One patient had a vasculitis reaction and six patients had an eczematous reaction. All allergic patients demonstrated a sensitivity to topically applied chromium.

One case of fatal allergic reaction has been described.[361] The patient, a 51-year-old woman, developed laryngeal edema immediately after the end of the first sclerotherapy session with undiluted Sclérémo and died after 2 hours of appropriate resuscitation. The patient had declared a past history of asthma but no cutaneous allergy. One patient treated with 72% glycerin with lidocaine and epinephrine for spider veins developed leg swelling with 3 to 4+ pitting edema several days following sclerotherapy (Joseph Ang, personal email communication, October 2007). In this case, 18 mL of nonfoam sclerosant was used in the treatment of one leg, the patient wore compression stockings following treatment, and there was no evidence of an underlying DVT. The etiology of this lower-extremity edema is unclear. Regardless, because of the potential for hemolysis, we recommend limiting the total volume of glycerin per treatment session to 10 mL.

Hematuria accompanied by ureteral colic has been reported to occur transiently after injection of large doses of CG. Ocular manifestations, including blurred vision and a partial visual field loss with resolution in less than 2 hours, have been reported by a single author.[362] Glycerin- or any sclerotherapy-induced hemolysis may not be a benign event. Hemoglobin can exert direct cytotoxic, inflammatory and pro-oxidant effects that adversely affect endothelial function.[363] Hemoglobin from destroyed RBCs dimerizes and is rapidly bound by the serum protein haptoglobin. The haptoglobin–hemoglobin complex causes endocytosis and degradation, which can lead to a variety of adverse effects.[364]

Although transient hemoglobinuria is common in athletes and is without known long-term adverse effects, hemoglobulinemia can cause renal failure.[365] More commonly, hemoglobulinemia can cause a dose-related GI dystonia and pain, including esophageal spasm and dysphagia.[364] The reader is referred to an excellent review that details more clinical manifestations of hemoglobinemia.[366]

An additional case was reported of transient hypertension and visual disturbance after the injection of 12 mL of 50% CG into spider and 'feeder' leg veins in a fourth treatment session.[367] These symptoms occurred 2½ hours after treatment and lasted more than 3 hours without treatment. This may have represented a retinal spasm or an ophthalmic migraine. Since we started using glycerin alone without chromium but mixed 2:1 with lidocaine 1% with or without 1:100,000 epinephrine, we have yet to see an allergic reaction. We have also yet to see hemoglobinuria or adverse effects with the use of up to 12 mL of this glycerin mixture, except for 1 or 2 minutes of epinephrine-induced 'rush', which can occur in rare patients who have a sensitivity to epinephrine.

POLYIODINATED IODINE

Polyiodinated iodine (marketed as Varigloban and Variglobin [Kreussler Pharma] as well as Sclerodine 6 [Omega Laboratories]) is a stabilized water solution of iodide ions, sodium iodine and benzyl alcohol. Sigg et al[368] reported their experience with over 400,000 injections of Variglobin. Paravenous injections readily produced tissue necrosis. In 1975, Sigg and Zelikovski[369] reported an incidence of 0.13 allergic cutaneous reactions per 1000. No systemic allergic reactions were observed. Obvious contraindications to the use of polyiodinated iodine are hyperthyroidism and allergies to iodine and benzyl alcohol.

High concentrations of iodine solutions may also produce bronchial mucosal lesions. Therefore, Wenner[370] recommended that a maximum of 5 mL of 12% solution be used in a single sclerosing session.

SODIUM SALICYLATE

In a literature review, a proprietary product, Saliject (Omega Laboratories), was not reported to cause allergic reactions. Dr. Beverly Kemsley reported 1 of 6000 patients who developed an anaphylactic reaction after the use of Saliject (personal communication, 1996). Thirty patients developed localized erythema and urticaria that responded to the oral antihistamine terfenadine 120 mg.

HYPERTONIC SALINE

Alone, HS solution shows no evidence of allergenicity or toxicity. Complications that may arise from its specific use include hypertension, which may be exacerbated in predisposed patients when an excessive sodium load is given; sudden hypernatremia; central nervous system disorders; extensive hemolysis; and cortical necrosis of the kidneys (Mary Helenek, American Regent, written correspondence, May 1990). These complications, among others, led American Regent to add to its label the warning 'For IV or SC use after dilution' in bold red ink.

As discussed previously, hematuria can occur with any sclerosing agent. Dodd[371] reported painless hematuria in five patients given HS injections. Sometimes blood appears in the urine after one or two acts of micturition and occasionally at other times throughout the day. Usually, there

are no other ill effects and the hematuria resolves spontaneously. Hematuria probably occurs because of hemolysis of RBCs during sclerotherapy.

Coverman (personal communication, 1989) described two patients who were given injections up to 6 mL of HS 23.4% and developed 'peculiar visual symptoms in just one eye'. This was described as either blurred vision or an aura. There were no other symptoms, and each incident passed quickly and spontaneously. Coverman speculated that this may have been caused by the addition of lidocaine to the HS solution.

HEPARIN IN HYPERTONIC SALINE

Whereas unadulterated HS solutions in concentrations from 15% to 30% are used for the treatment of varicose and telangiectatic leg veins, adding heparin to the solution to prevent the theoretic risk of embolization associated with sclerotherapy has been advocated.[22] Although the necessity for heparin has been discounted in a well-controlled, 800-patient randomized study,[24] Foley's solution, heparsal, consisting of HS 20%, heparin 100 U/mL, and procaine 1%, is commonly used in the treatment of telangiectatic leg veins. Therefore, the risk of adverse reactions to heparin should be mentioned.

Commercial preparations of heparin consist of straight-chain anionic polysaccharides of variable molecular weight (usually 7000–40,000). Heparin prepared from different tissues also appears to vary: More protamine is required to neutralize a unit of beef lung heparin than porcine mucosal heparin. Plasma lipolytic activity, anti–factor Xa activity and activated partial thromboplastin time ratios are significantly different.[372]

Fever, urticaria and anaphylaxis occur occasionally after administration of heparin.[372–376] Necrosis has been reported in patients receiving subcutaneous heparin[368,377–380] and has usually occurred 3 to 10 days after multiple subcutaneous injections. Pruritus, local tenderness and burning sensations associated with large, indurated, erythematous plaques were also reported to have occurred in six patients 10 to 20 days after beginning prophylactic doses of heparin.[381] Thus, there is a measurable risk of toxicity to heparin.

Although heparin is not a totally benign substance, those who use heparsal have not reported any adverse reactions that could be attributed to the heparin component.[8,22,24,195] Absence of side effects was reported in one series of 310 patients when volumes of 10 to 20 mL were injected into varicose veins.[195] In the doses used, heparin in heparsal may be without significant side effects, but one must be aware of the potential dangers associated with its use.

LIDOCAINE IN HYPERTONIC SALINE OR GLYCERIN

Alderman[9] and Duffy[8] advocate the addition of lidocaine (to achieve a 0.4% final concentration) to minimize patient discomfort during injection of HS. This addition introduces a potentially allergenic sclerosing mixture. Although the most common cause of patient-reported 'allergic reactions' to lidocaine is psychogenic or vasovagal phenomena,[382] allergic reactions may occur. Vasovagal reactions are caused by emotional or physical stimuli and are not directly caused by the local anesthetic. Besides vasovagal reactions, the majority of side effects to lidocaine are localized and include bruising and edema at the injection site.[383] The authors of a report on 28 patients who had a variety of adverse reactions to lidocaine, including skin reactions, loss of consciousness and vasovagal symptoms, evaluated the patients with skin testing and found them not to be allergic to lidocaine. Nineteen of these patients were subsequently treated with lidocaine without an adverse reaction.[384] In a more recent study, 183 patients with a reported allergy to lidocaine were patch-tested, and those patients who tested positive received a 0.1-mL intradermal challenge with lidocaine 1%. Of the 183 patients tested, 4 had positive reactions to lidocaine, 2 of whom had sensitivity to local injections of lidocaine manifested by dermatitis.[385] Impending anaphylaxis must be distinguished from vasovagal reactions, which occur more commonly. One important distinction is that in vasovagal reactions the patient demonstrates bradycardia, whereas a patient with anaphylaxis exhibits tachycardia.[386] As described previously in this chapter, vasovagal reactions also commonly include lightheadedness, hypotension and diaphoresis.

Unlike the ester class of anesthetics, which are much more commonly shown to cause allergic reactions, members of the amide class of anesthetics, to which lidocaine belongs, have a very low risk of allergic reaction.[387–392] There are two types of allergic reaction to local anesthetics: a type I immediate hypersensitivity or anaphylactic reaction and a type IV delayed hypersensitivity reaction. The former is mediated by antibodies and the latter by cell-mediated immunity. Allergy is most likely caused by the methyl parabens or sodium metabisulfite used as a preservative in anesthetic solutions.[387,388,393–395] To keep the allergic risk as low as possible, single-dose vials of lidocaine without preservatives should be used.

Despite the low risk of allergenicity to lidocaine, a few true allergic reactions, including anaphylaxis, have been reported.[396–403] The prevalence of anaphylactic reactions to anesthetics is approximately 1:3500 to 1:20,000 with mortality of between 3% and 6%.[404] One patient demonstrated a type I hypersensitivity reaction to lidocaine after undergoing intralesional injections to his keloids with a total of 0.5 mL of triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, NJ) diluted to 10 mg/mL with lidocaine 1% and epinephrine 1:100,000.[383] He was fine when he left the office, but approximately 15 minutes later he began to experience wheezing, lightheadedness and periorbital edema. These symptoms resolved several hours after treatment in the emergency room with an albuterol nebulizer and oral famotidine. Interestingly, this patient subsequently had a positive wheal-and-flare response to intradermal lidocaine 1% at a dilution of 1:10,000 during allergy testing. Thus, HS or glycerin, when adulterated with lidocaine, may place the patient at risk for allergic reactions.

SUPERFICIAL THROMBOPHLEBITIS

Before the advent of modern-day sclerotherapy, which uses graduated compression to limit thrombosis, thrombophlebitis—both superficial and deep—occurred in a significant number of sclerotherapy patients.[405] In fact, because phlebitis was such a common sequela of sclerotherapy, some doubted early on whether sclerotherapy was a legitimate treatment for varicose veins.[406] With the use of compression and the realization that many adverse effects result from

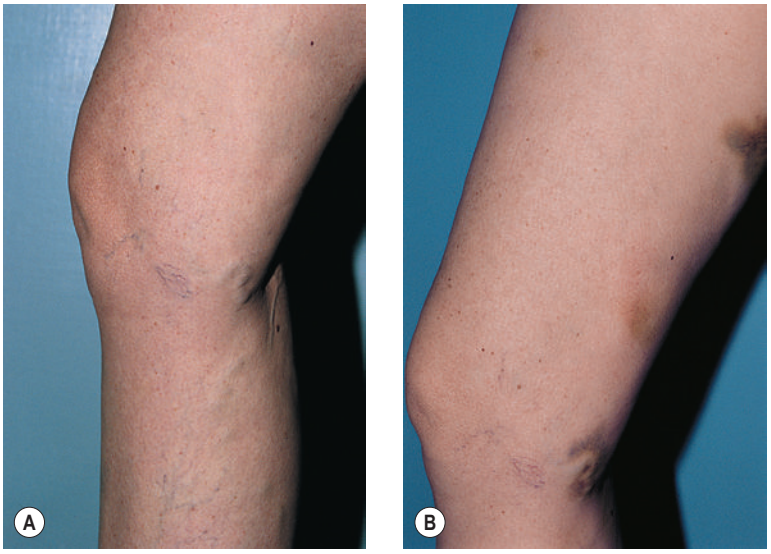


Figure 8.42 **A,** This 45-year-old woman had incompetence of the saphenofemoral junction and refused surgical ligation and stripping of the great saphenous vein. Therefore, all reticular, accessory and tributary veins were treated with polidocanol 0.75% for a total of 20 mL to the entire right leg. Localized compression with STD foam pads and a short stretch bandage was applied to the medial thigh only. This patient did not apply the graduated 30- to 40-mmHg compression stocking until 30 to 45 minutes after leaving the office. **B,** Acute thrombophlebitis developed 3 days after sclerotherapy. Note ecchymosis from compression padding.

thrombus formation in treated veins, the incidence of thrombophlebitis has greatly decreased.

Numerous underlying conditions may predispose a patient to develop thrombophlebitis through induction of a state of hypercoagulability (see 'Pulmonary embolism and deep venous thrombosis' section). The most common of these risk factors appears to be elevated factor VII.[407] In addition, the persistence of significant reflux into a vein that has been treated can also lead to phlebitis. Fegan[408] stated that this complication most commonly occurs when perforator veins in the region of treatment are not diagnosed and treated. When eosinophilia accompanies superficial venous thrombophlebitis, the practitioner should consider an underlying malignant blood disorder, neoplasia, vasculitis or hypereosinophilic syndrome (HES).[409] We have seen two patients who developed superficial thrombophlebitis as the presenting sign of ovarian cancer (RAW) or recurrent breast cancer (MPG). This has been reported by others as well.[410]

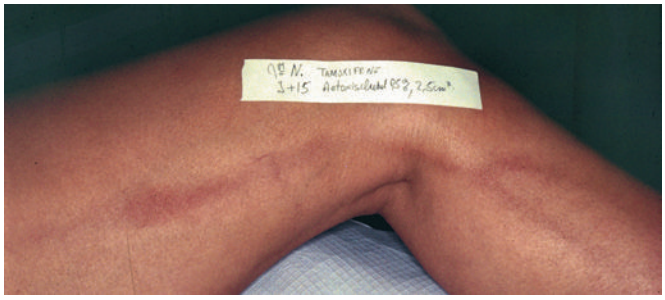


Figure 8.43 Extensive superficial phlebitis with very little to no thrombotic material within the vein lumen. The picture was taken 15 days after injection of 2.5 mL of polidocanol 0.5% in multiple reticular and spider veins of the same limb. The great saphenous vein had not been injected. The patient was treated with tamoxifen (for 3 years after breast cancer treatment), and no evidence of cancer recurrence has been observed. Evolution of pigmentation is unknown. Clinically, this phenomenon is very similar to Mondor disease.

ETIOLOGY

Superficial thrombophlebitis appears 1 to 3 weeks after injection as a tender erythematous induration over the injected vein (Fig. 8.42). Duffy[8] estimates that it occurs in 0.5% of his patients who have primarily small-vessel varicose veins and telangiectasia. Mantse[316] reported an incidence of 1% in the treatment of varicose (nontelangiectatic) veins despite the use of a tensor bandage for 6 weeks. Mantse noted that the patients who developed superficial thrombophlebitis found the bandage was too tight and reapplied it too loosely at home. In our 5-year retrospective study,[17] this complication occurred to some degree in approximately 1.7% of patients (6 of 351). Most patients have minimal phlebitis and require either no treatment or simple drainage of an associated coagulum with a 22-gauge needle. Rarely, in symptomatic patients, treatment with graduated compression and anti-inflammatory agents is given (0.001% of patients totaling more than 10,000 separate injections).

In certain cases, superficial thrombophlebitis presents as an extensive pigmented cord along the superficial venous pathway (Fig. 8.43). The content of the venous lumen can vary according to the etiology, emphasizing the need to distinguish between 'phlebitis' and 'thrombosis'. The patient presented in Figure 8.44 obviously represents a pure 'phlebitis'.

Patients may, although rarely, develop a chemical lymphangitis, sometimes confused with superficial thrombophlebitis. It typically appears within 24 hours after treatment but resolves spontaneously within 72 hours. It is not associated with pain or tenderness. Shown in Figure 8.45, this patient's chemical lymphangitis occurred after treatment with 1% STS liquid.

PREVENTION

The cause of thrombophlebitis is related in part to treatment technique as well as to lack of adequate posttreatment compression. In our experience, a decreased incidence of superficial thrombophlebitis may result from a greater degree and length of compression used after sclerotherapy is performed. An inadequate degree or length of compression results in excessive intravascular thrombosis. Sigg[411] noted that perivenous inflammation is observed only at those parts of the limb not covered by a compression

dressing. Thus, to avoid this complication, one should prevent or minimize the development of postsclerosis thrombosis by using compression pads and hosiery over the entire leg and not just over the treated veins.

However, even when appropriate compression is used, thrombosis and perivascular inflammation may still occur (Fig. 8.46). Ascending phlebitis in the small saphenous vein (SSV) or its long tributaries, starting at the upper edge of the compression stocking, is relatively common. Here, the sclerosing action continues up the abnormal vessel (even beyond what apparently is the extent of the abnormality). It is thought that the sclerosing solution destroys damaged endothelium to a greater extent than normal endothelium. Therefore, the placement of a foam pad extending above the compression stocking or bandage to create a gradual transition of pressure from compressed to noncompressed vein may provide a safety margin, as well as prevent damage to the vein by the otherwise abrupt cutoff of the pressure stocking.

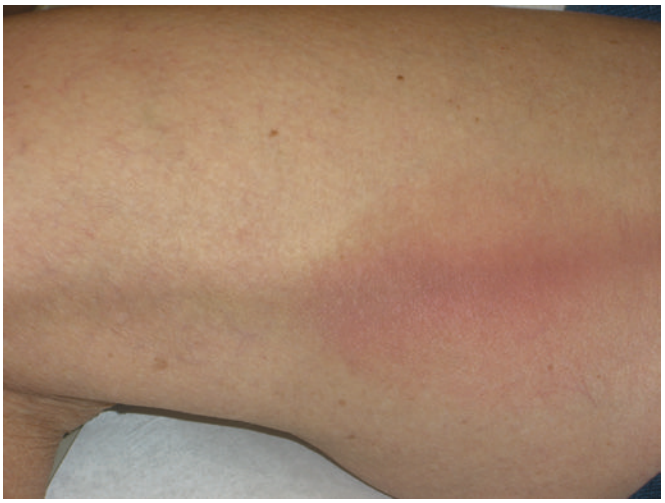


Figure 8.44 A 55-year-old woman presented with reticular and telangiectatic leg veins 1 year after diagnosis of breast cancer treated with bilateral mastectomy. She was treated with 1 mL of sodium tetradecyl sulfate (STS) 0.5% mixed 1:4 with room air to veins 3 to 5 mm in diameter, 1 mL of STS 0.25% mixed 1:4 with room air to veins 1 to 3 mm in diameter, and 4 mL of 72% glycerin/1% lidocaine mixed 2:1 with epinephrine, followed by 7 days, 24 hours per day, 30- to 40-mmHg graduated compression stockings. Six weeks after treatment, she presented with a tender erythematous streak over the proximal portion of the treated vein. Coagula were drained with a 22-gauge needle and oral ibuprofen was prescribed 400 mg t.i.d. with reapplication of the graduated compression stocking while ambulatory. She returned for additional draining of coagula at 4, 6 and 8 weeks with gradual resolution of erythema and tenderness. A complete onocologic workup did not disclose recurrent breast carcinoma. The patient was seen 2 years later for treatment of minor telangiectasia with glycerin and was in excellent health.

Thrombophlebitis is a complication that should not be taken lightly. If untreated, the inflammation and clot may spread through perforating veins to the deep venous system. This extension may lead to valvular damage and possible pulmonary embolic events.[412–417] In a study of a group of 145 patients with superficial thrombophlebitis, researchers found that 23% of affected limbs had proximal extent into the SFJ.[418] Pulmonary embolism (PE) was found in 7 (33.3%) of 21 patients with thrombophlebitis of the GSV above the knee[419]; 17 of the 21 patients had varicose veins. Interestingly, in that study, clinical symptoms suggestive of PE were present in only one of the seven patients. The occurrence of DVT in patients with below-knee superficial vein thrombosis (SVT) was 32% in one study of 78 patients.[420]

TREATMENT

In addition to adequate compression, drainage of thrombi after liquefaction (approximately 2 weeks after sclerotherapy) hastens resolution of the otherwise slow, painful resorption process.[411] Adequate compression and frequent ambulation should be maintained until the pain and inflammation resolve. Aspirin or other nonsteroidal anti-inflammatory agents may be helpful in limiting both the inflammation and the pain.

Patients with extensive involvement of leg varices should receive anticoagulation, particularly if the thrombosis extends into the proximal part of the SFJ. In addition to propagation of the thrombus through the SFJ, 11% to 40% of patients with SVT at the SFJ have evidence of concurrent DVT.[419–422] In these patients, anticoagulation for 6 months achieved resolution of the DVT/SVT while preventing PE. This success occurred despite duplex evidence of progression of SVT to DVT in 2 of 20 patients.[421] Of interest is the fact that the incidence of coincidental DVT with SVT was greater in patients without varicose veins (60% vs 20%), thus

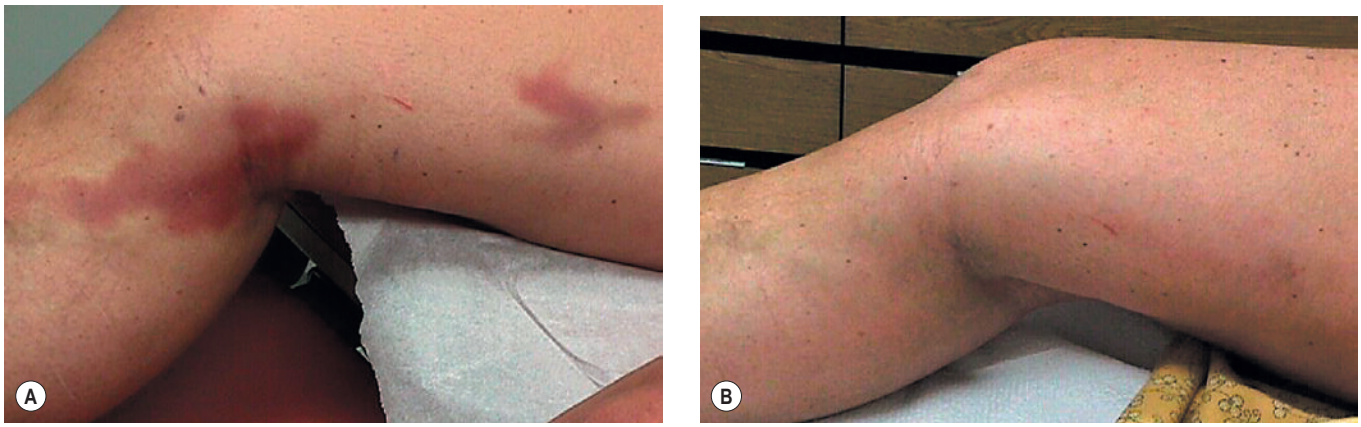


Figure 8.45 **A,** Appearance at 24 hours after STS 1% injection. **B,** Spontaneous resolution after 72 hours postinjection.

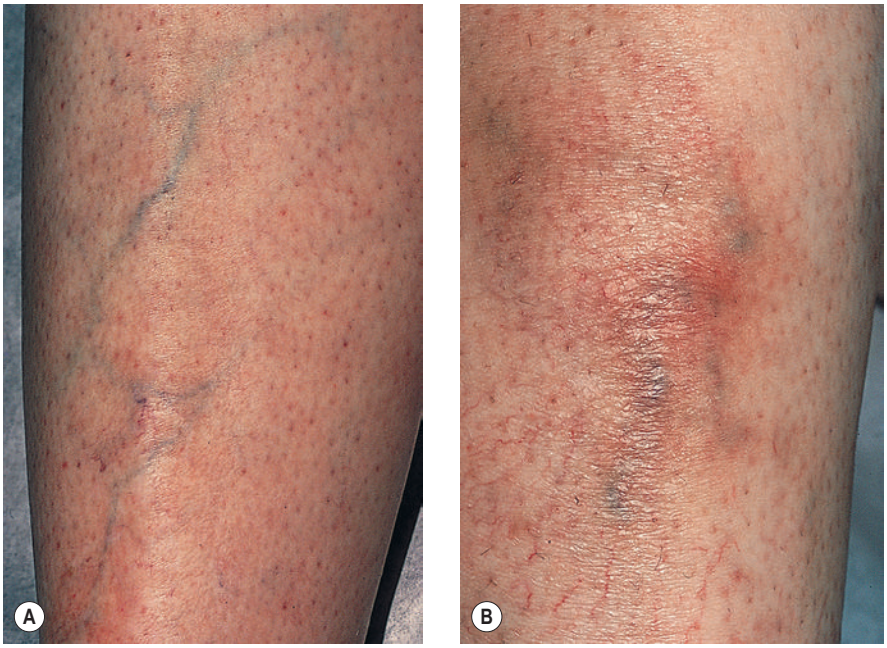


Figure 8.46 **A,** Clinical appearance of the vein over the anterior tibia before injection. **B,** Acute thrombophlebitis developed 10 days after sclerotherapy with polidocanol 0.5%.

indicating that other innate factors place patients with SVT at additional risk for DVT.

Anticoagulation is best achieved with fondaparinux 2.5 mg subcutaneously once daily for 45 days, which decreases symptomatic venous thromboembolism, SVT extension and recurrence with no increased risk of bleeding compared with placebo.[423,424] Low-molecular-weight heparin (LMWH) is an additional option that may also decrease perivascular inflammation. LMWH has been demonstrated to limit neutrophil extravasation.[425] Thus, LMWH has anti-inflammatory properties in addition to anticoagulant properties.

Other methods for enhancing thrombolysis may be considered for SVT as well as for DVT. Ultrasound-enhanced systemic thrombolysis has been found to augment arterial recanalization.[426] This procedure uses a 2-MHz Doppler ultrasound in conjunction with systemic tissue-type plasminogen activator (t-PA). Ultrasound increases enzymatic fibrinolysis through mechanisms that include improving drug transport, altering the fibrin structure and increasing the binding of t-PA to fibrin.[427]

A liposomal heparin spray (Lipohep Forte Spraygel; Medicom International, Brno, Czech Republic) applied after the onset of SVT has been found to improve symptoms as well as hasten resolution of the SVT.[428] This spray was as effective as LMWH injections. Distinguishing between HES-related and idiopathic superficial venous thrombophlebitis is important because anticoagulant therapy is probably indicated in the former, which carries an increased thrombotic risk.[409]

ARTERIAL INJECTION

The most feared complication in sclerotherapy is inadvertent injection into an artery, but fortunately this complication is very rare.[429–431] Five examples of this complication were reported to the Medical Defence Union in the United Kingdom in 1985.[432] Cockett[433] reported 18 cases, including those reported to the two medical protection societies in the United Kingdom, over a 10-year period. However, Cockett believes even this number is too low because many cases never reach the courts or the medical literature. Biegeleisen et al[434] reported seven cases in their practice history of more than 10 years. Forty cases from France over 17 years were reported,[435] and Bergan et al[436] reported on a series of cases from the United States. The authors of a recent review, published in 2013, identified 63 cases reported over the past 50 years.[437]

Arterial injection of a sclerosing solution causes the development of an embolus. This has been experimentally confirmed in the canine femoral artery.[438] These experiments demonstrate little effect on the artery itself with injection; spasm does not occur. The sclerosing solution acts to denature blood and endothelial cells in smaller arteries, producing a sludge embolus that obstructs the microcirculation (Fig. 8.47).[439] Stagnant blood flow, secondary thrombosis and necrosis soon follow.

Occlusion of small arteries may lead to the development of a compartmental syndrome. Intracompartmental pressures of 30 mmHg or more in humans usually produce neural deficits characterized by pain during stretching of the muscles involved, paresthesia, and then paresis and anesthesia in the sensory distribution of the nerve that courses through the affected compartment. The end result is paralysis.[320] Muscle necrosis then leads to leg atrophy. Sensory deficit in the first web space (deep peroneal nerve) implicates anterior compartment syndrome. Sensory deficit on the dorsum of the foot (superficial peroneal nerve) implicates the lateral compartment. The superficial posterior compartment is indicated by sensory deficit of the sural nerve distribution (lateral foot). Deep compartmental syndrome is likely if the sole of the foot is affected (posterior tibial nerve).

Unless large arteries are blocked, peripheral pulses will be intact, and capillary filling is easily identified because the compartmental pressure must be greater than 80 mmHg to

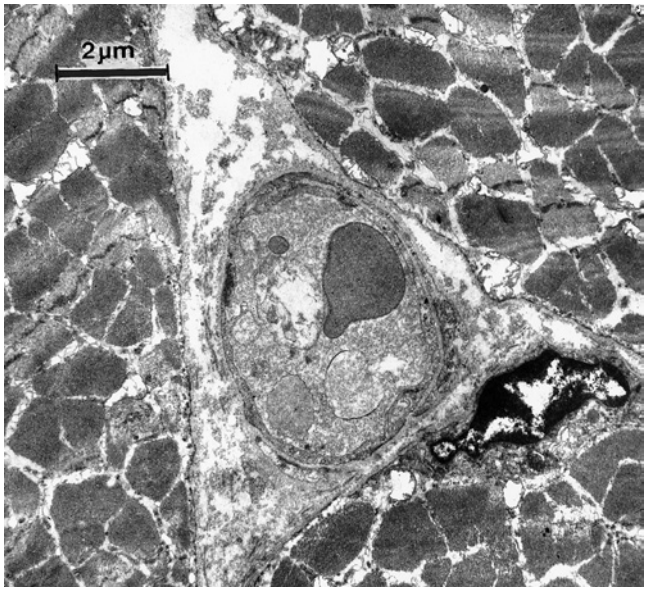


Figure 8.47 Terminal arteriole from the adductor musculature of the rat hind limb 60 minutes after injection of 4% Variglobin into the iliac artery through a Fogarty catheter. The lumen contains a large amount of cellular debris. Transmission electron micrograph, primary magnification ×3800; for final enlargement, see scale. (From Staubesand J, Seydewitz V. Phlebologie 1991;20:1.)

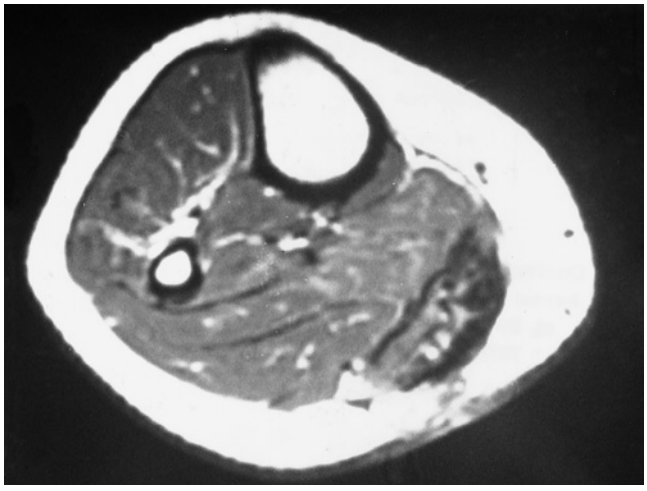


Figure 8.48 Magnetic resonance image of the medial calf a few weeks after inadvertent intra-arterial injection had produced muscular weakness and pain. Note atrophy of gastrocnemius muscles with significant edema within fascial compartments. (Courtesy Professor Jean Natali, Paris.)

occlude large artery flow.[440] This may lull the physician into a false sense of security, and the underlying compartmental syndrome may not be recognized. Intracompartmental pressures between 30 and 40 mmHg for 6 to 12 hours can cause irreversible damage to the nervous tissue because of impairment of microcirculation.[320] Magnetic resonance imaging (MRI) examination of the affected limb has been able to demonstrate muscle destruction (Fig. 8.48).

ETIOLOGY

Arterial injection occurs most commonly in the posterior or medial malleolar region, particularly when an effort is made

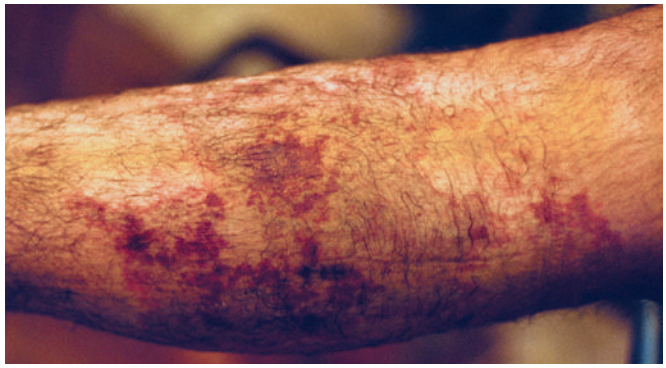


Figure 8.49 Postsclerotherapy necrosis at an early stage, 8 days after injection of 3 × 0.5 cm^3 of polidocanol 0.5% in medial leg postsurgical residual varicose veins of a 38-year-old man. Extreme pain appeared only 3 to 4 days after the injections. Limited surgical excising was carried out after 30 days, leaving small scars and no other sequelae. This complication is rare in this area. Despite the unfavorable initial aspect of the leg and the extreme pain, necrosis was limited to three zones smaller than 1 cm^2 each. The injection of an aberrant superficial skin artery was suspected, the alternative explanation being embolia cutis medicamentosa.[254]

to inject the internal ankle perforator vein, specifically in the posterior tibial artery.[408,432,434,441] Other areas predisposed to inadvertent arterial injection include the groin and the back of the knee, but any injected area can be prone to arterial injection.[442] The patient usually, but not always, notes immediate pain (it can be supposed that because it has a local anesthetic effect, intra-arterial injection of POL could be painless during the first days) (Fig. 8.49). Evidence is still lacking, and the decrease in incidence of these complications with the use of ultrasound guidance and foam will probably (and fortunately) not allow one to draw more precise conclusions. Pain then typically slowly propagates down into the foot and outer toes over the following 2 to 6 hours postinjection. During this time, arterial pedal pulses are palpable. At 10 to 12 hours later, the four outer toes are white, with the sole of the foot becoming painful. Cutaneous blanching of the injected area usually occurs in an arterial pattern associated with a loss of pulse and progressive cyanosis of the injected area.

Natali and Farman[442] reported 40 cases of arterial injection in their 20-year experience and review of the French medicolegal system. They found that injection of the SSV was the most common preceding event. Seven patients required amputations (two above the knee and five below the knee), six required peripheral amputations of one or more toes and 27 had abnormalities of the triceps and/or sural muscles. Muscle abnormalities consisted of infarction with subsequent fibrosis and retraction of the affected area, with or without limb atrophy. In one case, POL 0.5% was injected into the SSV in the popliteal fossa. An arteriogram showed thrombosis of the peroneal artery with clinical symptoms of a pale, numb foot with muscular necrosis.[443] In approximately 50% of cases, amputation after arterial injection may result despite treatment.[437]

Another area in which the artery and veins are in close proximity is the junction of the femoral vein and GSV. A review of one sclerotherapy practice spanning more than 20 years disclosed two cases of accidental arterial injection in

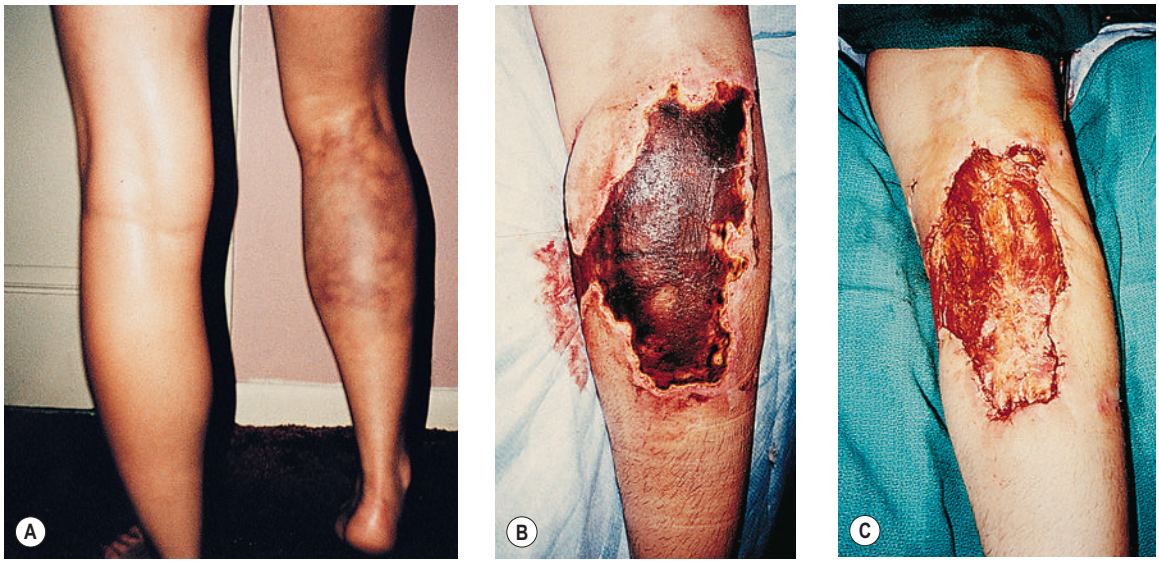


Figure 8.50 **A,** Two days after duplex-assisted sclerotherapy with STS 1.0% into the gastrocnemial area to treat cutaneous telangiectasia. Note mottled skin. Treatment consisted of pain medication and local infiltration with lidocaine. **B,** Three weeks after treatment, a well-circumscribed necrotic area is apparent. **C,** Intraoperative debridement of all necrotic tissue to fascia.

this area, requiring thigh amputations.[444] This also has been the experience of Biegeleisen et al,[434] who reported seven cases of arterial injection during attempts to inject the GSV or SSV in the groin or popliteal areas, even under color flow ultrasound control. In this location, the external pudendal artery bifurcates and may surround the GSV shortly after the location of its connection with the femoral vein. In addition, the junction of the GSV with the popliteal vein has been demonstrated to have a tortuous and variably located satellite arteriole.[445] Because these collateral arteries vary anatomically in these locations, duplex scanning may be useful before sclerosing these vessels but does not guarantee absolute safety, as detailed in a series of case reports.[436]

With the onset of duplex-assisted sclerotherapy, small arteries in the superficial and deep aspects of the thigh and calf have been inadvertently injected (Fig. 8.50).[436] As described previously, the usual sequelae are both loss of tissue (cutaneous and subcutaneous) and nerve damage, which may result in muscle atrophy or necrosis, or both. Color flow duplex scanning and the use of open needles or a long catheter when sclerosing these very tricky areas are recommended but still do not guarantee a completely risk-free procedure. Although the development of solid-state high-resolution duplex has allowed for more precise anatomic visualization, Duplex-guided injection should be performed only by experts with experience of thousands of sclerotherapy procedures. A physician should be present at all times to give immediate treatment if needed.

Reports cited in the previous discussion assume direct arterial injection as the cause of extensive tissue necrosis. However, another explanation may be valid. De Takats[446] described and illustrated preferential arterial and venous connections in the precapillary circulation by stating, 'These shunts permit more direct transmission of pressure from the arterial to the venous system. They offer less resistance to flow than the capillaries and help maintain venous pressure and flow'. In patients with prolonged chronic venous hypertension who develop dilated and elongated varicose and subcutaneous veins, free flow of blood from the venous to the arterial system may occur in this manner. Thus, injection into a varicose vein near these shunts may allow the sclerosing solution direct access to the arterial circulation (Fig. 8.51).

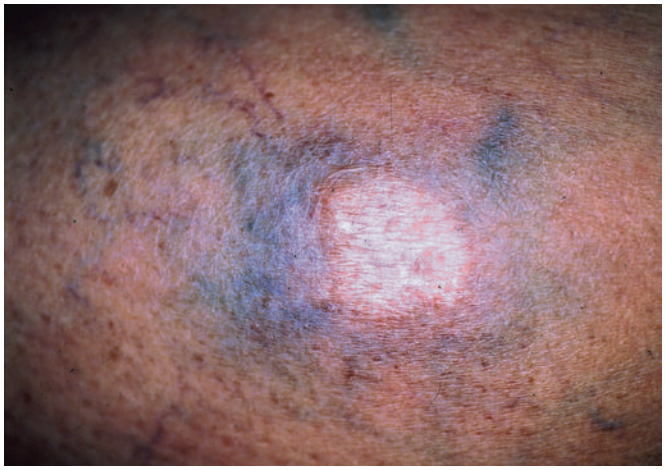


Figure 8.51 Late aspect of a skin necrosis after sclerotherapy (undocumented). The color of the scar suggests that the necrosis was deep.

PREVENTION AND TREATMENT

Arterial injection is a true sclerotherapy emergency. The most consistent sign of intra-arterial injection is the development of immediate pain at the site of injection that may radiate along the course of the injected vessel. Discoloration or cyanosis may then subsequently develop within hours and can have a sharply demarcated border corresponding to the area of the affected artery. Numbness, dysesthesias and paresis may follow within 12 hours of injection.[437] The extent of cutaneous necrosis is usually related to the amount of solution injected. Therapeutic efforts to treat this complication are usually unsatisfactory but should be attempted.[441]

Box 8.1 Arterial Injection Treatment

- Arterial and periarterial infiltration with procaine 1% (inactivates sodium tetradecyl sulfate)
- Cooling of injected area with ice packs
- Immediate heparinization (continue 6 days or longer)
- Intravenous dextran 10%, 500 mg/day for 3 days
- Consider direct thrombolytic therapy
- Oral prazosin, hydralazine or nifedipine for 30 days

Because its occurrence is extremely rare, we recommend that an emergency flow sheet be readily accessible (Box 8.1). Hobbs (personal communication, 1989) recommends that, upon realization of arterial injection, blood and sclerosing solution should be aspirated back into the syringe to empty the needle of solution. In addition, aspiration of the injected artery as rapidly and completely as possible, if performed immediately, may help remove the injected sclerosing solution. The needle should not be withdrawn, but the syringe should be replaced with one containing 10,000 U of heparin, which should be injected slowly into the artery. Unfortunately, this maneuver is difficult to accomplish because the patient usually is in considerable pain and may find it difficult to hold still (Hobbs JT, personal communication, 1991), and it also assumes that arterial injection has typical manifestations that make it recognizable while the vein is still cannulated.

Rarely, patients have no complaints of pain and demonstrate only a mild, sharply demarcated erythema that becomes dusky and cyanotic after a few hours.[434] More practical treatments include periarterial infiltration with 1 mL of procaine 3%, which will form a complex with STS and render it inactive.[408,441] The foot should be cooled with ice packs to minimize tissue anoxia. Immediate heparinization (continued for 6 days) and administration of IV dextran 10%, 500 mL per dose, for 3 days is recommended. Use of IV streptokinase or another thrombolytic agent may also be considered if there are no contraindications for its use. Use of oral prazosin, hydralazine or nifedipine for 30 days should be considered. Cockett[433] found that treatment which is delayed for more than 1 hour has no effect in limiting damage to the foot.

Use of IV heparin followed by subcutaneous heparin has been found to avert skin necrosis.[434] It was observed that warfarin (Coumadin; Bristol-Myers Squibb) did not appear as effective as subcutaneous heparin in these patients. The protective effect of heparin may be unrelated to its anticoagulant activity.[447] Postischemic endothelial cell dysfunction was prevented with heparin perfusion in the rat hind limb model.[448] Heparin infusion at 0.5 U/mL resulted in endothelial-dependent vasodilation. Serum levels less than 0.5 U/mL (the average serum heparin level in a patient undergoing therapeutic anticoagulation) were less effective. It is postulated that direct interactions of heparin with the endothelium, inducing maintenance of a strong luminal charge, may produce beneficial membrane-stabilizing effects. Heparin may also modulate TNF activity, contributing to this effect.[449] In addition, a favorable resolution of arterial injection occurred in one patient with injection of t-PA.[450] In this patient, promazine was injected into an artery. Use of heparin, axillary plexus blockade and IV sodium nitroprusside was not successful. Brachial artery injection of t-PA 50 mg over 8 hours (Actilyse; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) resulted in therapeutic efficacy. Thus, local fibrinolytic therapy should be considered if conservative treatments prove ineffective.

Given the known relationship of injection site to the development of this problem, one must consider the necessity of injecting vessels in the vicinity of the medial malleolus. The *British Medical Journal* published an interesting report of a legal case brought against a physician for performing such an injection, which resulted in a transmetatarsal amputation.[429] The case was found in favor of the physician after several renowned sclerotherapists stated that the injection should be attempted if the patient would benefit, because the risks are infrequent and the benefits significant.

Prevention of this dreaded complication is best accomplished by visualization of the blood emanating from the needle. If it is pulsatile and continues to flow after the leg is horizontal, injection should not be attempted at this site. Mantse[316] advised that when the medial malleolar area is treated, placement of the sclerosing needle should be performed while the patient is standing, so that the varix is bulged and the distance between the artery and vein is increased.

Theoretically, visualization of arteries and veins with duplex-assisted sclerotherapy should negate this risk. Indeed, newer color flow duplex imagery allows visualization of minute arteries and veins. However, a number of arterial ulcerations have occurred with this technique, even when injecting posterior calf, gastrocnemius and SFJ varicose veins. Thus, no technique is completely free from this complication.

EMBOLI WITHOUT PULMONARY INVOLVEMENT

Neurological symptoms following sclerotherapy can occur, with the authors of one review published in 2012 identifying 13 cases of stroke reported in the worldwide literature since 1994.[451–453] Of these 13 patients, 10 recovered without lasting sequelae. A previous history of cryptogenic stroke or recurrent classic migraine with aura were found to be risk factors for adverse neurological events.[454] In one case, 2 mL of POL 3% and 1 mL of POL 1% were injected into the varicose leg veins of a 41-year-old woman. One hour later, paresthesia developed in the right half of her body, with loss of visual field in the right upper quadrant. The neurologic signs and symptoms resolved within 2 days. There was no evidence of DVT, and all coagulation factors were normal except for a transient elevation of antithrombin III immediately after sclerotherapy, and this resolved within 5 days. Unfortunately, the patient was not evaluated for a patent foramen ovale (PFO), which was the probable causative event for this temporary cerebral vascular accident.

Another patient sustained an immediate hemiparesis that lasted for 24 hours after injection of a left leg varix with a hypertonic solution.[455] An open atrial septal defect was demonstrated on ultrasound; however, thrombosis was not detected in the varicose or deep veins of the leg or in the cerebral circulation.

A third patient was reported to have developed right hemiparesis soon after undergoing sclerotherapy of the

right GSV with 0.5% POL foam.[456,457] In this 61-year-old patient, an immediate carotid duplex scan as well as an MRI of the brain was performed, both of which yielded normal results. A subsequent echocardiogram revealed a PFO as well as an associated atrial septal aneurysm and a right-to-left shunt. The authors assumed that the stroke, which resulted in residual impairment in the patient's fine motor skills, was the result of a paradoxical embolism of the foam through the PFO. The ischemia could have resulted from either an air embolism or an arterial spasm induced by the POL sclerosant.

A case of middle cerebral artery air embolism was reported that resulted in a dense right hemiplegia with slurred speech shortly after administration of 2 mL of 0.5% STS foam and 1 mL of 0.3% liquid.[458] Symptoms began to resolve at 2½ hours posttreatment, and by 3 hours posttreatment the patient had a normal neurologic examination. A subsequent transesophageal echocardiogram performed 2 months later revealed no evidence of PFO or intra-arterial shunt.

Because 20% to 30% of unselected patients can be found to have a PFO with current ultrasound techniques,[459] this complication may occur more often than reported. Several studies have shown that, when evaluating a patient for a PFO, use of a contrast transcranial Doppler (cTCD) yields highly sensitive and specific results.[460,461] Compared with the transesophageal echocardiogram, which is currently the gold standard in PFO detection, cTCD is cheaper as well as easier to administer. The only disadvantage to the cTCD is that it can—in rare cases—occasionally fail to detect PFOs of very small diameter. However, current consensus does not advocate routine pretreatment PFO screening in sclerotherapy patients, because some reported serious adverse events occurring around the time of sclerotherapy are probably coincidental.[54] Specifically, adult patients choosing to undergo sclerotherapy usually fall within the same age range as those at highest risk for first manifesting pathologic cardiovascular and neurologic events. However, any patient who reports or manifests neurologic symptoms should be evaluated carefully for leg and cerebral thrombosis as well as a PFO. Consideration should be given to anticoagulation therapy in these patients.

PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

PE and DVT occur very rarely after sclerotherapy. The French registry reported one case of DVT after 12,173 sessions, and no PE; an incidence less than 1 per 10,000 sessions can be estimated.[228] It is hard to tell how many DVTs were to be expected in such a population during the time of the registry; thus, it is still difficult to ascertain whether sclerotherapy has some responsibility. However, in the same registry, several cases of thrombotic complications have been reported that do not require the same management, but which must be identified and followed carefully (especially gastrocnemius vein thrombosis). In an excellent review, Feied[462] summarized the major reports and risk factors for DVT.

The diagnosis of DVT is often clinically difficult, with up to 50% of cases going unnoticed. The most common clinical finding is mild enlargement of the calf or thigh, leg pain, pitting edema, warmth, dilated superficial veins and erythema. Unfortunately, these findings are not sensitive or specific for DVT and may be caused by other disease processes.[463–466] Plasma D-dimers are sensitive markers for thrombosis but lack specificity. They therefore cannot be used to make a positive diagnosis of DVT but have a high negative predictive value and are useful as an exclusionary test.[467] The reader is referred to a review of laboratory markers that may be useful in the diagnosis of venous thromboembolism.[468] An excellent decision tree diagnostic approach to evaluating a systematic review of the patient's risk factors, symptoms and physical signs, in addition to noninvasive testing, has been demonstrated to help guide further diagnostic testing and treatment strategies.[469]

Embolization of a thrombus occurs in more than 50% of patients[470] and is not diagnosed in up to 70% of cases,[471] with mortality approaching 35% without treatment.[472] Clinical suspicion and the use of precautionary measures are important in preventing this complication. Establishing the diagnosis of DVT on clinical grounds is accurate only 50% of the time as compared with the use of fibrinogen scanning.[473] Venous Doppler examination has a 30% to 96% accuracy, depending on the experience of the investigator.[474–476] Likewise, impedance phlebography has 40% accuracy.[476] Thus, the reported incidence of DVT after sclerotherapy may be greatly underestimated.

In the 1930s and 1940s, PE after sclerotherapy of varicose veins occurred in at most 0.14% of patients.[477,478] In a series of 45,000 injections given to 7500 patients, only one episode of PE was reported.[479] In 1928, Sicard reported 325,000 injections without a pulmonary infarction.[480] Linser and Vohwinkel[481] reported four cases of PE after 75,000 injections, only one of which was fatal. With the introduction of compression techniques in combination with sclerotherapy, this complication has become even less common. Sigg[482] reported PE occurring only once with 42,000 injections. A French vascular surgeon who treats approximately 75 sclerotherapy patients per week, amounting to 25,000 yearly injections, reported only one case of PE in 20 years.[325] Fegan[314] reported never having seen conclusive evidence of DVT after injection treatment of 16,000 patients in his clinic. Researchers in the 2-year Australian Polidocanol Trial reported one case of major DVT and two cases of minor DVT that occurred after injection of 4 mL of POL 0.5%, 4 mL of POL 0.5% and 0.5 mL of POL 1%, respectively, in 12,544 injected legs, for an incidence of approximately 0.02% (Fig. 8.52).[245] In a review of 28 cases of PE after sclerotherapy, most cases occurred in patients at bed rest and occurred 1 to 21 days after the treatment session. The incidence of PE in this series was estimated as 1 per 10,000 patients.[483]

To evaluate the true incidence more accurately, Stevenson et al[484] used continuous screening ascending venography to study 13 patients undergoing compression sclerotherapy with Fegan's technique. Not more than 1 mL of STS 3% was injected, with the total amount not exceeding 5 mL. Patients were seen in follow-up 1 week later for comparison venography. Radiographic studies of the patients showed no evidence of DVT.

An additional study using impedance plethysmography and Doppler ultrasonic examination was performed before and after sclerotherapy by the classic Fegan technique in 67

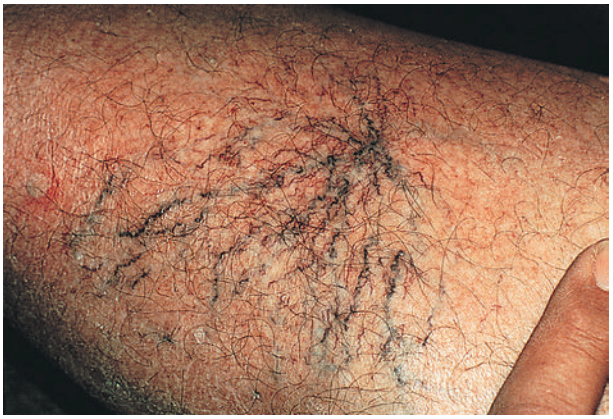


Figure 8.52 A 73-year-old man whose leg telangiectasia shown here developed pulmonary embolus after sclerotherapy treatment. He was later shown to have leukemia and a clotting disorder. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (Courtesy David Duffy, MD; from Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishing; 1999.)

legs.[485] This study confirmed no alterations in deep venous blood flow at 1 and 2 weeks after injection treatment. This confirmed the clinical experience that sclerotherapy using the Fegan technique is highly unlikely to be complicated by the development of DVT. Venographic evaluation of the injection of 0.5 to 1.0 mL of sclerosing solution in 15 patients with incompetent perforator veins failed to demonstrate extension of radiocontrast media into the deep venous system.[484]

Another reason why sclerotherapy does not usually result in DVT may be related to platelet inhibition by sclerosing solutions.[486] It has been shown that platelet aggregation, the first step in thrombogenesis, is inhibited by the concentrations of sclerosing solution that usually occur in the deep venous system after sclerotherapy of superficial varicosities.[487,488] However, an additional study with serial measurement of thrombin–antithrombin III complexes (TAT), D-dimer, fibrinogen and C-reactive protein (CRP) before and on the 7th and 28th days after sclerotherapy in 23 patients contradicts the latter three studies.[489] Here, a higher incidence of superficial thrombosis was observed, and the TAT concentration at day 7 and day 28 was higher than the preoperative level. The sclerosing agent used was HS 14.6%, with a maximum amount of 20 mL injected, followed by an unspecified type of compression. Thus, latent activation of the coagulation system does occur with sclerotherapy, possibly as a result of damage of both superficial and deep venous endothelial cells. Sclerotherapy may be a risk factor for venous thromboembolism, especially in patients with an underlying hypercoagulability.

CAUSE

The cause of DVT, with or without PE, after sclerotherapy is unclear. The three major factors responsible for DVT were first elucidated more than 100 years ago by Virchow:[490]

- Endothelial damage
- Vascular stasis
- Changes in coagulability

Sclerotherapy always produces the first two causes in the triad, with coagulability changes related to endothelial damage as well as to the coagulability properties of sclerosing solutions and predisposing hypercoagulability factors in the patient. Chemical endophlebitis produced by sclerotherapy should anchor the thrombus to the site of injection. Histologic examination of treated varicose veins has demonstrated that firm thrombosis occurs only on the damaged endothelium. Nonadherent thrombosis occurs on normal endothelium.[491] Therefore, the most logical explanation for the development of emboli is damage to the deep venous system by migration of sclerosing solution or a partly attached thrombosis into deep veins from treated superficial veins. This may occur as a result of either injection of excessive volumes of sclerosing solution or physical inactivity after injection.[492]

An additional possibility concerns injection of tributary perforator veins, which may directly communicate with the deep venous system. In this situation, inadequate compression or injection of even 0.5 mL of sclerosing solution may force nonadherent thrombi into the deep circulation with muscle contraction. Ascending venography and digital subtraction phlebography in women with leg telangiectasia revealed that 0.7 mL of contrast medium injected into telangiectatic branches spread into the saphenous system in 8 of 15 patients.[493] Two of the eight patients had telangiectasia as the only clinically perceptible abnormality. Therefore, it is possible that up to 13% of patients with telangiectatic veins are at risk for the spread of sclerosing solution directly into the deep venous system. This further emphasizes the importance of limiting injection volumes.

Amount of Injection per Site

The circulation and direction of blood flow in varicose veins have been determined radiographically as stagnant or reversed (away from the heart), so the chemically induced thrombus is forced distally toward the smaller branching veins.[494] However, cinematographic studies documented that a small amount of sclerosing solution entered the deep circulation after injection of 0.5 to 1.0 mL of solution into a superficial varicosity during 7 of 15 injections in nine subjects (Figs 8.53 and 8.54).[495] No adverse effects were noted in these patients treated with POL 2%, probably because of rapid compression and ambulation of treated individuals and the resulting rapid dilution of the sclerosing agent within the deep venous system.

Although studies demonstrating the rarity of DVT after sclerotherapy are reassuring, DVT and embolic episodes usually occur 4 to 28 days after the sclerotherapy session,[477] and therefore longer follow-up is necessary. In addition, nearly 40% of patients with DVT have symptomatic PE.[496]

Both DVT and PE have been reported to occur with injection of large quantities of sclerosing solution (12 mL) in a single site.[497] Two separate case reports of this complication, occurring with injection of less than 0.5 mL of POL 1% in two patients in each report, have been published.[245,497] In both reports, the injected veins were leg telangiectasias. In addition, the injection of 0.5 to 1 mL of sclerosing solution above the midthigh resulted in a presumed thrombus at the SFJ with resulting PE.[305] This prompted Reid and Rothnie[305] to recommend that injections not be given above the midthigh.

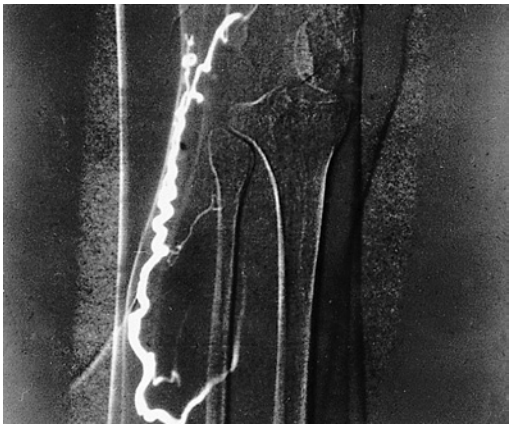


Figure 8.53 Injected contrast media (1.5 mL) shown 9½ seconds after injection into a varicose vein with the patient supine. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishing; 1999.)

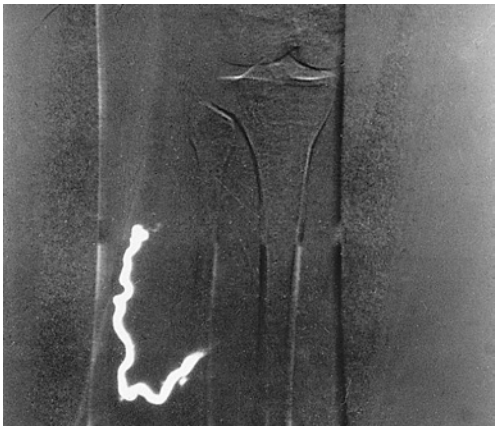


Figure 8.54 Injected contrast media (1.5 mL) shown 9½ seconds after injection into a varicose vein with the patient standing. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishing; 1999.)

Thus, the quantity of sclerosing solution per injection site must be limited to ensure that the agent remains within the superficial system, and blood flow in the deep venous system must be rapidly stimulated by compression and muscle movement after sclerotherapy.

Sclerotherapy of pedal veins may be hazardous because the lack of valves or reversal of valves allows inward flow from superficial to deep veins,[499] which may produce DVT. Therefore, when treatment of pedal veins is necessary, phlebectomy may be preferable to sclerotherapy.

Combining Sclerotherapy with Surgical Procedures

As stated previously, endothelial damage, vascular stasis and changes in coagulability are the major predisposing factors for DVT. Because sclerotherapy produces endothelial damage and the sclerosing agent changes coagulability, the addition of surgical immobilization with relative vascular stasis places the patient at risk for DVT and PE. A case report illustrates this problem.[500] Here, the patient had a high ligation of the GSV at the SFJ under local anesthesia, followed by sclerotherapy of distal varices with POL 3%. A total of 3 mL was injected into six sites. Compression was applied, and the patient was ambulatory but remained in the hospital after treatment. On the first postoperative day, the patient collapsed after starting to walk, and massive PE was diagnosed and appropriately treated. Obviously, the sclerosing solution had traveled into the deep venous system through perforating veins not ligated during the surgical procedure. We have evaluated similar cases that occurred in the United States under similar circumstances. The common denominator in all these cases is the combination of sclerotherapy with surgery. Therefore, it appears prudent to separate these two procedures by an appropriate time interval to allow the patient's coagulation system to normalize, as well as to allow the patient sufficient time to resume normal ambulation.

Inappropriate Compression

The inappropriate tourniquet effect of an excessively tight wrap on the thigh is a rare cause of the development of DVT.[501] Occlusion of deep venous flow results in popliteal vein thrombosis, which can be resolved with conservative treatment. The adverse effects of nongraduated compression emphasize the importance of using properly fitted graduated support stockings in sclerotherapy.

Hypercoagulable States

A number of primary and secondary hypercoagulable states exist that can be ruled out through the use of an appropriate patient history and a review of systems in the presclerotherapy evaluation (Box 8.2). The prevalence of inherited thrombotic syndromes in the general population is 1 in 2500 to 5000, but it increases to 4% in patients with a past history of thrombosis.[502] In addition, a past history of DVT raises the likelihood of new postoperative venous thrombosis from 26% to 68%, whereas a past history of both DVT and PE gives nearly a 100% incidence of thrombosis.[503] Thus, sclerotherapy should be undertaken cautiously in patients with previous DVT. Further detail on all hypercoagulable states is beyond the scope of this chapter. The most common states are discussed later. The reader is referred to multiple review articles on this important subject.[462,502,504,505]

Oral Contraceptive Agents and Estrogen Replacement Therapy

The mechanism for thromboembolic disease in women who use oral contraceptives is multifactorial. Both estrogens and progestogens have been implicated in promoting thrombosis despite low-dose therapy.[506–508] All studies have indicated that the increased risk occurs only while the preparations are actually in use and perhaps for 1 week or so after discontinuation.[509,510] Total correction of the potentially hemostatic changes that occur during oral contraceptive therapy requires 4 weeks of abstinence.[511]

The highest rate of thromboembolism occurs with the use of higher levels of estrogen[506–509,512]; some studies show an 11-fold increase.[510,513] Nevertheless, the risk of postoperative PE still appears increased in women who use oral contraceptive agents with minimal amounts of estrogen.[514]

Box 8.2 Hypercoagulable States

Primary hypercoagulable states

Deficiency in inhibitors of coagulation
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Disorders of the fibrinolytic system
Plasminogen deficiency
Plasminogen activator excess
Dysfibrinogenemias
Vascular damage
- Homocystinuria

Platelet damage
- Paroxysmal nocturnal hemoglobinuria
- Lupus anticoagulant

Secondary hypercoagulable states

Abnormalities of coagulation and fibrinolysis
- Pregnancy
- Malignancy
- Nephrotic syndrome
- Oral contraceptives
- Estrogen/progestin supplementation
- Inflammatory bowel disease

Infectious diseases
- Secondary syphilis
- Psittacosis

Platelet abnormalities
- Myeloproliferative disorders
- Diabetes mellitus
- Hyperlipidemia
- Paroxysmal nocturnal hemoglobinuria
- Lupus anticoagulant
- Heparin-associated thrombocytopenia

Stasis or aberrant blood flow
- Varicose veins
- Congestive heart failure
- Immobilization
- Obesity
- Advanced age
- Perioperative state
- Polycythemia vera, sickle cell disease
- Dehydration
- Paraproteinuria

Endothelial damage
- Intravenous catheters
- Intravenous solutions
- Intravenous drug abuse
- Vasculitis
- Behçet's disease
- Thromboangiitis obliterans

Modified from Thomas JH. Am J Surg 1990;160:547; and from Samlaska CP, James WD. J Am Acad Dermatol 1990;23:1.

Interestingly, a detailed review of the statistical methodologies of these studies did not prove a definite risk.[515] The following paragraphs provide a brief review on this topic.

The incidence of DVT after oral contraceptive use varies depending on the type and concentration of estrogen. In addition, there is at least a 200-fold difference in potency between the native estrogens estrone, estradiol and ethinyl estradiol and the estrogens found in oral contraceptive agents.[516] Hormone replacement therapy with 0.625 mg of conjugated equine estrogens and 2.5 mg of medroxyprogesterone has an elevated risk of DVT 2.0 to 3.6 times higher than among nonusers.[517]

It has been estimated that oral contraceptives are responsible for one case of SVT or DVT per 500 women users per year.[518] This estimate of hypercoagulability may be low because an examination of plasma fibrinogen chromatography demonstrated a 27% incidence of silent thrombotic lesions in 154 new contraceptive users of either mestranol 100 mg or ethinyl estradiol 50 mg.[519] Oral contraceptive users as a group have numerous alterations in their coagulation system that promote a hypercoagulable state. They include hyperaggregable platelets, decreased endothelial fibrinolysis,[520] decreased negative surface charge on vessel walls and blood cells,[521] elevated levels of procoagulants, reduced RBC filterability,[522] increased blood viscosity secondary to elevated RBC volume,[523] and decreased levels of antithrombin III.[524–526] Any of these factors, alone or in combination, may predominate in women taking oral contraceptives. The extent of this derangement in the hemostatic system determines whether thrombosis will occur. When endothelial damage with sclerotherapy is initiated in this population, an increased incidence of thrombosis may result.

The most important factors preventing clot propagation are antithrombin III and vascular stores of t-PA.[524,527–529] Antithrombin III levels have been demonstrated to be 20% lower in some women taking oral contraceptive agents[527] and estrogen replacement therapy.[530] Of women using oral contraceptive agents who have thromboembolic events, 90% have a 25-fold decrease in releasable t-PA[524,527,528]; 51.6% have an abnormally low plasminogen activator content in the vein walls.[529] Therefore, a certain subgroup of women taking birth control pills is at particular risk for thromboembolic disease.

In addition, increased distensibility of peripheral veins may occur with use of systemic estrogens and progestins.[531] This may promote valvular dysfunction and a relative stasis in blood flow to add to the hypercoagulable state. Because it is practically impossible and also impractical at this time to determine which women are at risk, it appears prudent to recommend that patients consider discontinuing this medication before sclerotherapy.

Alternatively, because oral contraceptive agents and estrogens have peak levels 3 to 5 hours after administration, alternative routes of administration, such as transdermal and vaginal, should be considered. For women who cannot discontinue oral estrogen replacement therapy, the use of transdermally administered 17β-estradiol may be an option.[532] By delivering estrogen directly into the peripheral circulation, the 'first-pass effect' of liver metabolism is eliminated. This decreases hepatic estrogen levels with subsequent minimization of estrogen-induced alteration of coagulation proteins. Thus, it is recommended that transdermal estrogen be used in patients at risk for thromboembolism, because alterations in blood clotting factors have not been demonstrated during such treatment.[533] In addition, the use of esterified estrogens as opposed to conjugated estrogens has been shown not to increase the incidence of venous thrombosis in perimenopausal and postmenopausal women.[534]

Tamoxifen

For multiple reasons, including prevention of breast cancer in high-risk populations, adjunctive treatment of breast cancer, and possibly treatment and prevention of osteoporosis, tamoxifen is not an uncommon medication for patients who are seen for leg vein treatment. An unusual and poorly understood complication of tamoxifen use is the development of thrombophlebitis and DVT (see Fig. 8.43). This occurs in up to 1% of treated patients.[535,536] Results of evaluation of various coagulation parameters and factors, including sex hormone–binding globulin, antithrombin III, fibrinogen, platelet count, protein C and fibrinopeptide A, have been normal.[536–540] Until more is known about this theoretical predisposing factor to thrombosis, note should be taken of patients receiving tamoxifen.

Pregnancy

It was common medical practice as early as 1579 not to tamper with varicose veins during pregnancy.[541] However, some physicians advocate removal of varicose veins to prevent postpartum venous thrombosis.[542] These authors reported a distinct lack of complications to both mother and baby with this practice, even though treatment spanned the first to the eighth month of gestation. However, in addition to the possible effects on the fetus through passage of sclerosing solution via the placental barrier, there is a potential for stimulating thrombosis.

Endothelial cell damage (presumably through sclerotherapy) releases t-PA to promote coagulability on the already formed clot, which invariably occurs in the immediate postsclerotherapy period.[543] In addition, coexistent hypercoagulability may promote excessive (uncontrolled) thrombosis. The hypercoagulable state in the immediate antepartum period is largely responsible for the development of superficial thrombophlebitis and DVT in 0.15% and 0.04% of this patient population, respectively.[544] Even more important is the immediate postpartum period, during which the incidence of superficial thrombophlebitis and DVT is 1.18% and 0.15%, respectively.[544] DVT developed by the second postpartum day in 50% of patients. This development may be a result of the rapid decrease in coagulation factors at partum, which normalizes in most patients on the third day.[545] However, additional factors also must play a role, because DVT develops in an additional 21% 2 to 3 weeks postpartum. Interestingly, two thirds of the patients who developed postpartum DVT had varicose veins. The age of the mother also was linked to venous thrombosis, with the rate changing from approximately 1:1000 in women younger than 25 years of age to 1:1200 in women over 35 years.[512]

During pregnancy, most procoagulant factors increase and fibrinolytic activity decreases. Plasma fibrinogen levels gradually increase after the third month of pregnancy to double those of the nonpregnant state. In the second half of pregnancy, factors VII, X, VIII and IX are also elevated.[546] Decreased fibrinolytic activity is probably related to a decrease in circulating plasminogen activator.[547] In addition, a 68% reduction in protein S levels has been measured during pregnancy and in the postpartum period.[548] Protein S levels do not return to normal until 12 weeks postpartum. These changes are necessary to prevent hemorrhage during placental separation. Thus, in addition to the potential adverse effects on the fetus, sclerotherapy in the near term should be avoided until coagulability returns to normal—at the earliest, 6 weeks postpartum.

Inherited Clotting Factor Abnormalities: Thrombophilia

Another subgroup of patients, composed of those with an underlying thrombophilia, is also at increased risk for DVT development.[549–552] Hamel-Desnos et al assessed postsclerotherapy thrombotic complications in a prospective study of patients having one or more of the three most common forms of thrombophilia.[553] Specifically, patients had a factor V Leiden mutation, a factor II mutation, an elevated level of factor VIII or a combination of these. Owing to ethical concerns, thromboprophylaxis with LMWH or warfarin accompanied sclerotherapy. None of the 105 patients who were studied developed a symptomatic DVT, a symptomatic PE or an asymptomatic, ultrasound-detected DVT.

Protein C and protein S are two vitamin K–dependent proteins that are important anticoagulant factors preventing thrombosis. Protein S is a cofactor for activated protein C (APC) on factor Va. It has been estimated that the prevalence of heterozygous protein C deficiency is 1:300 to 1:60 healthy adults in the United States.[554] More than 95% of these persons are asymptomatic and without a history of thrombotic disease. However, these deficiencies may predispose them to the development of DVT. Seventy-five percent of patients homozygous for protein S deficiency develop venous thrombosis before the age of 35 years.[555]

It has been speculated that damaged endothelium in combination with this deficiency may be necessary for symptomatic thrombosis to occur.[556] In otherwise healthy patients under 45 years of age referred for evaluation of venous thrombosis, the prevalence of deficiencies of antithrombin III, protein C and protein S is approximately 5% each.[557] In the general population, the overall prevalence of inherited and acquired thrombophilia cases is estimated to be between 10% and 15%.[558] A resistance to APC is at least 10 times more common than any known genetic defect for venous thrombosis and has been found in approximately one third of patients referred for evaluation of DVT.[559,560] Precipitating factors for thrombosis, such as pregnancy and the use of oral contraceptives, were present in 60% of these patients. Therefore, patients who exhibit excessive thrombosis with sclerotherapy and patients with a family history of thrombotic disease should be screened for deficiencies of protein C and protein S before treatment.

A heterozygous mutation for APC, with an incidence of 2% to 5%, also exists.[561] This results in an 8- to 10-fold increased incidence of venous thromboembolism.

A transient circulating autoantibody is a rare cause of acquired protein S deficiency. An 11-year-old boy with varicella was described as having this transient abnormal immune response, which resulted in severe thromboembolic disease.[562] With chickenpox, endotheliitis may disrupt normal production of protein S.[563] In this patient, thrombosis was resistant to heparin therapy, and it was postulated that infusions of protein S would have been therapeutic. Although this is an extremely rare cause of DVT, the withholding of sclerotherapy in febrile patients, especially those with varicella, Rocky Mountain spotted fever and vasculitis, is recommended.

Antithrombin III deficiency occurs in 1:2000 to 1:5000 people in the general population.[564,565] Acquired antithrombin III deficiency may result from liver disease and from the use of oral contraceptives, as previously discussed.

Defects in the fibrinolytic system, specifically plasminogen, occur in up to 10% of the healthy population.[566] When they occur alone, there is little risk of thrombosis. Abnormal plasminogen levels may also predispose to thrombosis.

Lupus-like anticoagulants are present in 16% to 33% of patients with lupus erythematosus, and they are also associated with a variety of autoimmune disorders.[567–569] Thrombosis develops in 30% to 50% of patients with lupus-like anticoagulants.[569–571]

If thrombophlebitis or DVT develops in a patient after sclerotherapy and a workup for hypercoagulability is normal, a search for an occult malignancy must be considered. We observed thrombophlebitis of superficial reticular veins develop despite adequate compression in one patient who was found to have an occult breast carcinoma on further examination.

Malignant Disease

The association of DVT and the subsequent diagnosis of malignancy was made in 1865 by Armand Trousseau.[572] Malignant tumors produce thrombin, which aids in tumor cell adhesion and tissue factors that act as potent coagulants.[573] Transformed malignant cells also produce vascular endothelial growth factor and cancer procoagulants.[574] This has been shown to occur most commonly in lung cancer, but it has also been seen in colorectal, breast, bladder, pancreatic and thyroid cancer.[575] However, studies defining the need for investigations for underlying malignant disease in patients with DVT of unknown origin are mixed.[576,577] We have seen two patients who were found to have an underlying breast carcinoma and one with an underlying ovarian carcinoma who developed SVT after sclerotherapy. Because 15% to 20% of cases of venous thromboembolism are associated with malignancy, and because early diagnosis improves the prognosis for most patients with a malignancy, this potential underlying diagnosis deserves attention any time a DVT or a PE is first diagnosed.[578]

Venous thromboses are not the only potential warning signs for an underlying malignancy. Thrombophlebitis can also be associated with an underlying malignancy. Kobus et al described a case of a 48-year-old woman who was diagnosed with advanced breast cancer several days after experiencing extensive thrombophlebitis of the SSV and a perforating vein of that same leg following foam sclerotherapy for small varicose veins with Aethoxysklerol 0.5% foam.[579] The authors recommend a meticulous workup of any patient who develops thrombophlebitis involving an unusually long vein segment or who displays particularly strong signs of inflammation (redness, pain), regardless of whether it occurs around the time of sclerotherapy or spontaneously without an obvious trigger.

PREVENTION

Because of the potentially lethal nature of excessive thrombosis, all attempts should be made to minimize its occurrence. Certain authors suggest that the quantity of sclerosing solution should be limited to 0.5 to 1 mL per injection site to prevent leakage of the solution into the deep venous system.[441] Other techniques that minimize damage to the deep venous system include rapid compression of the injected vein with a 30- to 40-mmHg pressure stocking, followed by immediate ambulation or calf movement of the injected extremity and frequent ambulation thereafter to promote rapid dilution of the solution from the injected area. Full dorsiflexion of the ankle empties all deep leg veins, including muscular and soleal sinuses.[580] Fegan[581] reported no cases of DVT or PE in 13,352 patients when the quantity of sclerosing solution was limited to 0.5 mL and rapid compression was used.

The critical time period for thrombus formation in sclerotherapy-treated vessels is approximately 9 hours after treatment. Therefore, compression stockings or bandages are most beneficial during the night after sclerotherapy and during other periods of relative vascular stasis when an intravascular thrombus is being formed.

Foley[582] advocated the addition of heparin 100 U/mL to HS to prevent the theoretical possibility of embolization associated with 'microthrombus formation' in sclerotherapy. However, in a well-controlled, randomized study of 800 patients treated with and without heparin in the sclerosing solution, researchers found no evidence for embolization and no difference in the incidence of thrombophlebitis or microthrombosis requiring puncture evacuation.[583]

Consideration must be given to treating elderly patients because they have a reportedly increased risk for DVT.[282,584–586] It is hypothesized that the major cause of this increased risk is the relative pooling of blood in the soleal venous sinuses, which occurs from decreased calf muscle pump infusion.[587] In the elderly population, it may be best to perform small treatments, with calf pumping given manually immediately after injection.

Venous stasis is the most likely mechanism for DVT after sclerotherapy. This can be caused by an improperly bandaged extremity or by immobilization of a treated limb. At least one case of fatal PE after sclerotherapy has been blamed on improper bandaging coupled with a prolonged car ride immediately after treatment.[588] If a patient becomes ill or injured after sclerotherapy, he or she must avoid immobilization. In this scenario, heparin prophylactic anticoagulation is strongly recommended until ambulation is restored.[462]

French phlebologists are in favor of sclerotherapy in patients with thrombophilia. They recommend performing sclerotherapy with prevention using injection of one dose of 50 mg of LMWH immediately before the sclerotherapy session.[589] In a retrospective study of 134 patients with thrombophilia, 56 of whom received sclerotherapy, 9% developed DVT without any serious adverse event.[589] An additional study of 105 patients with a variety of conditions producing thrombophilia, including 75 with factor V Leiden mutation, 18 with prothrombin 20210A mutation and 7 with high levels of factor VIII were randomized to receive LMWH or warfarin. A total of 199 sclerotherapy sessions were performed (160 with foam) with no episodes of DVT or PE. Therefore, this study suggests that the three common forms of thrombophilia do not preclude performing sclerotherapy with adequate prophylaxsis.[590]

TREATMENT

DVT has many sequelae and is also a potentially life-threatening complication. The most serious manifestation

of DVT is the development of PE, which can be life-threatening. Late sequelae of DVT are common and frequently symptomatic. In a study of 86 patients in whom DVT developed, researchers found that 70 of the patients were symptomatic 5 to 10 years later.[591] Typical leg symptoms were evening pain, edema, restless legs and pigmentation. Up to 50% of the patients judged their symptoms to be severe 10 years after the DVT. Simple leg elevation improved symptoms in only 56% of patients. No difference was reported between calf DVT and proximal DVT. Thus, DVT treatment must be rapid and decisive.

PE usually occurs during the first 5 to 7 days of thrombus formation.[592] The classic anticoagulation method involves a bridging protocol with IV heparin followed by maintenance oral anticoagulation with warfarin and other inhibitors of vitamin K metabolism. IV heparin or subcutaneous LMWH should be continued for 3 to 5 days after initiation of warfarin to prevent an early reduction in anticoagulant protein C and protein S function before procoagulant activity is affected. Patients should receive at least 6 to 12 weeks of oral anticoagulation therapy to decrease the risk of recurrent DVT to less than 4%.[593–596]

Peripheral infusions of lytic agents may be superior to anticoagulation in reducing clots more rapidly, which should reduce late symptoms and the risk of recurrent thrombosis.[597] One study demonstrated a reduction in the incidence of adverse effects, mortality rate and length of hospital stay when urokinase was used compared with when it was unavailable.[598]

If peripheral systemic lytic therapy is ineffective, direct infusion of lytic agents into the thrombus may be useful.[599] Catheter-directed thrombolysis appears to reduce the bleeding risk of systemic lytic treatment, as well as its expense.[600,601] One study of 653 consecutive patients treated with either catheter-directed urokinase or t-PA showed less peripheral bleed with urokinase.[602] Percutaneous mechanical thrombectomy with a lytic agent facilitates thrombus extraction and improves patient outcome.[603]

To prevent recurrence, thrombolytic therapy should be followed by the use of antiplatelet agents such as aspirin or warfarin, or both. In a study published in 2003, catheter-administered L-arginine, a nitric acid precursor, after thrombectomy in an experimental animal model improved vessel patency and endothelial vasoreactivity.[604] A more complete discussion of the various lytic agents currently available is beyond the scope of this chapter. A complete review of treatment options published in March 2000 is recommended.[605,606]

In recent years, newer, unmonitored oral anticoagulants have been used successfully in both the treatment of acute venous thromboembolism and the prevention of recurrence. Dabigatran etexilate, an oral, potent, direct inhibitor of thrombin has been found to be as effective and safe as warfarin in the treatment of acute DVT and is more convenient than warfarin, as it does not interact significantly with food or medications and does not require clinical monitoring.[607] Two oral factor Xa inhibitors—rivaroxaban and apixaban—gained FDA approval for treatment of DVT in 2011 and 2014, respectively.[608–610] The decision to administer anticoagulation therapy with traditional vitamin K antagonists or with newer oral anticoagulants is dependent on individual patient characteristics and is beyond the scope of this text.[606,610]

NERVE DAMAGE/PARESTHESIA

Because of their close proximity to veins, the saphenous and sural nerves may be inadvertently injected with solution during sclerotherapy. Injection into a nerve is reportedly very painful and, if continued, may cause anesthesia and sometimes a permanent interruption of nerve function.[213] Five episodes of injection into a nerve were reported from France over 18 years.[434] Various degrees of nerve paralysis or paresis occurred.

One patient with a large vascular malformation was treated with sclerotherapy into vessels overlying the lateral aspect of the knee. During the third injection of sodium morrhuate, a foot drop developed, lasted 3 months, and fully recovered. The authors postulated that the venous anomaly involved the perineal nerve and that the inflammatory edema and/or reaction resulted in neuropraxis.[296]

Occasionally, a patient complains of an area of paresthesia in the treated leg. This is probably caused by perivascular inflammation extending from the sclerosed vein to adjacent superficial sensory nerves. Two cases reported in 2000 of limited areas of paresthesia along the course of the GSV treated with ultrasound-guided sclerotherapy detail the uneventful injections with the sensory impairment noted only upon removal of the graduated compression stockings.[611] In each case, full sensory function returned between 4 and 6 months without treatment. One must remember that occurrence of nerve pathology is much more frequent after surgery, especially stripping of the GSV below the knee (see Chapter 10).

We advise decreasing inflammation with the use of nonsteroidal anti-inflammatory medications to hasten resolution of this minor annoyance. However, this complication may take 3 to 6 months to resolve.[313]

AIR EMBOLISM

When the airblock[612,613] or foam techniques are used to inject sclerosing solutions, the theoretical possibility of air embolism is raised. The danger would be that if enough air enters the heart at one time, it might lead to vascular collapse. In addition, if air enters a cerebral vascular artery, a cerebral vascular infarction may occur. More likely, transient ischemic symptoms might occur with this injection technique.

Although only a single case of non-ST elevation myocardial infarction following foam sclerotherapy has been reported,[451] asymptomatic bubble emboli can be visualized in the heart routinely during foam sclerotherapy of the saphenous veins.[452] Introduction of air in small amounts into the venous system does not lead to clinical air embolism.[612,613] It appears that small amounts of air are absorbed into the bloodstream before the blood enters the pulmonary circulation. The pulmonary system is an excellent filter for gas bubbles and, as such, can also handle relatively large volumes of air. In the absence of an intracardiac shunt, an arterial gas embolism is an incredibly rare occurrence.[614] It has been estimated that it would be necessary to put 480 mL of air into the venous system within 20 to 30 seconds to

cause death in a person weighing 60 kg.[615] This occurrence has never been reported in the medical literature and has not occurred in perhaps over 100,000 patients injected with foamed sclerosant in the authors' and other physicians' experience or in a series of 297 cases involving the airblock technique.[612]

With the use of larger volumes of air in foam sclerotherapy, complications such as visual disturbances can and do occur.[616] This may be secondary to the presence of a PFO. It has been estimated that between 18% and 30% of adults have a PFO that is between 1 and 10 mm in diameter (mean, 4.9 mm).[617,618] PFO is also an etiology for migraine, which raises interesting questions when discussing the occurrence of migraine after foam injections.[619,620] Visual disturbances do occur with injection of foam. In the French prospective registry, 6395 foam sclerotherapy sessions were reported by 22 French phlebologists, who observed 16 episodes of visual disturbances after treatment of reticular and telangiectatic leg veins.[228] All cases spontaneously regressed without sequelae. In 8 of the 16 episodes, visual disturbances were associated with headache and/or nausea. Interestingly, in the four cases of visual disturbances reported with liquid sclerosant, three of the procedures were carried out using the airblock technique. When this observation is added to the fact that a session of sclerotherapy for telangiectasia lasts much longer than a session of sclerotherapy for varicose veins, and leaves the foam time to change into liquid plus large bubbles, it is necessary to wonder if the phenomenon is not due solely to large bubbles and not to foam.

Willenberg et al[616] conducted a systematic review of the literature in 2013. In their review, the incidence of visual disturbance was found to be between 0.09% and 2%. As expected, foam sclerotherapy was almost always the culprit, although two cases were observed when liquid sclerotherapy was used exclusively. All reported events were transient, and no lasting visual disturbance was identified.

Weiss et al[621] demonstrated the presence of bubbles in the general circulation. However, it is extremely unlikely that the interface of these bubbles could still carry a significant amount of sclerosing agent, thus limiting the effect of the bubbles to a transient phenomenon of ischemia without direct and specific endothelial lesions such as where the foam is injected.

A study of foaming detergent sclerosing solutions with either room air or carbon dioxide and oxygen in a proprietary formulation (Varisolve; BTG International, London, UK) in an animal model demonstrated that bubble size was larger and existence was prolonged in foam made with air.[622] However, it is unclear whether this difference has any practical significance in patients. The somewhat higher incidence of side effects (the majority of which were considered tolerable by patients) seen with foam compared with liquid sclerotherapy does not outweigh the superior efficacy demonstrated by the former.[55,623–628]

SCINTILLATING SCOTOMATA

Scintillating scotoma is defined as an abnormal area in the visual field. Although reported rarely in the medical literature, many physicians have told us of the development of temporary blindness or unusual visual disturbances after sclerotherapy.[629–631] These physical findings most likely suggest ischemia of the calcarine cortex, which may occur through either embolism of ophthalmic arteries via the internal carotid or a vasospastic event. Arterial embolism appears unlikely unless the patient has a PFO, because venous injection and possible embolic events terminate in the pulmonary system.

MIGRAINE

Triggering of migraine headaches in patients who have an underlying history of recurrent migraines has occurred after sclerotherapy.[8,631] This can occur with and without the use of foamed sclerotherapy but most likely is more common with foamed sclerosing solutions.[631] Monocular retinal migraine may occur in patients with a migraine diathesis. In such a case, the patient's history is helpful and the outcome is usually benign. A complete ophthalmologic examination is recommended in these patients to rule out other, more serious and treatable causative factors. Künzlberger et al described a 23-year-old woman who abruptly developed homonymous hemianopia and paresthesia in the hands and feet, followed by a headache, shortly after sclerotherapy with POL 1% liquid.[632] This patient subsequently underwent an ophthalmologic as well as a neurologic examination, both of which were otherwise normal. A PFO was ruled out, and the patient's constellation of symptoms completely resolved within 2 hours after its acute onset. In this case, an acute thrombosis of the cerebral artery, showing spontaneous and rapid resolution in an otherwise healthy, young patient, seemed highly unlikely. The lack of an underlying PFO did not support a paradoxical embolism caused by the IV injection of POL. Thus, the authors concluded that this patient's homonymous hemianopia was caused by a vascular spasm in the contralateral cerebral hemisphere. This case demonstrates a phenomenon described as 'migraine ophthalmique', which is characterized by homonymous hemianopia without macular involvement, often accompanied by migraine, dizziness and nausea. Whether certain patients have cortical regions more susceptible to systemically administered triggers (e.g., sclerotherapy at a distant site) is unclear. However, this case does demonstrate that this rare complication of sclerotherapy can occur independent of an air embolism, as liquid as opposed to foam POL was used as the sclerosant.

In patients with symptoms of a migraine or visual disturbance after sclerotherapy, the practitioner should search for a PFO. If positive and future sclerotherapy sessions are desired, the practitioner should consider using liquid rather than foam, though the former can also occasionally, albeit less frequently, cause neurologic sequelae in susceptible patients. Coleridge Smith estimated that approximately 2% of his sclerotherapy patients experience visual or chest symptoms after sclerotherapy and that these typically last less than 1 hour (e-mail communication, March 27, 2009). He recommended that patients who have had previous visual disturbances following sclerotherapy remain supine for 10 to 30 minutes after treatment, as well as that they are prevented from performing inadvertent Valsalva maneuvers in the immediate posttreatment period. Strejcek noted that he had regularly performed foam sclerotherapy for more than 6 years, with an estimated 35,400 treatments over that period, and that he had not noted any complications in any

Table 8.3 Summary of Complications of Sclerosing Agents

Solution	Pigmentation	Allergic Reaction	Necrosis	Pain
Sodium morrhuate	++	++	+++*	+++
Sodium tetradecyl sulfate	++	+	++*	+
Ethanolamine oleate	+	++	++*	++
Polidocanol	+	+	+*	0
Hypertonic saline	+	0	+++*	+++
Sclerodex (10% saline + 25% dextrose)	+	0	+	++
Chromated glycerin	0	+	0	++
Glycerin	0	0	0	+
Polyiodinated iodine	++	+	+++*	+++

*Concentration-dependent.
+, Minimal; ++, moderate; +++, significant.

case (e-mail communication March 29, 2009). He attributed this lack of complications to the fact that he always injects foam into an elevated leg and subsequently has the patient remain supine for 10 minutes following the procedure. Our experience is similar to Strejcek's. We rarely observe migraines in our patients, and we treat reticular veins with foam sclerotherapy routinely. We do not treat truncal varicose veins with foam, except in segmental recanalization following endovenous saphenous ablative procedures.

Recent work has suggested that the pathophysiology behind migraine development with aura and visual disturbance is driven by an endothelin-1 (ET-1) response triggered by sclerotherapy.[633,634] In a clinical study involving 11 human subjects, POL foam sclerotherapy triggered a significant systemic increase in ET-1 within 3 minutes after treatment.[635] Furthermore, when tested in an experimental in vitro and in vivo setting, the anti-ET-1 drug aminaphtone demonstrated the ability to significantly reduce ET-1 after exposure to sclerosing detergents.[636] Additional clinical study remains to be done to explore the utility of this finding.

MEMBRANOUS FAT NECROSIS

A case of a patient with multiple tender erythematous subcutaneous nodules that occurred after sclerotherapy with HS solution has been reported.[637] This rare dermatologic entity is the result of subcutaneous inflammation with alteration and necrosis of adipose tissue. It also may be caused by trauma, thromboangiitis obliterans, arteriosclerosis or scleroderma. Essentially, it is a diagnosis of exclusion made on the basis of the biopsy result. In the reported patient, extravasation of HS solution or vessel rupture with subsequent exposure of HS to subcutaneous tissues was the probable causative event.

SUMMARY

Sclerotherapy of varicose and telangiectatic leg veins may be associated with a number of complications and adverse sequelae, which may occur despite expert and optimal treatment. Some adverse sequelae are preventable to a limited degree, but, given a large enough number of procedures, these adverse sequelae will occur in any practice. Complications can be minimized with adherence to principles of slow injection, minimal sclerosant concentration, low injection pressures and watchful technique. As with any procedure, sclerotherapy has inherent risks, although with low incidence, considering the millions of procedures performed worldwide. Each patient should be evaluated and informed accordingly before initiating treatment. A summary of the common complications that can occur with the commonly used sclerosing agents is presented in Table 8.3.

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9 Clinical Methods for Sclerotherapy of Varicose Veins

Mitchel P. Goldman, Jean-Jérôme Guex, with contributions by Joanna Bolton and Lisa Zaleski-Larsen

We feel from our three and one-half years' experience that the surgeon who believes that there is nothing more required than a syringe, some solution, and a patient to effect permanent obliteration of varicose veins, still has much to learn.[1]

The opening, timeless quotation from Henry Faxon, Assistant in Surgery at Harvard Medical School in 1933, resulted from a careful analysis of 314 cases from the peripheral circulatory clinic of the Massachusetts General Hospital. Unfortunately, this quotation is timeless in that only through a continual careful evaluation of past results and review of our colleagues' experience can sclerotherapy treatment be provided in an optimal manner.

Varicose veins represent tortuous dilations of existing superficial veins. They arise because of multiple factors but are always associated with a relatively elevated venous pressure.[2] Therefore, it has been considered for decades that treatment initially consists of cutting off the point of high-pressure inflow to the veins (through either surgical or sclerotherapeutic methods) before treating the varicose veins themselves.[3,4]

Although this approach has been questioned, in certain cases, the importance of the 'siphon' effect generated by the underlying varicose reservoir is strong enough to generate a reflux in saphenous trunks. It has been observed that suppression of the varicose network reduces reflux in the saphenous trunks. The development of varicose veins in the reticular network and centripetal progression of the disease, as advocated by Hébrant and Collignon, is a hypothesis that could explain a number of varicose patterns, and an increasing number of specialists are currently applying a more distal and conservative approach, whether surgical or sclerotherapeutic.[5]

Because varicose veins are not life threatening, their treatment should be efficacious, cosmetic, relatively free of adverse sequelae and complications, and without significant pain. Gaius Marius, the Roman tyrant, was in extreme pain both while and after his varicose veins were treated with surgery. When the same surgeon recommended the same treatment for the other leg, which was also involved with venous disease, Gaius Marius refused treatment and was quoted as saying, 'I see the cure is not worth the pain.' This chapter describes sclerotherapy treatment of varicose veins that patients will submit to and even request for further therapy when recommended.

HISTORICAL REVIEW OF TECHNIQUES

Modern sclerotherapy started at the beginning of the twentieth century.[6,7] Tournay in France, Sigg in Switzerland and Fegan in Ireland developed different schools of practice. More recently, ultrasound-guided sclerotherapy has been popularized, mainly for the treatment of saphenous trunks and incompetent perforating veins. The precise diagnosis of varicose vein disease and the recognition of the most proximal point of reflux dictates the choice of optimal treatment technique and reduces the risk of recurrence and complications such as pigmentation and matting[7] (see Chapter 8).

TOURNAY (FRENCH) TECHNIQUE

The Tournay procedure encompasses the basic principle of 'French phlebology' developed by Tournay et al:[8] treating varicose veins 'from high to low' ('de haut en bas'). The rationale for this technique is in first eliminating high-pressure reflux blood flow at the point of occurrence. Treating from proximal to distal sites also eliminates the weight of the column of blood on the sclerosed point. This has the advantage of minimizing thrombosis and the extravasation of red blood cells (RBCs) from a sclerosed vein segment. The French school advocates placement of very few injections at this 'high' (proximal) point before treating more distal veins or sections of the same vein at a later date. This same philosophy toward treatment was also reported from the Mayo Clinic in 1941 by Heyerdale and Stalker.[9] The principle of eliminating reflux from the saphenofemoral junction (SFJ) was espoused even earlier by Moszkowicz[10] in Germany in 1927 and by de Takats and Quint[11] in the United States in 1930. Thus the 'French technique' is multicultural in its origin.

In addition to developing a treatment regimen with the tenet just mentioned in mind, it is critical to obliterate the SFJ accurately because its location and anatomy are so variable (see Chapter 1). To determine the origin of high pressure in the varicose vein, a noninvasive diagnostic evaluation of the patient should be performed first (see Chapter 5). The handheld Doppler device helps detect points of reflux from the deep to the superficial veins, through either incompetent saphenofemoral or saphenopopliteal junctions or perforating veins. In certain circumstances, additional testing

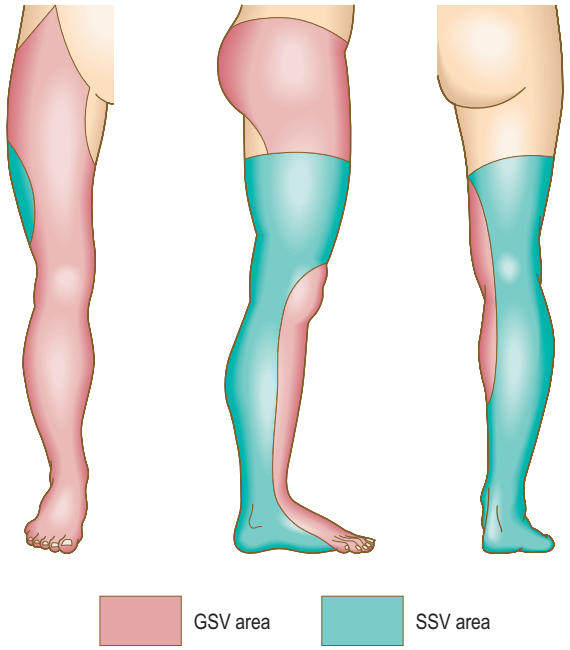


Figure 9.1 Diagram of the great saphenous vein (GSV) and small saphenous vein (SSV) 'systems'. (Redrawn from de Groot WP. J Dermatol Surg Oncol 1989;15:191.)

is required. If any points of reflux are detected, they should be treated first. After the high-pressure flow has been eliminated, treatment should proceed first with injection of the largest varicose veins, then injection of the reticular feeding veins and finally treatment of the remaining 'spider' veins.

In defense of the logic of the French technique, de Groot[4] pointed out that any vein in the leg belongs to either the greater saphenous system or the lesser saphenous system (Fig. 9.1). This concept implies that a vein within the defined area of the great saphenous vein (GSV) eventually drains into the GSV. Therefore, reflux in that vein is derived from reflux at the SFJ. This concept directs treatment toward the reflux point. Unfortunately clinical examination of the location of a vein does not always correctly determine the point of reflux. Therefore the clinical examination must be correlated with a noninvasive examination to establish the optimal order of therapy.

SIGG (SWISS) TECHNIQUE

In contrast to the French technique, the Swiss technique of Sigg[12] and the modification by Dodd and Cockett[13] advocate total sclerosation of the entire varicose vein, including incompetent perforator veins (IPVs) and the SFJ. This technique has also been adopted by some physicians who modify Fegan's technique of sclerotherapy of the IPVs (described in the following section). Included in this school are Reid and Rothnie,[14] who treated 1358 legs of 974 patients and found that selective injection of perforator veins was ineffective, requiring multiple additional treatments of the entire vein. They evolved a technique of placing multiple injections at intervals along the varicose veins to produce diffuse sclerosis and have reported very favorable results. This latter technique is called the total-vein sclerotherapy technique.

FEGAN (IRISH) TECHNIQUE

Fegan et al[15] proposed a view opposite to the previously mentioned one, namely that saphenofemoral incompetence could occur as a result of perforator incompetence alone. They reached this conclusion by demonstrating that the calf muscle pump is more powerful than the abdominal or femoral muscles regarding venous flow in the leg. They proposed that sclerotherapy of the IPVs should be performed first, to restore normal function. Fegan's examination of the SFJ and GSV with phlebography after sclerotherapy of IPVs showed narrowing of the vessel lumen in 9 of 11 patients.[16] However, surgical exploration of clinically diagnosed areas of perforator vein incompetence has found at best a 60% incidence of perforator veins being correctly identified clinically.[17] In addition, phlebographic examination performed on 112 patients with clinically suspected incompetent perforators showed that the clinical examination correctly identified only 38% of perforator veins below the knee and only 17% of thigh perforators.[18] An additional study of 180 limbs with primary varicose veins studied with clinical examination, ascending deep-to-superficial venography, Doppler ultrasound and ambulatory venous pressure measurements showed that only 40% of these patients had evidence of perforator incompetence. Of these, 30% had no hemodynamic significance to the perforator veins.[19] Thus, the rationale for Fegan's technique is open to dispute.

Despite the lack of accuracy of clinical diagnosis of IPVs, many authors have found Fegan's technique gives excellent results. Tolins[20] reported favorable results using Fegan's technique; he injected varicose veins in areas of fascial defects with 0.5 mL of sodium tetradecyl sulfate (STS) solution at up to 23 sites per leg. Although this many injections may seem similar to the number with total vein sclerotherapy, three quarters of the patients had two to five injections. Doran and White[21] concluded after 2 years of follow-up that there was no difference between the results from Fegan's technique and ligation and stripping procedures for varicose veins. Hobbs[22] concluded from his comparative study of sclerotherapy with Fegan's technique versus traditional surgery that sclerotherapy is the best treatment of nontruncal varicose veins and IPVs of the lower leg. Tretbar and Pattisson[23] have found in their follow-up examinations of 264 patients treated with Fegan's technique that treatment failures usually occurred in patients with very large or fat legs with varicosities originating above the knee. They believed this failure was caused by the difficulty of placing injections accurately within the veins of these patients and maintaining adequate compression. Sladen[24] analyzed 263 limbs with up to 7 years of follow-up and found that more than 95% of his patients were satisfied with the treatment and said they would have it repeated. He estimated a retreatment rate of approximately 5% per year. His patients averaged 3.6 to 5.25 injections per treatment session, and 46% to 74% required one treatment session only. Sladen, in agreement with Hobbs, found that all patients with saphenofemoral reflux eventually required surgery. Therefore, although varicose veins treated with Fegan's technique respond well to treatment, the supposition of Fegan's technique—that sclerosis of the IPVs is of primary importance and may reverse the remaining pathology in the GSV system—may not be correct universally.

Hobbs[25] provided evidence that when saphenofemoral and perforator incompetence occur together, both abnormalities should be corrected. Kerner and Schultz-Ehrenburg[26,27] studied the functional effects of sclerotherapy with photoplethysmography (PPG) and concluded that the greatest functional improvement occurred with obliteration of the SFJ. Obliteration of the IPVs of the lower legs was of variable importance. Treatment of perforator veins of the upper leg had no functional significance that could be ascertained with PPG.

TREATMENT OF REFLUX FROM THE SAPHENOFEMORAL JUNCTION

There are at least three schools of thought regarding which type of therapy is appropriate for initial treatment of the junctional points of reflux: surgical ligation (with or without limited stripping) of the SFJ versus sclerotherapy of the SFJ versus sclerotherapy of IPVs alone. Bergan (see Chapter 10), Goldman,[28] Hobbs,[22,29] and others argue that surgical treatment of the junctions is the most appropriate and successful mode of treatment, but this was before the use of endovenous ablation techniques. Neglen,[30] in a comprehensive review, determined that with proper follow-up, including functional testing at 5 years, surgical therapy of the GSV in a patient with incompetence of the SFJ, is significantly better than sclerotherapy.[30] Color-flow duplex evaluation, from 3 to 55 months after treatment (mean of 27.5 months) of 89 limbs in 55 patients with an incompetent SFJ treated with the Sigg technique, found that only 6% of veins remained sclerosed despite improvement in symptoms in 50%.[31] Butie[32] has shown that sclerotherapy of the SFJ is difficult and unreliable with the use of liquid STS 3%, which is the strongest sclerosing agent approved for use by the US Food and Drug Administration (FDA). This has been confirmed even when sclerotherapy was performed at the SFJ under angioscopic guidance (see 'Endoscopic injection' section).[33] In this case, 12 GSVs were occluded at the SFJ through angioscopically guided sclerotherapy with STS 3% liquid (before the use of foamed detergent sclerosants). A total of 2 to 5 mL was injected into the GSV just below the junction, which was occluded by manual pressure. Nine veins were evaluated at follow-up, and all were reopened and incompetent between 1 and 12 months. Although these carefully performed, unbiased studies have been carried out in the 1990s, this opinion is not new. As far back as 1934, Cooper,[34] in a series of more than 85,000 injections in more than 3000 patients, documented that the number of sclerosing injections required to produce obliteration of the varicose vein was markedly decreased after ligation of the SFJ.

In addition to its lack of consistent success, sclerotherapy of the SFJ has the inherent risk of damaging the deep venous system and the femoral vein when sclerosing solution is injected in the upper thigh region. This has been demonstrated by radiologic examination showing the rapid flow of contrast media from a varicose GSV into the femoral vein when injections are performed in the upper thigh.[35] With incompetence of the SFJ, it is recommended that sclerotherapy be used for treating residual varicosities after surgery.

Despite the information in the preceding paragraph, multiple phlebologists have demonstrated that the junctions can be successfully closed with sclerotherapy alone in 50% to 91% of patients.[36–42] A comprehensive illustrated discussion of the technique is presented in other sources.[43] The difficulty in properly evaluating these conclusions results from the natural evolution of varicose veins, which obscures the results of both surgical and sclerotherapy treatment. It is sometimes difficult to distinguish between a recanalized vein and a new vein. Results also depend on the type of follow-up examinations (i.e., clinical or objective with duplex or Doppler ultrasound) of patients. One study with clinical 6-year follow-up demonstrated a nearly 90% success rate with sclerotherapy.[36] By whatever method, closure of the SFJ has been shown in pressure studies to prevent retrograde flow in the saphenous and perforator systems.[44] This suggests that incompetence of the perforator veins occurs as a result of a primary development of saphenofemoral reflux. Therefore, when the GSV or its tributaries are involved, the SFJ, when incompetent, should be the first area to be treated.

Treating incompetence of the SFJ may differ from treating an incompetent saphenopopliteal junction (SPJ). The small saphenous vein (SSV) has a variable termination (see Chapter 1) that is often difficult to approach surgically, but can be approached with modern endovenous ablation techniques. Ligation alone at the SPJ has a 95% failure rate at 1 year.[45] Sclerotherapy is much more effective, perhaps because of the larger extent of destruction of abnormal feeding veins into this region.[45]

In summary, long-term comparative studies with objective methods for evaluating outcome of the various techniques are lacking. The literature consists mainly of anecdotal reports and clinical studies with short follow-up periods.

A comparison of three independent observers regarding treatment outcome of varicose vein surgery shows 60% agreement in assessing visual improvement, with 30% agreement among observers when symptomatic response and visual impression are compared.[46] It is my opinion that no one 'school' is absolute but that the correct order of treatment should be individualized for each patient. Some patients have only perforator incompetence and a normal SFJ; thus, Fegan's technique would be adequate. Patients with saphenofemoral incompetence require treatment of that junction before treatment is initiated elsewhere. Still other patients have no obvious hemodynamic cause for the origin of their varicose veins, thus directing treatment toward the entire varicosity, as described by Sigg.[47] A careful workup of all patients is necessary before therapy is begun. In addition to deciding on the sequence of treatment, the physician must consider the various modifications of the injection procedure that some physicians profess have various benefits. As before, comparative and objective studies of these treatment modifications have not been reported. This chapter discusses sclerotherapy treatment of varicose veins, perforator veins and the SFJ, and reviews the available literature. Variations in treatment are addressed and illustrative cases are presented. A summary of the three schools of sclerotherapy is found in Table 9.1.

Foam sclerotherapy (whether ultrasound-guided or not) changes the outcome of the techniques mentioned earlier. This 'new' or at least 'newly appreciated' sclerotherapy technique has such advantages that it allows treating long segments in a single injection. This aspect is close to the

Table 9.1 Summary of 'Schools' of Sclerotherapy

School	Injection Site	Compression	Instruction Prescribed after Procedure
Tournay	Proximal to distal	No	None
Sigg	Entire varicosity	Yes	Walking
Fegan	Perforating vein	Yes (6 weeks minimum)	Walking

total-vein sclerotherapy technique. Although there remains no general consensus on when to use conventional liquid versus foam sclerotherapy, multiple studies and a consensus published in the US literature in 2014 suggest most authors and clinicians agree that telangiectasias and reticular veins less than 2 mm in diameter are treated by conventional liquid sclerotherapy, whereas larger reticular veins and varicosities may be more effectively treated with foam sclerotherapy.[48–50] The US consensus further states foam should be reserved for those vessels that are greater than 1 mm (i.e., reticular veins, perforating veins, larger telangiectasia, GSV, SSV and truncal varicose veins).[48] However, the US consensus additionally emphasizes that when used with smaller vessels, foam runs the risk for rupturing the thin-walled vessels with a resulting increase in pigmentation and matting. Therefore, liquid sclerotherapy should be reserved for these vessels. With time and with a growing field of literature supporting its safe and efficacious use,[51–56] we believe that foam sclerotherapy is likely to replace all other techniques for sclerotherapy of veins greater than 2 mm in diameter.

With the reservations indicated earlier about the probable role of the venous reservoir, ultrasound-guided sclerotherapy can be used for treating most varicose veins, including trunks of all diameters. The fate of junctions has been completely revised after evaluation of patients treated by endovenous ablation (radiofrequency and laser; see Chapter 11) and it is obvious that a revolution in varicose vein management continues to be in progress.

INJECTION TECHNIQUE

PATIENT POSITION

STANDING

Although the previous description of the treatment of varicose veins seems simplistic, the actual treatment methods for achieving effective sclerotherapy are numerous. Until the 1950s, sclerotherapy was performed with the patient standing throughout the procedure. The purpose was both to distend the varicose vein, allowing easier needle insertion, and to produce firm thrombosis of the treated vein.[57] Multiple disadvantages of varicose thrombosis were realized (see Chapter 8), and various methods were devised to limit postsclerotherapy thrombosis. Additionally, injecting sclerosing solution while the patient is standing forces the injection to occur against the hydrostatic pressure of a large column of blood. This may cause the solution to seep along the needle into the perivenous tissues, possibly leading to a chemical phlebitis or tissue necrosis.[58]

Another disadvantage of the total standing technique is the sclerosing solution may escape through a perforator vein and damage the deep veins, especially if more than 1.5 mL of sclerosing solution is injected in a single site.[59] Another radiographic study has shown that an injection of 0.5 mL of contrast media travels rapidly (in 5 seconds) 8 cm distal to the injection site.[60] Also, this amount of contrast does not completely fill the vein. An additional radiographic study of the standing position, using metrizamide (Amipaque) 150 as the contrast medium (diluted to an isomolarity and specific gravity similar to that of polidocanol [POL]), showed that the injection of 1.5 mL remained in contact with a convoluted varicosity for approximately 10 seconds before flowing rapidly into the deep venous system through a presumed perforator vein (Fig. 9.2A, B).[61] In contrast, when the patient was supine, the contrast media extended proximally along the varicosity and remained relatively undiluted for more than 18 seconds (Fig. 9.2C, D).[61] However, injections in some patients, when using the latter technique, also resulted in the contrast media remaining in contact with the varicosity for a longer period with the patient in the standing position (Fig. 9.3). Therefore, multiple variables, including the type of varicosity, its location, the location of associated perforator veins and the movements of the patient (with associated calf and foot muscle contraction) while standing, may all affect the distribution of the sclerosing solution. For these reasons, the standing technique is not recommended.

STANDING AND RECLINING

A modification of the standing technique, the standing and reclining technique, was described in 1926 by Meisen.[62] In the standing position, the needle was inserted while the vein was distended. With the needle still in the vein, the patient reclined on a table and the leg was elevated. This produced a relative emptying of blood from the vein. The sclerosing solution was then injected into an 'empty' vein that was immediately compressed to prevent or minimize thrombosis.

One of the earliest methods used to limit thrombosis was that of isolating the injected vein segment with pressure placed above and below the needle insertion site after first milking the blood out of the vein.[63] One of the first books on sclerotherapy treatment of varicose veins is *Varicose Veins and Their Treatment by 'Empty Vein' Injection.*[64] In this book, Ronald Thornhill of London detailed his success with injection of a quinine solution into the elevated leg. He massaged the solution throughout the vein, injecting from distal to proximal. He even sclerosed 'hair veins' with a dilute solution. Unfortunately, he did not use compression except when ulcers were present, and his patients had to endure weeks of tender veins until they resolved in approximately 12 months.

Lufkin and McPheeters[65] emphasized the importance of empty vein injections in a histologic evaluation of treated veins in 1932. Orbach[66] has stressed the significance of compressing the vein to minimize thrombosis since 1943. Thus, these modifications are not new. They result both in improved efficacy and in a decreased incidence of complications when the treatment is directed at the SFJ.[21] The

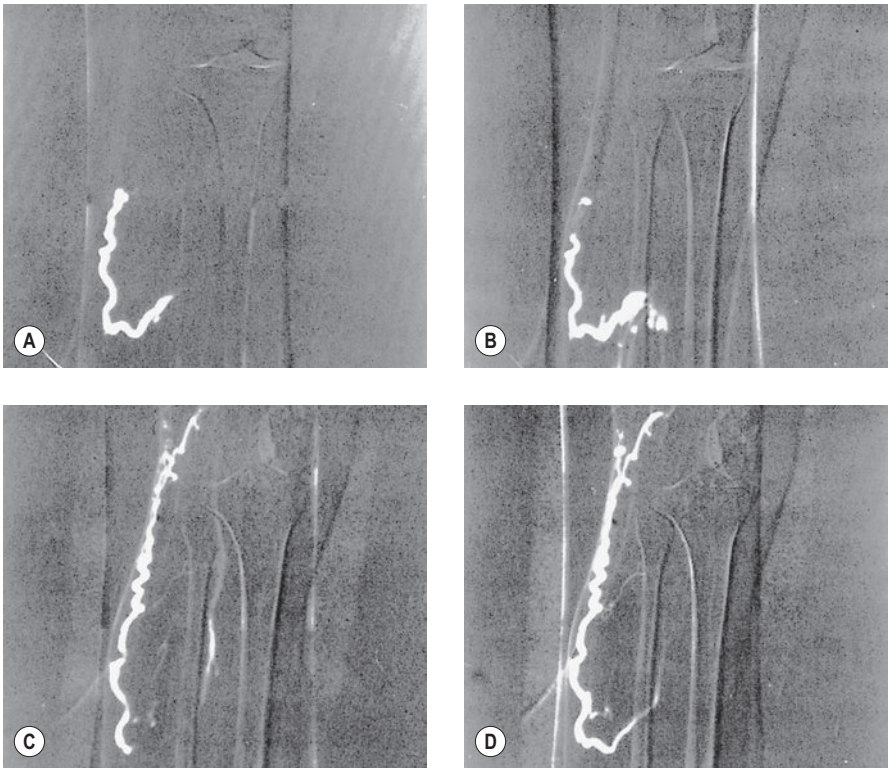


Figure 9.2 Injected contrast media, 1.5 mL, shown, **A,** 9½ seconds and, **B,** 18½ seconds after injection into a varicose vein while the patient was standing. Injected contrast media, 1.5 mL, shown, **C,** 9½ seconds and, **D,** 18 seconds after injection into a varicose vein while the patient was supine. (Courtesy George Heyn, MD, Department of Vascular Surgery, Berlin, Germany.)

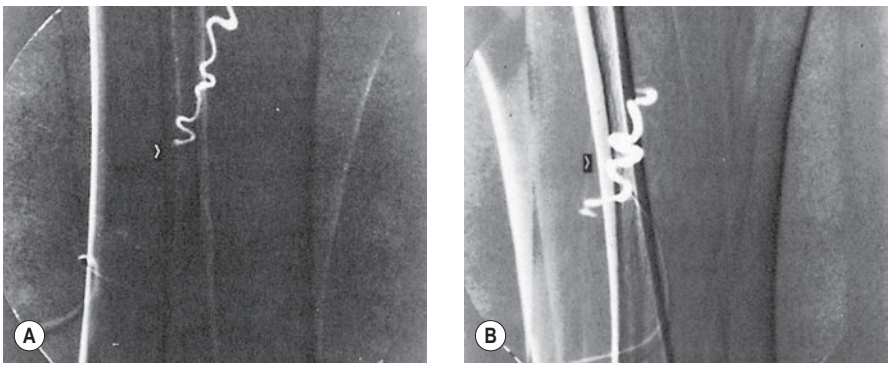


Figure 9.3 **A,** Contrast media, 1.5 mL, shown 10 seconds after injection into a varicose vein while the patient was supine. Note the distribution of the contrast media proximally within the varicose vein. **B,** Contrast media, 1.5 mL, shown 10 seconds after injection into a varicose vein while the patient was standing. Note the contrast media remains for a relatively long time within the venous convolution. (Courtesy George Heyn, MD, Department of Vascular Surgery, Berlin.)

improved efficacy may be the result of a longer length of sclerosis of the varicose vein, caused by gravitational flow of the sclerosing solution. However, recent evaluations comparing standing and reclining methods of treating varicose veins below the SFJ have not been performed.

LEG ELEVATION (FEGAN)

Another obvious disadvantage of the standing technique is the vasovagal reaction (see Chapter 8). To prevent the sequelae of a vasovagal reaction, Fegan[67] recommended that patients sit at the end of the examining table with their legs hanging down while the physician, sitting in front on a low stool, inserts the needle. The leg is then raised while the patient fully reclines for 1 to 2 minutes to empty the leg of blood. The physician stands to support the raised leg, which is rested on the shoulder or against the chest, and the varicose veins are injected. With this or any technique that moves the patient after the needle is inserted, it is important to ensure that the needle is not displaced from the vein, either by fixing it to the skin with tape (if butterfly catheters or needles attached to syringes are used) or by holding the needle while the leg is raised. Because the varicose veins will collapse when the leg is raised, blood withdrawal must be checked as soon as possible after the leg is raised to ensure that the needle has not slipped out of the vein. The lack of spontaneous pulsatile flow from the needle without an attached syringe is proof of nonarterial placement of the needle.

To ensure that the sclerosing solution acts on the intended vein segment during injection, Fegan[67] recommended applying pressure with fingers a few centimeters proximal and distal to the injection point. Finger pressure is maintained for 30 to 60 seconds, and the leg is then bandaged from the toes to the injection site. With this method, injections are made only at the points of fascial defects (which are thought to represent sites of IPVs). Injections proceed from distal to proximal sites, with each vein segment or fascial defect treated.

After injection of varicose veins in the elevated leg, compression should be applied immediately to prevent the veins

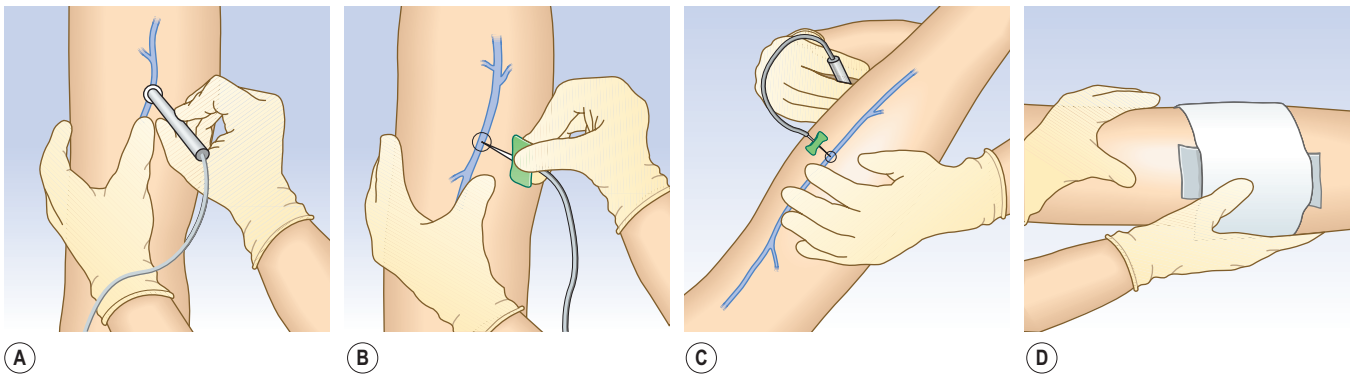


Figure 9.4 **A,** Localization of an incompetent perforator vein (IPV) through the use of a handheld Doppler device. **B,** Cannulation of the IPV with a 26-gauge butterfly needle. **C,** The leg is elevated 45 degrees, and 0.5–1.0 mL of sclerosing solution is placed into the now empty perforator vein under minimal pressure. Note placement of a finger distal to the injection site to feel for extravasation of solution (which would indicate improper placement of the needle and necessitate immediate discontinuance of treatment and infiltration of the injection site with lidocaine 1%). **D,** Immediate compression of the treated vessel with an STD foam pad and tape dressing.

filling with blood. This can be performed easily with the use of the following method. Before insertion of the needle, a compression stocking is placed over the foot and heel and allowed to bunch up at the ankle. After the needle is inserted into the varicosity, the leg is raised. Proper placement is then confirmed through blood withdrawal, and the sclerosing solution is injected. A foam pad is placed over the injection site and secured in place with foam or elastic tape. The compression bandage then can be advanced over the injection site and foam pad in a distal to proximal manner (Fig. 9.4). With this technique, radiographic studies after injection of 0.5 mL of contrast medium show that when the leg is raised above the horizontal plane, the contrast medium travels rapidly for 30 cm before reaching the deep venous system.[60] The sclerosing solution is diluted and probably inactivated by the time it reaches the deep venous system (see Chapter 7). With this technique it may not be necessary to repeat injections every few centimeters in the varicose vein.

With the leg-raising technique the varicose vein would be presumed empty of blood, but this is not the case. Duplex examination demonstrates that the GSV is not totally emptied of blood, even with an 80-degree incline, although tributaries to the GSV are emptied at 45 degrees.[68] In 'huge' varicosities, as much as 18 mL of blood can be withdrawn when the leg is raised 45 degrees above the horizontal.[69] Therefore Perchuk[69] developed a method for ensuring an 'empty' vein. His method consists of inserting the needle into the varicose vein, elevating the leg 45 degrees, and then withdrawing blood through that needle into a syringe until further blood withdrawal is impossible. Then a syringe with sclerosing solution is attached to the needle and the injection is made, followed by application of local pressure for 5 minutes. The use of compression bandages or stockings after treatment was not mentioned. A two-way stopcock may also be used for this technique. Perchuk, in an evaluation of 84 patients, found that this technique produced excellent results and limited all complications.[69] Pigmentation, thrombophlebitis and recurrence were very rare. Fegan, however, disagreed with Perchuk's conclusions and stated that the vein would empty of blood if raised for a longer time and at a more acute angle (Fegan WG, personal communication, 1990).

TWO-PHASE (SIGG) TECHNIQUE

A variation on the method described earlier is the two-phase technique of Sigg.[12] This variation involves the way the needle is inserted into the vein. Sigg recommended the needle be passed through the vein with the syringe unattached or with a finger placed over the hub and then slowly drawn back until the escape of blood indicates proper placement. The needle is left open and unobstructed while an assistant places a basin beneath it to catch the dripping blood. The leg is then raised above the horizontal plane, and bleeding stops. A syringe is then attached, and blood is withdrawn. After proper placement is confirmed by withdrawal of venous blood and the vein is emptied of blood, the sclerosing solution is injected and the vein compressed, as described earlier, with a stocking, bandage or both. Because Sigg uses mainly iodinated iodine solutions, he developed this technique to ensure continual intravascular placement of the sclerosing solution (see Chapters 7 and 8).

For both the Fegan and Sigg methods described, either all of the needles are positioned and inserted while the varicose veins are distended or each needle is inserted separately, one at a time before each injection. When the latter is performed, distal compression prevents dilation of the preceding vein segment when the leg is lowered for each subsequent needle insertion.

RECLINING

Another method for injection advocated since the 1920s is that of having the patient remain horizontal throughout the procedure.[70] If the varicose veins easily collapse in this position, they can be marked with indelible ink before the procedure, while the patient is standing. A radiologic study has shown a 0.5-mL bolus of contrast medium injected into a varicose tributary of the GSV travels proximally 8 cm and remains within the vessel for approximately 2 minutes before being drawn into the deep venous system.[60] The relaxation of the calf muscles permits the injected fluid to stay within the vein, because blood flow in this position is slow. Thus, this position produces the longest lasting and most uniform contact between the injected solution and the vein wall. The European guidelines for sclerotherapy released in 2014 recommend injections be given with the patient's limb in the horizontal position.[49]

To produce a relatively bloodless vein during injection in the horizontal position, some authors advocate rubbing along the vein in both a proximal and distal direction away from the injection site.[70] Manual compression is then maintained at the proximal and distal sites along the vein to prevent the vein segment from refilling with blood. After the injection, a compression pad and bandage are immediately applied to the treated vein segment.

FOAM SCLEROTHERAPY

Since the earlier editions of this textbook, the use of foam sclerosants has increased dramatically. Far from the primitive techniques described by so many authors and well detailed in Wollmann's history of sclerosing foams,[71] it is now considered as a completely new treatment for varicose veins.[72,73] Shaking the syringe[70] or aspirating in a closed glass syringe,[74] to quote only two of the well-known historic methods, are now obsolete. Three main options remain: high-speed beating in a carbon dioxide-rich atmosphere (Cabrera's technique[75]), specific gas mixture combined with POL and passed through a patented sieve in an aerosol canister (Varithena, BTG International Inc., West Conshohocken, PA) (see Chapter 7) and Tessari's method, using the transfer between two syringes of sclerosant and room air. The latter technique offers different variations: a three-way stopcock as initially described[76] (Fig. 9.5), a two-way female connector like in the double syringe system technique[77] (Fig. 9.6), or an automated foaming device, Turbofoam (KreusslerPharma, France), described in Chapter 7, which has the ability to mix the sclerosant with different types of gases through the use of a three-way connector. The Tessari technique is the most common means for foam creation.[78]

Immediately following the injection of foam sclerosant, the bubbles displace blood and contact with the sclerosant and endothelium begins. Clinically, this is apparent as vasospasm within seconds or minutes, erythema of the feeding telangiectasias or no immediate visible change (Table 9.2A). After several days, venous inflammation is present with thickening of the venous wall and presence of a sclerus. This is evidenced clinically by induration, erythema and tenderness. Weeks to months later, fibrosis results in a progressive decrease in the diameter of the treated vein and clinically by the absence of the varicosity. Occasionally, a fibrous cord may be palpated (Table 9.2B). At times, complete clearance of the varicose veins does not take place, owing to either partial or total recanalization of the treated vein (Table 9.2C).

Foam sclerotherapy is now regarded as far more efficacious than liquid sclerotherapy for larger veins because of an increased time of contact between the sclerosant and the vein wall.[78] The temporal relationship between foam bubbles and the endovenous wall is related to patient position, injection technique, foam viscosity and the number of bubbles per milliliter.[79] To investigate the effects of foam on smaller vessels, Uncu completed a head-to-head study of 100 women comparing POL in foam versus liquid form to clear telangiectasias and small varicose veins less than 4 mm.[51] Lower extremity veins that did not have insufficiency at the SFJ were divided into three groups as less than 1 mm, 1 to 2 mm

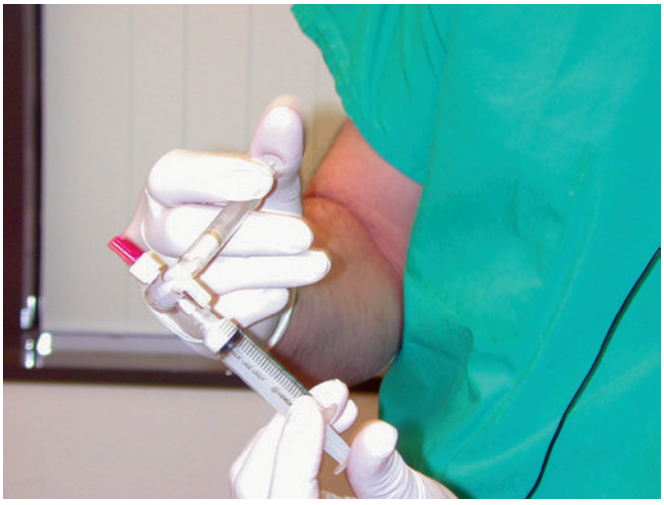


Figure 9.5 Generation of a foam sclerosing solution using a three-way connector: 1 mL of sclerosing solution was mixed with 4 mL of room air.

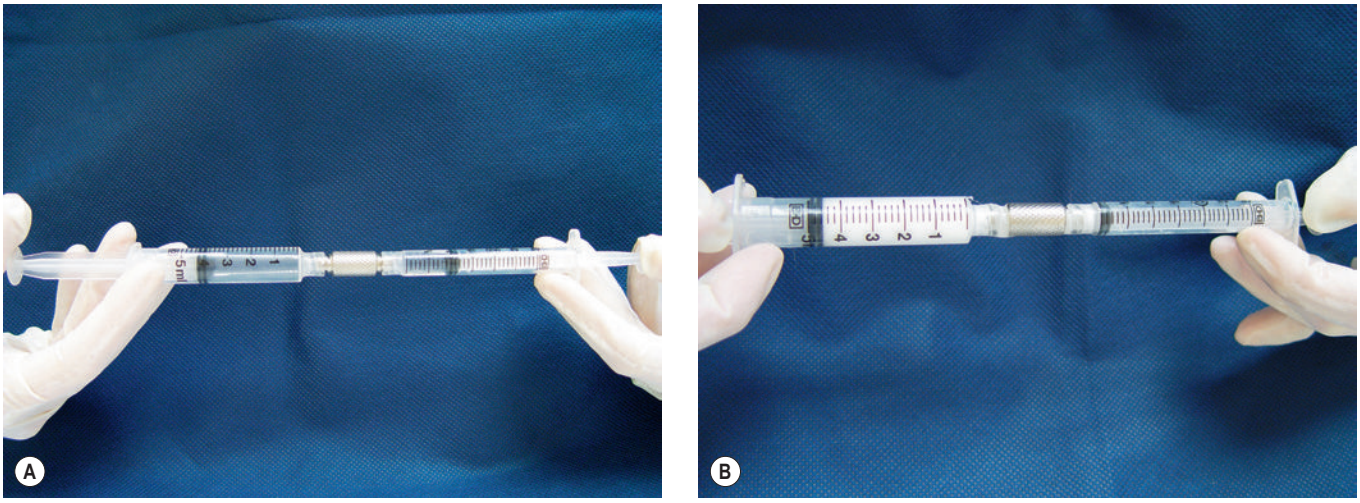
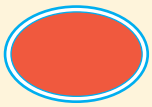
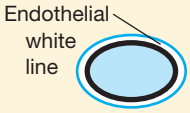


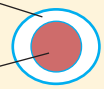
Figure 9.6 Generation of foam using a two-way female-to-female connector. **A,** 1 mL of detergent sclerosing solution is in one syringe and 4 mL of room air is in the other syringe. **B,** when the air and detergent sclerosing solution is mixed, a foam is generated.

Table 9.2 A–C Pathophysiologic and Clinical Effects from Foam Sclerotherapy

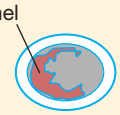
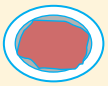
A

Time Frame	Reaction	Clinical Observations	Duplex Schematic Aspect
Before injection	None	Presence of varicose veins	
Immediately after injection of foam (seconds)	Foam present, beginning of endothelial lesion: internal white line	Variable	
After minutes	Venous spasm	Varicose veins spasm transiently, skin creases where veins were bulging	

B

Time Frame	Reaction	Clinical Observations	Duplex Schematic Aspect
After several days	Inflammation	Induration, possible inflammation, redness, tenderness.	
After weeks or months	Fibrosis	Varicose vein not visible anymore, possibly palpable hard cord.	Progressive reduction of diameter 

C

Time frame	Reaction	Clinical Observations	Duplex Schematic Aspect
After months	Partial recanalization	Variable clinical recurrence	
After months or years	Total recanalization	Recurrence	

and greater than 2 mm but less than 4 mm, and the veins were treated with 0.25%, 0.5% or 1% of POL, respectively. Tessari's foam sclerotherapy method was used for the 50 patients treated with foam POL. Although more successful clearing of the vessels with foam POL was demonstrated (84% foam versus 72% liquid complete clearance), the results did not reach statistical significance ($P = 0.148$). There was no significant difference in the side effects between each group.

Hamel-Desnos et al[77] investigated efficacy rates of a single treatment session of foam or liquid ultrasound guided sclerotherapy of GSVs. The induction of venous spasm was more common following foam sclerotherapy. At 3 weeks' follow-up, reflux was absent in 84% of foam sclerotherapy–treated veins and 40% of liquid sclerotherapy–treated veins. A similar study was performed by Yamaki et al[80] to investigate single treatment foam versus liquid sclerotherapy in GSVs and tributary veins. At 12 months, complete occlusion rates were 67.6% and 17.5% in the foam and liquid groups, respectively. Statistically significant increased rates of recurrent varicose veins and recanalization with reflux were identified in the liquid sclerotherapy cohort. A 2009 meta-analysis revealed a 76.8% efficacy of ultrasound-guided foam sclerotherapy (UGFS) compared with a 39.5% efficacy rate for ultrasound-guided liquid sclerotherapy.[81] An additional benefit from foam is its appearance on ultrasound as an intravenous contrast agent. Multiple randomized controlled studies comparing the incidence of adverse events with foam and liquid ultrasound-guided sclerotherapy of the saphenous veins have shown no statistical difference between these techniques.[77,81,82]

A meta-analysis by van den Bos and colleagues[83] compared occlusion rates following endovenous laser ablation (all wavelengths included), radiofrequency (RF) ablation, UGFS and high ligation with stripping from 64 studies and 12,320 limbs. At 3 years, success rates were 94.5% for laser ablation, 84.2% for RF, 77.4% for UGFS and 77.8% for high ligation with stripping. After 5 years, the respective treatment

success rates were 95.4%, 79.9%, 73.5% and 75.7%. The authors found efficacy for high ligation and stripping, RF ablation and UGFS were equal, but endovenous laser ablation therapy (EVLT) was more effective than the other three regimens. In 2011, Rathbun and colleagues[53] completed a meta-analysis to provide accurate estimates of the efficacy and safety of endovenous foam for treatment of venous disorders. Their systematic and comprehensive search of published literature that met inclusion criteria resulted in the analysis of 104 manuscripts and abstracts. They concluded endovenous foam sclerotherapy to be effective and safe with similar vein occlusion rates to laser therapy, but less effective than surgery and with rare major adverse effects.

All foams are not the same, as explained by Wollmann.[71] Even if prepared with the same agent (foams can be produced only with detergents—namely, STS and POL and, rarely, sodium morrhuate—see Chapter 7), foams can have different properties depending on the mode of preparation and the gas to air ratio (dilution factor). Foams are wet or dry, accordingly. This difference is thought to have some impact on efficacy. Drier foams tend to break down on passage through a needle whereas wet foams act more like liquids. Between these extremes, foam is relatively stable and will displace blood from the vein. Liquid sclerosant to gas dilution ratios of 1:4 (1 part liquid to 3 parts gas) or 1:5 (1 part liquid to 4 parts gas), have been found to produce the most stable foams.[84] Currently, most physicians use a foam prepared just before injection with a method derived from Tessari and a ratio of solution to air varying from 3 to 5 mL of air to 1 mL of solution (we recommend 4 mL). Some standardization has happened spontaneously. The injectable foam associated with Varithena is generated after activation of the POL canister with oxygen from a second aluminum canister (see Chapter 7). This results in a final gas mixture of oxygen/carbon dioxide in a ratio of 65:35 with low (<0.8%) nitrogen content.[85] The foam is then transferred to a syringe through the canister transfer unit, with a final liquid to gas ratio of approximately 1:7 by volume. Following purging instructions, an activated canister of Varithena is sufficient to yield 45 mL of usable injectable intravenous foam.

FOAM STABILITY

Foam stability is affected by foam composition, foam volume and injection technique.[86] Composition variables, including the homogeneity of bubble size, viscosity and temperature, all influence the 'quality' and longevity of foam (Table 9.3).[87] Heat increases the stability of foam.[88]

Bubble size is inversely related to the difference in density between a liquid and gas, as represented in the following equation.[87]

$$d_p = \left(\frac{6 d_o \sigma}{\Delta \rho g}\right)^{1/3} \quad [9.1]$$

where
d_p = bubble diameter
d_o = orifice diameter
σ = surface tension
$\Delta\rho g$ = difference in density between a liquid and gas.

Carbon dioxide is 1.5 times denser than room air; therefore, foam bubbles prepared from carbon dioxide are smaller than those of air. Foam bubbles produced via turbulent flow in the Tessari technique and the double syringe system are smaller (less than 100 µm) in size compared with the larger bubbles produced in the Monfreux technique. This smaller bubble size is associated with an increased surface area of sclerosant, increased displacement of blood inside the vessel and decreased likelihood of mixing with blood following the initial injection. Therefore an increased amount of sclerosant can be delivered to the endothelial cells.[89,90] In addition the bubble size created correlates to the stability of the foam created, with small micro foam of less than 50 µm being more stable than larger foam of greater than 100 µm.[48] Interestingly, the Monfreux method of foam creation has been associated with an increased incidence of side effects. It is speculated that the larger bubbles produced in this method advance more readily in the venous system.[89] The prescribing information for foam POL (Varithena) reports the median bubble diameter for the activated product is less than 100 µm and no bubbles are greater than 500 µm.[85] Of note is that in the process of receiving FDA approval, Varithena was subject to years of testing to assess its safety including risk for microemboli, and the FDA was satisfied to proceed with approval in 2014.[91] Moreover, the bubble size, bubble size distribution and stability of Varithena endovenous microfoam proved better in overall performance compared with physician-compounded foam.[92]

The majority of phlebologists use readily available room air for foam creation in sclerotherapy; however, carbon dioxide is becoming increasingly popular.[93] Carbon dioxide foam bubbles quickly disintegrate; this effect is more pronounced as the sclerosant to gas ratio is increased.[71] The following equation describes foam stability in vivo:

$$TP = \frac{r^2 d}{2DSf} \quad [9.2]$$

Table 9.3 Stability of Foam According to Gas

Percent Sodium Tetradecyl Sulfate (%)	Room Air Stability (Seconds)	Carbon Dioxide Stability (Seconds)	77% Carbon Dioxide/23% Oxygen Stability (Seconds)
0.25%	87	24	52
	84	27	55
	86	25	56
	(mean 85.7)	(mean 25.3)	(mean 54.3)
0.5%	89	26	58
	91	27	59
	87	24	57
	(mean 89.0)	(mean 25.7)	(mean 58)
1%	91	29	50
	89	27	50
	92	29	49
	(mean 90.7)	(mean 28.3)	(mean 49.7)

From: Peterson J, Goldman MP. An investigation on the influence of various gases and concentrations of sclerosants in foam stability. Dermatol Surg 2011;37(1):12–7.

where
TP = time of bubble persistence
r = radius
d = air density inside the bubble
D = gas diffusibility through the bubble
Sf = saturation factor of gas in blood.

Carbon dioxide has a much greater diffusibility into blood compared with nitrogen (the most prevalent gas in room air), and as a result, the foam half-life is reduced for carbon dioxide. When carbon dioxide is mixed with oxygen for foam creation, the foam half-life is increased as a result of the decreased diffusibility of this mixture.[94]

Room air foam half-life varies according to the percentage of sclerosant solution. In the study by Rao and Goldman,[95] they found a 1% concentration of STS or POL had the maximal foam half-life (90 and 120 seconds, respectively) (Tables 9.4 and 9.5). In a study published in 2011 we discovered carbon dioxide foam half-life did not vary according to the concentration of sclerosant solution; however, a mixture of 77% carbon dioxide/23% oxygen did. We also found that foam half-life for room air is over three times longer than carbon dioxide half-life and 1.5 times longer than a combination of 70% carbon dioxide/30% oxygen (see Table 9.3).[96]

Table 9.4 Times for 0.5 mL of Sodium Tetradecyl Sulfate (STS) to Settle from a Foam Mixture Containing 1.0 mL of Various STS Concentrations*

Sclerosing Agent	Time 1 (Seconds)	Time 2 (Seconds)	Average Time (Seconds)
STS 0.25%	96	98	97
STS 0.50%	88	90	89
STS 1.0%	104	103	103.5
STS 1.5%	87	86	86.5
STS 3.0%	83	82	82.5

From: Rao J, Goldman MP. Dermatol Surg 2005;31:19.
*A stainless steel two-way connector was used in each trial to create foam.

Table 9.5 Times for 0.5 mL of Polidocanol (POL) to Settle from a Foam Mixture Containing 1.0 mL of Various POL Concentrations*

Sclerosing Agent	Time 1 (Seconds)	Time 2 (Seconds)	Average Time (Seconds)
POL 0.25%	94	96	95
POL 0.50%	50	52	51
POL 1.0%	124	124	124
POL 1.5%	124	124	124
POL 3.0%	132	128	130

From: Rao J, Goldman MP. Dermatol Surg 2005;31:19.
*A stainless steel two-way connector was used in each trial to create foam.
POL, Polidocanol.

Silicone coating is present in syringes and syringe connectors to provide lubrication, but silicone is also an antifoaming agent. Prior studies by Rao et al and Lai et al have shown the amount of silicone in syringe connectors does not affect foam stability; however, foam stability varies between syringe manufacturers because of variances in the silicone content of their syringes.[95,97] Hill[98] investigated the effect of a 5-µm syringe filter on carbon dioxide foam half-life. In the absence of the filter, foam half-life was 22.7 and 30.1 seconds for STS 2% and POL 2%, respectively. Half-life was prolonged to 35.9 and 48.9 seconds, respectively, with the addition of a 5-µm filter. Of note, carbon dioxide foam stability was greater in POL versus STS throughout the study. Following their own studies that validated silicone-free syringes can increase foam longevity by 70% compared with foam made with silicone oil lubricated syringes, Whiteley and Patel[99,100] subsequently described a three-syringe technique which allows foam to be made using the Tessari 'three-way stopcock' principle, but with foam ending up in a third syringe which has not undergone multiple passages of the plunger. The plungers in silicone-free syringes start sticking after several passages when making foam for sclerotherapy, preventing the smooth injection of the resultant foam. The three-syringe technique demonstrated a smoother injection of the foam, which is particularly useful when injecting small diameter veins under ultrasound control.

Foam has a spontaneous evolution before and after being injected in varicose veins. Before injection, small bubbles tend to group as bigger units (known as LaPlace's law) and after some time foam is replaced by large bubbles whose effect will be what was observed with Orbach's air-block. Stability of the foam can be evaluated by several techniques.[95] The preparation of foam does not change the concentration of sclerosing agent. This is completely different from what happens to the foam when injected. If injected into an isolated segment, a plug of foam is created and behaves as in a syringe, remaining in contact with the endothelium long enough to destroy it and induce venospasm. As the foam is forced from the contracting segment of vein, it mixes at the expanding interface with blood. This is responsible for dilution of foam and the scattering of bubbles, and surface sclerosing agent is rapidly deactivated by attachment to plasma protein and cell membranes. This explains why bubbles, when found far from the injection site for example, in the lung, heart or brain, consist of air and do not carry detectable amounts of sclerosing agent or have any sclerosing properties.[101] Although lung bubble microembolism may occur it is not a typical effect of foam sclerotherapy and the onset of pulmonary embolism following the procedure is negligible. However, dry cough and chest tightness are frequently reported.[102] Their pathogenesis is theorized to be related to endothelin-1, involved in the mechanism of cough through modulation of the transient receptor potential vanilloid 1 (TRPV1), expressed by airway sensory nerves and involved in the genesis of cough. Regarding the use of foam, the trend in Europe has been to develop a consensus for volumes and concentrations.[93,103] At the 2nd European Consensus Meeting on Foam Sclerotherapy in 2006, experts agreed than no more than 10 mL of foam per injection should be injected into a GSV. The range of volume injected

into the GSV varied between less than 2 mL up to 10 mL per injection. The maximum recommended volume of foam per leg and per session was thought to be 10 mL. The Monfreux technique of foam creation was no longer recommended for any subtype of vein.[93] In France there appears to be a reduction in concentrations,[104] with vessel spasm used as an indicator for the correct amount of foam injected. However, this option is true only for a proximal and direct injection of terminal parts of the saphenous veins.

Updated European guidelines for sclerotherapy of chronic venous disorders were released in 2014.[49] These guidelines were drafted on behalf of 23 European Phlebological Societies during a 2012 Guideline Conference. With regard to foam volumes, they state there is no evidence-based limit for the maximum volume of foam per session. However, remaining consistent with the previous guideline, a maximum of 10 mL of foam per injection session remains the recommendation in routine cases. Higher foam volumes are considered applicable according to the individual risk-benefit assessment. The European authors suggest foam sclerotherapy as an alternative treatment method to liquid sclerotherapy for telangiectasias and reticular varicose veins. They further recommend foam sclerotherapy over liquid sclerotherapy for the treatment of saphenous veins, venous malformations and recurrent varices after previous treatment, accessory saphenous veins, nonsaphenous varices and incompetent perforating veins.

The safe treatment of veins using more than 10 mL of foam in a single session is reported by many authors according to the 2014 US consensus.[48,55,56] In a retrospective review of 325 patients who received foam sclerotherapy for reticular and nonsaphenous varicose veins, Palm et al[54] reported volumes of foam sclerosant averaging 16.9 mL, higher than the current European consensus of 10 mL, as safe and effective with a low incidence of side effects and no serious cardiovascular or neurologic events.

With regard to the concentration of the sclerosant used, the updated European guidelines recommend choosing the concentration in relation to the diameter of the venous segment to be treated based on the judgement of the injector (Table 9.6).[49]

We have previously advocated a more distal approach[72] with placement of an open vein access ('butterfly' needle or catheter; Figs 9.7 and 9.8), filling the vein with relatively low volume concentrations, and massaging to the desired area under duplex control (Fig. 9.9). With several years of experience, this is no longer deemed necessary. Direct puncture technique of the targeted vein is favored using a 3-cc syringe with 30-gauge, ½-inch needle, without the use of duplex guidance for lower extremity intracutaneous veins. The necessary volume can be estimated from the diameter and the length of vein, as indicated in Table 9.7. In our practice, however, we do not currently use volumes above 10 to 12 mL of foam into a single GSV, and 7.5 mL of foam (30 mL total of room air; 1:4 sclerosant/room air ratio) in a single treatment session for lower extremity reticular veins and varicosities. It should not be forgotten that although foam is not air and usually occupies the entire vessel lumen, foam floats, so that in large-diameter veins it will principally be in contact with the upper part of the vein, where gravity leads it to rise (Fig. 9.10). The only solution to this problem is a reduction in the diameter, which can be obtained by compression, leg elevation or induction of venous spasm. Ten to thirty milliliters of normal saline can be injected perivenously, in a technique similar to tumescent anesthesia for endovenous laser or RF ablation, to cause venous compression and decrease recurrence rates.[105]

The most common technique for foam sclerotherapy is via ultrasound guidance[94] and using the direct puncture technique.[93] Although many authors employ short catheters, long catheters with balloon tips have become more prevalent because of possible increased efficacy. However, long catheters may cause an increased incidence of deep venous thrombosis[94] owing to a passage through perforators, even if foam is reaspirated at the end of the procedure. The recommendations from the European guidelines is to inject the GSV at the proximal thigh if using the direct

Table 9.6 Suggested POL and STS Concentrations in Foam Sclerotherapy*

Indications	Concentration (%) of POL	Concentration (%) of STS
Telangiectasias	Up to 0.5	Up to 0.25
Reticular varicose veins	Up to 0.5	Up to 0.5
Tributary varicose veins	Up to 2	Up to 1
Saphenous veins (mm)		
<4	Up to 1	Up to 1
≥4 and ≤8	1–3	1–3
>8	3	3
Incompetent perforating veins	1–3	1–3
Recurrent varicose veins	1–3	1–3
Venous malformations	1–3	1–3

From: Rabe E, Breu FX, Cavezzi A, Coleridge Smith P, et al. European guidelines for sclerotherapy in chronic venous disorders. Phlebology 2014;29:346.
*Concentrations proposed are just indicative and may be changed according to the judgement of the therapist.
POL, Polidocanol; STS, sodium tetradecyl sulphate.

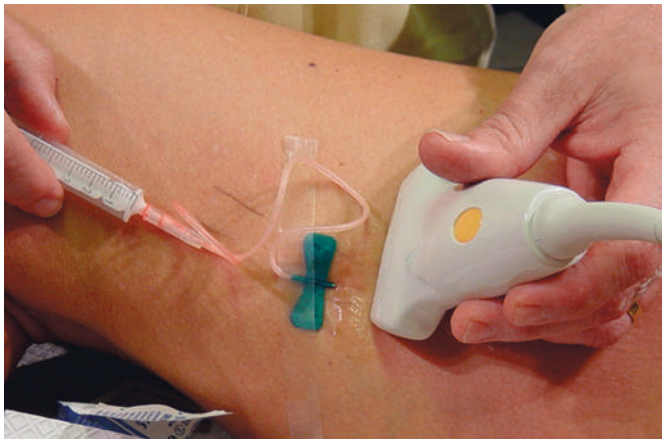


Figure 9.7 Great saphenous vein (GSV) butterfly injection. Injection of the GSV trunk is often facilitated by an access through a more superficial, incompetent and varicose extrafascial tributary. An initial concentration of foam around 1% is usually sufficient, provided the injected volume allows filling up of the tributary and the GSV up to the upper level of valvular incompetence.

puncture technique and distal to the knee if using long catheters. For the SSV, injection should be at the level of the mid calf to minimize adverse events including cannulization of the popliteal artery.[93]

Even if every phlebologist using foam sclerotherapy has been impressed by results (see Case Study 13 later in this chapter), evidence-based medicine applies to phlebology too and controlled trials are needed to demonstrate the validity of the technique. Efficacy of foam sclerosants is more substantially documented today than it was when writing the previous editions of this textbook and evidence is now available.[48–56,77,80,106–108] Cabrera et al[109] have followed 500 lower limbs treated with their unique carbon dioxide-foam mixture, with no greater than 81% of the GSV and 96.5% of the superficial branches remaining closed at over 3 years. Results have not been as impressive when room-air-generated foam is used. Fruillini and Cavezzi[89] found an 88% success rate when the foam was generated with the glass syringe/Monfreux technique versus 93% when generated with the Tessari technique. Although their follow-up was 20 to 180 days, it is clear that the method for generating

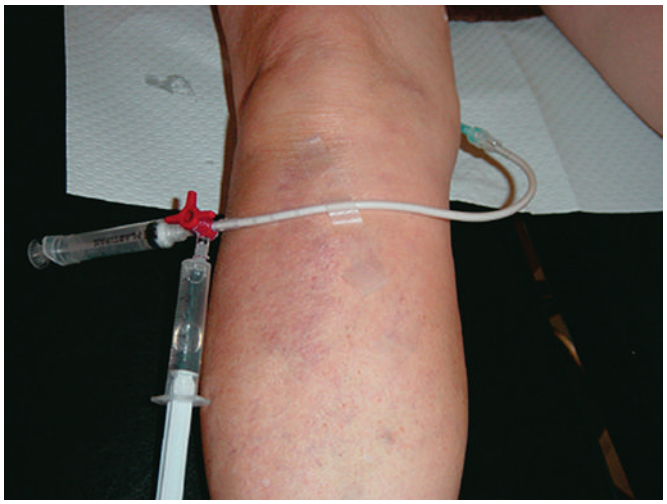


Figure 9.8 Venous access with catheter and injection. Use of catheters and connectors is a little more complicated than the use of simple butterfly needles but is necessary to access the trunks when remote injection through extrafascial tributaries is not feasible. Use of a three-way stopcock allows to fill up with saline and to rinse the connector.

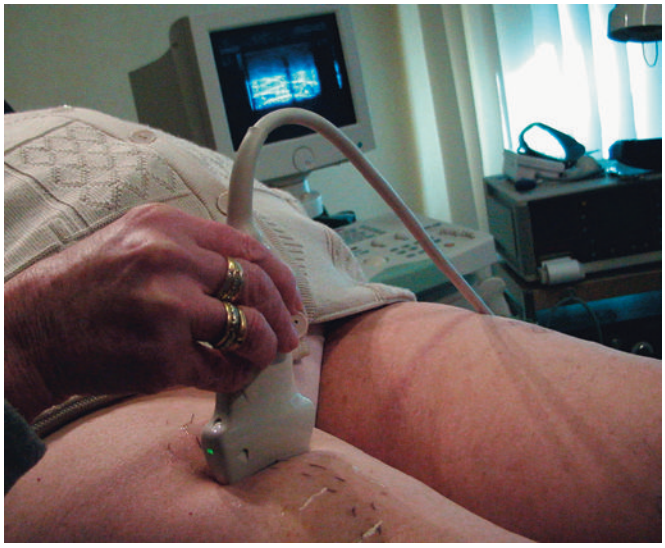


Figure 9.9 Massage foam to desired areas. Hyperechogenicity of foam makes it the perfect contrast medium for remote sclerotherapy. With little practice it becomes really easy to place foam in any vein from a distant open vein access (butterfly or catheter). Use of low or medium concentrations avoids adverse reactions, and the massage stimulates the appearance of a spasm, ensuring the efficacy of the method. In this case, the long-time feared sclerotherapy of the anterior saphenous vein becomes a simple and reliable procedure.

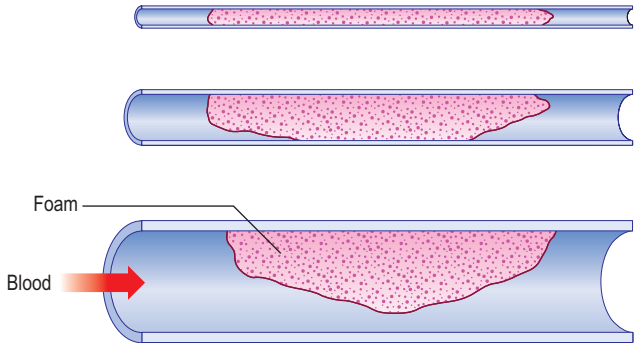


Figure 9.10 Effects of Archimedes' law on foam contact with venous wall in veins of various diameters.

Table 9.7 Volume in cm³ of a Venous Segment Calculated from the Formula of the Cylinder

	Vein Length (cm)							
Vein Diameter (cm)	**5**	**7**	**10**	**15**	**20**	**25**	**30**	**35**
1.00	3.93	5.50	7.85	11.78	15.71	19.63	23.56	27.49
0.90	3.18	4.45	6.36	9.54	12.72	15.90	19.09	22.27
0.80	2.51	3.52	5.03	7.54	10.05	12.57	15.08	17.59
0.70	1.92	2.69	3.85	5.77	7.70	9.62	11.55	13.47
0.60	1.41	1.98	2.83	4.24	5.65	7.07	8.48	9.90
0.50	0.98	1.37	1.96	2.95	3.93	4.91	5.89	6.87
0.40	0.63	0.88	1.26	1.88	2.51	3.14	3.77	4.40
0.30	0.35	0.49	0.71	1.06	1.41	1.77	2.12	2.47
0.20	0.16	0.22	0.31	0.47	0.63	0.79	0.94	1.10

foam is important regarding treatment efficacy. Even Tessari reports a 74% efficacy of complete obliteration in a 2-year evaluation of 38 GSVs and SSVs and 194 collateral branches treated.[110] In a randomized controlled trial, proprietary pharmaceutical polidocanol microfoam (PPPM; Varisolve, rebranded as Varithena) was compared with superficial vein surgery or sclerotherapy in 654 patients with moderate to severe saphenous vein (GSV or SSV) incompetence. The overall success rates were 83.4% for PPPM and 88.1% for control at 3 months, and 78.9% and 80.4%, respectively, at 12 months; at neither time point was the difference significant.[111]

A 3-year follow-up study in UGFS using either STS or POL for the GSVs, SSVs and their tributaries revealed a 52.4% success rate. Veins that failed the primary treatment session were retreated. The 3-year success rate for this group was increased to 76.8%.[112] A 5-year 56% efficacy rate was found in a prospective study investigating UGFS prepared from STS of the GSVs. This protocol consisted of weekly foam sclerotherapy treatments until reflux was no longer detected by ultrasound. Additional treatments were performed if recanalization was detected. Currently, this study contains the longest follow-up duration of all published studies on foam sclerotherapy.[113] In a meta-analysis published in 2007 that included 9000 patients, the median efficacy of foam sclerotherapy was 87% with a median recurrence rate of 8%.[78]

Darke and Baker[114] investigated the number of UGFS treatment sessions required for clinical evidence of complete occlusion of varicose veins. Clinical complete occlusion rates at 6 weeks following the last treatment were as follows: 74.1% with a single treatment, 89.1% with two treatments and 89.5% with three treatments. O'Hare et al[115] found no difference in efficacy rates at 6 months in veins of less than or greater than 7 mm in diameter that were treated with UGFS. However, Myers et al[112] found that treatment success was decreased in veins greater than 6 mm compared with veins of less than 5 mm. This report also concluded success rates were higher in GSVs versus SSVs.

Multiple studies have investigated the influence of various sclerosant concentrations in relation to the efficacy rate of foam sclerotherapy. Efficacy rates were highest for POL 1.5% or STS compared with 3% or more dilute concentrations in a study investigating saphenous veins and their tributaries.[112] A similar study investigating POL for UGFS of GSVs less than 8 mm found short-term (3 week) success rates of 96% and 88% in subjects receiving POL 3% foam and POL 1% foam, respectively (difference was not statistically different). After 2 years, the success rates were 69% in patients treated with POL 3% foam and 68% in those treated with POL 1% foam.[104] Ceulen et al[116] initially found a significant difference in efficacy rates of UGFS between 1% and 3% POL foam at 1-year follow-up (69.5% and 80.1%, respectively). However, when these subjects were followed for 2.5 years, there was no difference in efficacy between the two concentrations of POL (66.7% and 66.8%, respectively).[117] No exclusion criteria were made in this study with regards to the diameter of the GSV.[116,117]

SIDE EFFECTS

A foam bolus can even occur when a small quantity of foam is injected. Hill et al[86] showed that leg elevation, but not manual pressure of the SFJ, decreased the migration of foam in sclerotherapy in UGFS of the great saphenous vein. At least this could ensure that bubbles will be washed of their sclerosing molecules, but will release much bigger bubbles. Other methods to decrease foam migration include multiple, sequential injections of foam sclerosant volumes less than 0.5 mL.[118]

Lattimer and colleagues[119] tested a 'stocking pull-up maneuver' during foam injection into the GSV to help prove pulling-up a stocking from the ankle may inadvertently flush foam into the femoral vein, which may increase the risk of systemic side effects and reduce GSV occlusion rates. This maneuver involved a below-the-knee 23- to 32-mmHg graduated elastic compression stocking placed over the foot, leaving a cuff of redundant stocking around the ankle before injection of the sclerosing solution. In their study, a duplex ultrasound over the SFJ was used to measure peak velocity (PV) and volume flow (VF) before and while the stocking was being pulled up to knee level. There was a 17.7-times increase in PV and a 9.4-times increase in VF at the SFJ during the pull-up maneuver, proving the presence of a significant force in producing hemodynamic effects that can cause foam to shift into deep veins through perforating veins, especially if an intense venospasm has occluded the saphenous flow. The authors, therefore, advocate partial application of a stocking to knee level before foam injection of the GSV above the knee to avoid the significant force associated with pulling up a stocking from the ankle after injection. In their paper, Lattimer and colleagues also provide a concise review of technical modifications suggested by various authors, from 2005 up to the time of their study, to limit foam migration into deep veins.[119]

A meta-analysis investigating side effects in over 9000 patients by Jia et al[78] found the median rates of deep venous thrombosis and pulmonary embolus were less than 1% each. The median values of visual changes and headache were 1.4% and 4.2%, respectively. Chest tightness and coughing occurred in less than 1%. In a large, prospective, multicenter study of foam sclerotherapy in 1025 patients the incidence of migraine was 0.78% (with aura 0.59%;.19% without aura), visual disturbance 0.68%, chest tightness 0.68%, chest tightness with visual disturbance 0.49%, deep venous thrombosis 0.98%, pulmonary embolism 0.1%, and transient ischemic attack 0.1%.[120]

A study of patients with incompetent GSVs treated with UGFS created from either carbon dioxide or room air, in a 1:4 sclerosant to gas dilution ratio, demonstrated decreased incidences of foam bubble–related side effects including chest tightness (3.1% to 18%), cough (1.6% to 16%), and dizziness (3.1% to 12 %). There was a trend toward decreased visual disturbances in the carbon dioxide versus room air group (3.1% to 8.2%), though this difference was not found to be statistically significant. There were no differences in vital signs or echocardiogram (ECG) changes between the two cohorts. An overall 71.79% decrease in bubble-related side effects (compared with room air) was attributed to the carbon dioxide foam.[121] When cerebral emboli were monitored via transcranial Doppler ultrasound in patients treated with foam created from either room air or a 70% carbon dioxide/30% oxygen mixture, no statistical differences were found between these two cohorts with regard to the rate

of high-intensity transient signals in the middle cerebral artery.[122]

One can speculate that the decreased upstream foam-related side effects are attributable to the short carbon dioxide foam half-life[96] and the increased diffusibility of this gas into blood in comparison to nitrogen and oxygen.[94,96] In a study of 116 patients with stasis ulcers, the incidence of visual changes and cough occurred in less than 2% of patients treated with carbon dioxide–created UGFS.[123] In a large multicenter prospective study by Guex et al, visual disturbances occurred in 0.28% of patients treated with foam sclerotherapy created using room air.[124]

Intravenously injected bubbles of less than 10 μm do not produce symptoms in patients, regardless of the presence of a patent foramen ovale.[125] Ceulen et al[126] noted foam microbubbles created from room air appeared in the right atrium and ventricle 0.75 to 15 minutes following injection. In the small study by Morrison et al,[127] foam bubbles were identified in the deep venous system and the right atrium within 10 seconds of the initial injection of foam sclerotherapy into a 1-mm telangiectatic vein. This finding was reproducible in all 15 subjects. In a related study, these bubble emboli 'showers' could last minutes and were present in the left side of the heart in 33% of subjects, indicating a shunt. Of interest, 57% of this group of patients showed transcranial Doppler evidence of bubble emboli.[128]

Four cases of transient ischemic attacks and cerebrovascular events have been reported in the literature. All patients had examples of right to left cardiac shunting, such as patent foramen ovale and atrial septal defects, discovered on further workup.[120,129,130] These bubbles can appear in the middle cerebral artery in under 35 seconds.[131] Treatment for foam-induced neurological events includes administration of 100% oxygen followed by immediate transfer to an emergency department and the initiation of hyperbaric oxygen therapy.[130] As the most prevalent gas in room-air bubbles is nitrogen, foam bubble half-life is decreased as the concentration of oxygen increases and the nitrogen decreases.[132] Theoretically, in the event of cerebral emboli, the osmotic diffusion of oxygen and nutrients should be able to compensate for small bubbles but not larger bubbles.[133]

Deep venous thrombosis is a rare occurrence in foam sclerotherapy, with an incidence of 0.015%.[124] Shadid et al[134] recommend maintaining a high index of suspicion for the development of deep venous thrombosis when superficial thrombophlebitis occurs distant from the treatment area. Pulmonary emboli have been reported following UGFS.[120,135] Infection is a rare event following foam sclerotherapy, but cases of cellulitis and *Klebsiella* sepsis have been reported.[136]

OUR TECHNIQUE FOR THE TREATMENT OF RETICULAR AND TELANGIECTATIC LEG VEINS

Our classification for veins is as follows: varicose veins are tortuous and larger than 4 mm, reticular veins range from 1 to 4 mm and telangiectactic veins are less than 1 mm. For the most successful outcome of foam sclerotherapy of telangiectatic leg veins, the feeding incompetent reticular veins must be treated simultaneously. At our clinic, we initiate with treatment of refluxing veins, the largest veins, and proceed in a proximal to distal fashion. The double syringe system with room air in a 1:5 dilution (1 part sclerosant solution to 4 parts gas) is our preferred method for foam creation. For reticular veins between 1 and 3 mm, we prefer STS 0.25% or, alternatively, POL 0.25% to 0.5%. We increase the concentration of STS to 0.5%, and POL up to 1%, for veins 3 to 5 mm in diameter. Telangiectatic leg veins are treated with liquid STS 0.25%, liquid POL 0.5%, or glycerin 72% with lidocaine 1% or without epinephrine (adrenaline). Our patients remain in the supine position without leg elevation for the duration of the treatment, Volumes of foam typically used in our practice were discussed previously in this chapter. Methods for sclerotherapy of telangiectasias are further discussed in Chapter 12.

Following treatment, the patient remains supine as nursing staff apply 30- to 40-mmHg compression stockings. Immediate ambulation for 15 to 30 minutes is required. For the next week, 24 hours a day (for one author RAW, only during waking hours), the patient remains in their compression stockings.[137,138] Of note, the updated European guidelines recommend wearing compression stockings (23–32 mmHg) after sclerotherapy daily for 3 weeks to improve results.[49]

COMBINATION THERAPY

Foam sclerotherapy with saphenofemoral ligation versus high ligation, stripping and multiple phlebectomies was evaluated by Kalodiki et al.[144] With 3-year follow-up, there was no statistical difference in the recurrence rates between these two treatment regimens on Doppler ultrasound evaluation. A Turkish study published in 2011 showed the safety and efficacy of same-day SFJ ligation plus foam sclerotherapy (3% POL with air to liquid ratio 4:1) as an alternative technique to classic conventional vein stripping for the treatment of varicose veins.[145] There were no differences between treatments in terms of postoperative symptoms, Doppler findings or CEAP (clinical, etiology, anatomy, pathophysiology) class. Five-year symptom-free survival rates were 51% ± 0.8% in the foam sclerotherapy group and 46% ± 0.9% in the stripping group. Of note is the much higher rate of both symptom-free and Duplex reflux–free rates in patients treated with endovenous laser or radiofrequency laser treatment of the GSV (see Chapter 11).

Foam sclerotherapy can be combined with endovenous laser ablation at the time of surgery or can be performed at follow-up visits. In a study by King, UGFS was combined with either the 980-nm or 1320-nm endovenous laser for the treatment of incompetent saphenous veins. At 1-month follow-up, treatment success was seen in 97% of patients.[146] Further long-term data and controlled clinical trials will be necessary to evaluate whether combined endovenous laser ablation combined with foam sclerotherapy is superior to endovenous laser ablation alone. Any varicosities remaining at 6 weeks postprocedure and distal to the site of endovenous ablation should, in our experience, be treated by foam sclerotherapy.

CONTRAINDICATIONS TO FOAM SCLEROTHERAPY

Patent Foramen Ovale

Patent foramen ovale (PFO) is present in 27% of the general population,[128,129,147] and decreases in prevalence with increasing age. Transesophageal echocardiogram with contrast is the recommended screening test for the detection of PFO, but transcranial Doppler ultrasound is almost as sensitive.[148]

Right to left cardiac shunting can occur in the presence of a PFO, atrial septal aneurysm or any opening between the atria, ventricles or the great vessels.[149] Pulmonary arteriovenous malformations can lead to extracardiac shunting and occur in 10% of the population.[128] All of the previously listed forms of shunting can result in cerebral vascular system emboli. The incidence of cryptogenic stroke is greater in patients of all ages with PFO[149] compared with the general population.[150] Two prospective studies found migraines associated with an aura occur more commonly in patients with PFO.[151,152]

In a report by Morrison et al,[127] 15 patients were screened for a PFO with an ECG before foam sclerotherapy. Although echocardiogram screening revealed no PFO, intraoperative transthoracic ECG monitoring revealed the presence of four PFOs which were accentuated because of the increased visibility of foam. A 2010 study by Wright et al[148] found 58.8% of patients with varicose veins (CEAP C3–5) had a right to left cardiac shunt as evidenced by the appearance of bubbles in the middle cerebral artery on transcranial Doppler (at rest or with a Valsalva maneuver) using agitated saline. Next, 61 patients with a right to left heart shunt were treated with UGFS with 1% POL foam created from a 70% carbon dioxide/30% oxygen mixture; 89% had evidence of bubble emboli in their cerebral vascular system. No patients were symptomatic throughout this study. In a study of 3259 patients treated with UGFS, 7 patients (0.21%) experienced foam-related side effects including visual disturbances, chest tightness, and migraine with aura. Of these seven patients, five tested positive on transcranial Doppler examination, indicating the presence of right to left cardiac shunting such as with a PFO.[153]

A known symptomatic PFO is considered an absolute contraindication for foam sclerotherapy by the 2nd European Consensus Meeting on Foam Sclerotherapy, and remains stated as such in the updated guidelines. However, the committee agreed that it is not necessary to screen for a PFO in an asymptomatic patient before foam sclerotherapy treatment.[93]

Thromboembolism and Thrombophilia

An absolute contraindication for foam sclerotherapy is the presence of an acute deep or superficial venous thrombosis. If a patient has a prior history of a deep venous thrombosis or thrombophilia, it is considered a relative contraindication. These patients should undergo a full workup to determine the etiology of thrombophilia, treatment for 7 days with prophylactic low molecular weight heparin and be administered limited volumes and decreased concentrations of foam sclerotherapy.[93] In the study by Wright el al,[111] the incidence of deep venous thrombosis decreased when small volumes were used per injection and the injection was ceased and compression applied when foam was present 5 cm from the saphenofemoral or saphenopopliteal junction. An in vivo study has shown minimal effect of foam in terms of inflammation and coagulation on the peripheral blood, either with or without posttreatment compression, and foam did not appear to have an effect on the myocardial risk.[154]

Migraine

A straightforward migraine is not considered a contraindication to foam sclerotherapy.[93] However, we found that patients with history of ophthalmic migraine (see Chapter 8) were likely to have visual disturbances more frequently after foam sclerotherapy; this must be explained at the time of informed consent. Neurological disturbances, including migraine, following previous foam sclerotherapy is considered a relative contraindication in the updated European guidelines.45b

General contraindications to sclerotherapy treatment are addressed at the end of the chapter.

OTHER INJECTION TECHNIQUES

AIR BOLUS

The air-bolus technique was first advocated by Orbach[70] to ensure that sclerotherapy treatment of varicose veins occurred with minimal thrombosis. The rationale for instilling air before injecting the sclerosing solution is that clearing the vessel of blood allows undiluted contact to occur between the solution and the vessel wall. This procedure was thought to minimize the concentration and quantity of solution required to produce endothelial injury. A comparative evaluation of this technique demonstrated enhanced efficacy of treatment regardless of the type of sclerosing agent used.[155] In reality, the potential complications of air embolism, as addressed in Chapter 8, are nil. A disadvantage of this technique is that air proximal to the sclerosing solution in the syringe causes compression of the solution, producing leakage of solution from the needle after depression of the plunger has stopped. This may cause extravasation of solution on needle withdrawal.

Radiologic studies have shown air-bolus injections into large varicose veins in the area of the GSV are ineffective in clearing the vessel of blood, even when 0.5 mL of air is injected immediately before the injection of contrast medium.[60] In addition, the air inhibits complete and even filling of the varix both proximal and distal to the injection site. In smaller varicosities, injected air forms several bubbles and does not act as a bolus. It also moves independently of the position of the patient and is not totally under the influence of gravity. Therefore, the air-bolus technique may not be advantageous for use in treating varicose veins.

USE OF A TOURNIQUET

The use of a tourniquet is not recommended as an aid to injection. Although it may distend the vein for easier cannulation, the increased pressure in the varicose vein may force sclerosing solution into normal veins. In addition, the tourniquet impedes flow in the normal vein, thus limiting the normal dilution of sclerosing solution. However, the tourniquet may be used to facilitate placement of the needle into the vein. It is then removed, ensuring that the intended vein has been cannulated, and the solution is then injected.

ULTRASOUND-GUIDED INJECTION

Ultrasound is a useful tool to help visualize injection of a varicose vein in patients who have deeply situated perforator veins, in the obese patient in whom the varicose vein is not easily palpable, in patients with recurrent varicose veins and in patients with an unusual or complex anatomy that makes finding the point of maximum reflux difficult. Ultrasonic guidance alone does not compensate for lack of dexterity or experience. In fact, injection may be riskier, because of the complex reasons that necessitate its use.

Earlier experience with less detailed ultrasound imaging demonstrated multiple complications, with the most severe being arterial injection with loss of significant amounts of tissue (see Chapter 8).[156] The use of foamed sclerosant has also decreased the risks.

Ultrasound-guided injection was first described in 1989 and is a natural extension of the use of ultrasound in patient evaluation.[157–161] The technique for injection is similar to that for standard sclerotherapy except that the needle used is usually longer and of larger a diameter. The author generally uses a 1.5-inch, 22-gauge needle, which is sufficiently large to be echogenic. Smaller needles (25-gauge) could not be easily seen with earlier Duplex ultrasound devices, but with newer high resolution devices even needles of 30-gauge diameter can be visualized.

The needle is introduced into the vein open (not attached to a syringe) to ensure venous placement, because arterial injection must be avoided (Fig. 9.11A) (see Chapter 8). Injection of the foamed sclerosing solution is seen as echogenic flow (Fig. 9.11C). The injection continues until the vein goes into spasm, thrombosis occurs or foam is seen filling the vein (see Fig 9.11D, Figs 9.12 and 9.13).

To provide an even safer method for injection, Grondin and Soriano[162] advocate the use of a 20-gauge, 44-mm Teflon or radiopaque catheter to cannulize the vein under ultrasound guidance to further enhance accurate visualization of proper needle placement. Their reported rate of complications in 500 patients is 19.4% postinjection pain, 6.4% superficial phlebitis, and no cases of intra-arterial injection, pulmonary emboli (PE), deep vein thrombosis (DVT) or extravasation necrosis. Parsi and Lim[163] also advocate this 'long line' echosclerotherapy and comment on the lack of any arterial injection using this technique in their 3-year experience.

Kanter and Thibault[164] reported their 2-year experience in treating 202 limbs with ultrasound-guided sclerotherapy. Of these limbs, 23.7% had recanalized at 1 year with no additional veins recurring at 2 years. No complications were reported in their patients. They injected 3% STS in 1-mL increments beginning 3 to 4 cm distal to the SFJ and continued with distal injections every 30 to 90 seconds until persistent vessel spasm occurred or a maximum of 15 mL was injected. This is not possible with foam as the vein will spasm too quickly. Compression with a class II stocking was maintained for 1 week. Two weeks after treatment, any additional nonsclerosed veins were again treated in this manner. For liquid sclerotherapy, the best results were seen in patients treated with larger volumes of STS. Thibault[165] followed 35 of his patients for 5 years and noted 25.7% with recurrent veins and 40% with persistent reflux. Thus, duplex-guided GSV sclerotherapy with liquid sclerosing solution is only moderately effective.

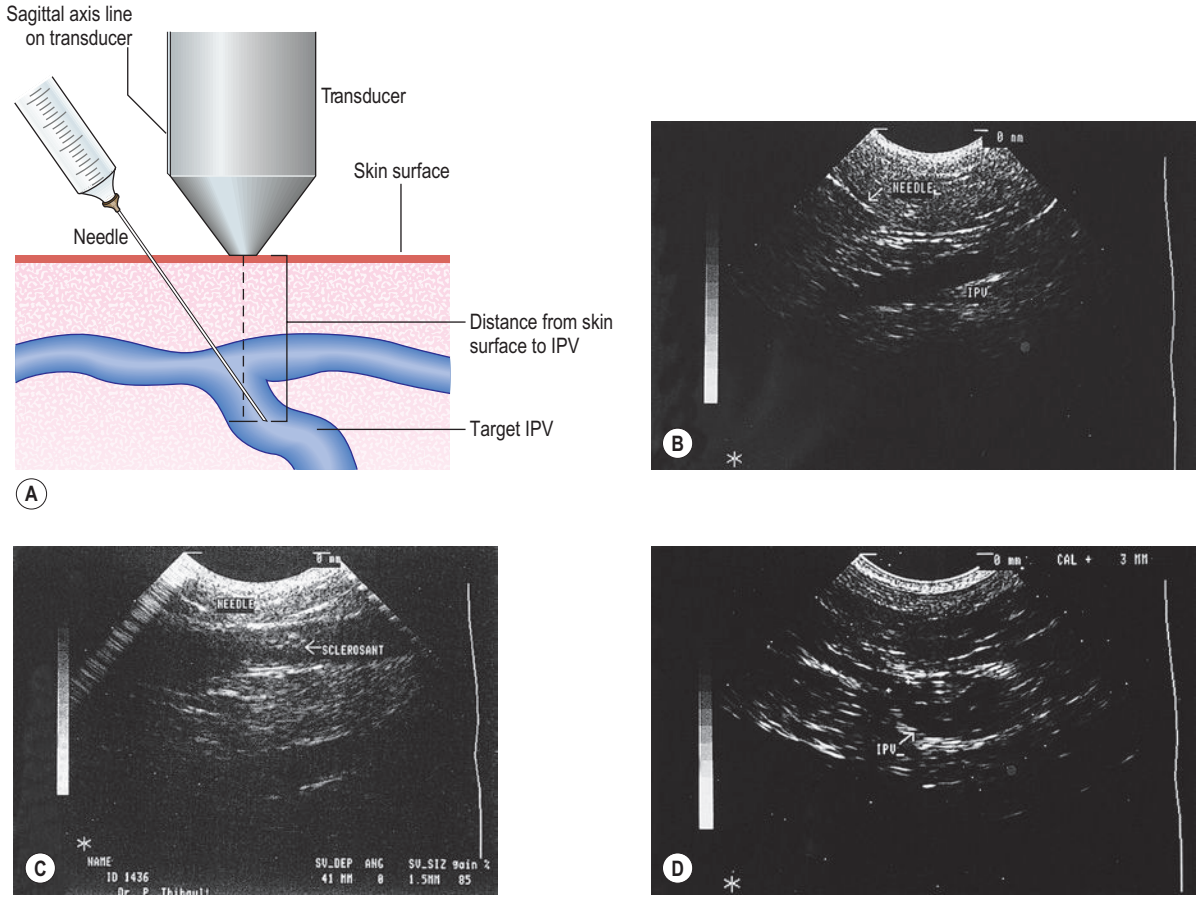


Figure 9.11 **A,** Needle is inserted close to the transducer tip and along the sagittal plane of the transducer. Depth of target incompetent perforator vein (IPV) is measured on the B-mode image from skin surface to segment of IPV. **B,** B-mode ultrasound image showing needle approaching IPV. **C,** B-mode ultrasound image of needle located in vein with sclerosant flowing in the vein. **D,** Postinjection B-mode image of IPV showing vessel spasm. (From Thibault PK, Lewis WA. J Dermatol Surg Oncol 1992;18:895.)

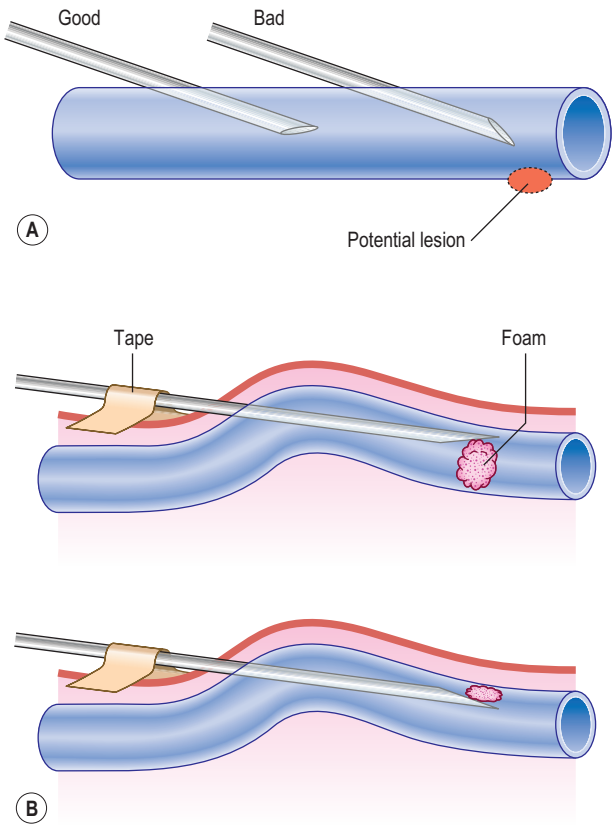


Figure 9.12 Keep needle bevel down. **A,** When using butterfly needles (and syringe-attached needles too), attention must be paid not to damage the opposite venous wall; thus it is suggested to turn the bevel down. **B,** Turning the bevel down has another advantage: it limits the obstruction of needle lumen when in contact with the venous wall. This is especially important when attaching the butterfly needle to the skin with adhesive tape.

Hammahata et al completed a retrospective analysis of 104 patients who completed ultrasound-guided sclerotherapy over a 5-year period. Visible veins were treated with 1 to 2 mL of 1% POL foam and the ultrasound guided veins were treated with 1 to 2 mL of 3% POL foam followed by compression for stocking use for more than 6 months. At 24 months 62.2% of the previously treated veins continued to be successfully treated. Patients who had more than one sclerotherapy treatment had a 75.8% rate of continued treatment success. The lower success rate was felt to be a result of the lower dose of POL.[166]

Additionally, Abbassi-Ghadi and Hafez completed a prospective study with 213 lower limbs treated with 3% sodium tetradecyl sulfate (STS; Fibrovein, CP Pharmaceuticals, Wrexham, UK) with approximately 5 mL of foam to treat the SSV and 8 to 10 mL to treat the GSV with a maximum of 12 mL foam in one session. Fifty-eight percent of the patients needed only one treatment, 31% needed two treatments, 8% needed eight treatments and 3% needed four treatments. Patients who were over 50 are more likely to need more than one treatment session. Adverse effects included skin discoloration at 17.8% and phlebitis at 7.9%. One patient developed a DVT and subsequent pulmonary embolus who was later found to have an underlying myeloproliferative disorder. Overall, UGFS is a safe and effective treatment for patients with chronic superficial venous insufficiency.[167]

Finally, a Doppler ultrasound-guided 18- or 20-gauge (2.75-inch or 1.5-inch, respectively) introducer needle (SmartNeedle, Advanced Cardiovascular Systems, Temecula, CA) is commercially available. This device has the proposed benefit of allowing distinction of arterial from venous flow before treatment and has been used to prevent erroneous arterial puncture during placement of a central venous catheter.[168]

Foam is the best contrast medium for ultrasound-guided injections. Microbubbles are perfect reflectors and when injected into a vein, foam appears as a white cloud responsible for a subjacent black shadow cone (see Fig. 9.9). Being completely opaque to ultrasound it does not allow control on the deeper part of the injection, and in large veins, where foam floats along the more superficial venous wall, some doubt remains regarding appropriate contact of the whole venous wall.

Duplex ultrasound is also useful in assessing the response to initial treatment. When patients return for follow-up examination, duplex evaluation can guide subsequent injections to sections of the vein that have not sclerosed fully or to a previously unrecognized area of reflux. When sclerotherapy is successful, the venous wall appears thickened, particularly at the intimal layer, with ultrasound (Fig. 9.14). The vein is noncompressible. When endofibrosis is subtherapeutic, the lumen is open with partial intravascular thrombosis. These findings indicate the need for a further sclerotherapy injection. Incomplete sclerosis appears as a series of multiple echoes represented as intraluminal white dots.[157] Superficial thrombophlebitis appears as an enlarged luminal diameter with minimal parietal changes, partial compressibility, echogenic blood flow and a lumen partially filled with echogenic material.[169]

Thibault and Lewis[170] found that IPVs are the most common site of reflux from deep to superficial veins in patients with recurrent postsurgical varicose veins. In their series of 122 limbs in 76 patients, after ligation and stripping of the SFJ or SPJ, 71.3% of patients had recurrent incompetent superficial thigh veins in the distribution of the GSV. Thirty-two percent of patients had incompetent veins in the distribution of the SSV. These veins can then be injected with sclerosing solution.[161] In this setting, ultrasound-guided injection is particularly helpful, because an obvious varicosity does not always occur over an incompetent perforator.[171] In addition, surgical exploration for the perforator in this setting is often difficult.[172] Thirty-six patients (38 limbs) with IPVs after surgical stripping were injected with 0.5 to 1 mL of STS 3% under ultrasound guidance.[161] Repeat injections were required at 6 to 8 weeks in six patients. Thirty-six of 38 limbs were successfully closed at 6- and 12-month follow-up without notable complications.

Chen et al treated 233 patients with GSV insufficiency with 3% STS foam (Fibrovein, STD Pharmaceutical, Hereford, UK) and found occlusion was achieved in 89.6% of incompetent veins in two treatment sessions with a mean of 1.53 treatments. It was concluded that UGFS is simpler and less painful than stripping and endovenous laser treatment.[173] However long-term follow-up was not available.

Some surgeons apply direct pressure to the saphenovenous junction during the UGFS treatments to theoretically

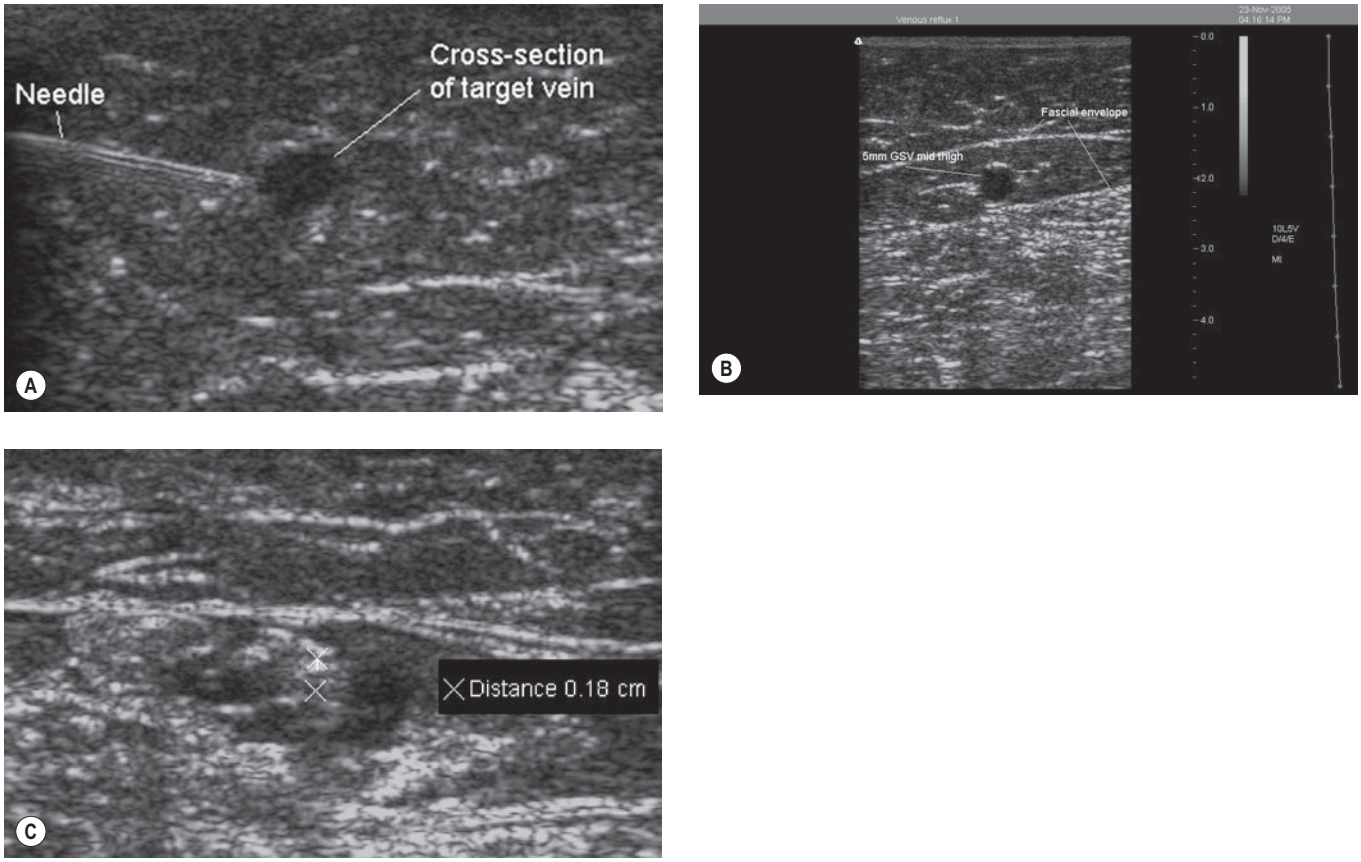


Figure 9.13 **A,** Cross section of needle preinjection into 5-mm-diameter vein; **B,** GSV before treatment 5 mm in diameter; **C,** Immediate post perivenous tumescent anesthesia, the vein has decreased in diameter to 1.8 mm. (Courtesy Paul Thiabault, MD.)

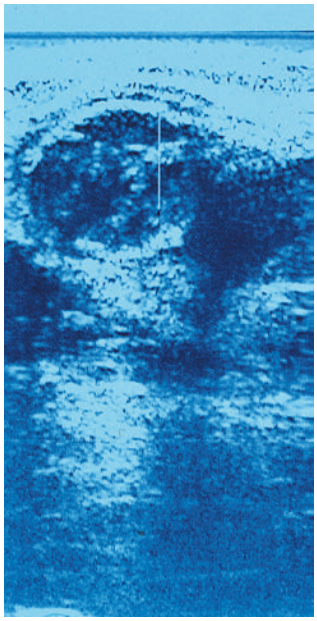


Figure 9.14 Duplex ultrasound transverse image of the great saphenous vein after sclerotherapy. Note presence of adherent heterogeneous material within the lumen and thickening of the endothelium. (From Raymond-Martimbeau P. Semin Dermatol 12:123, 1993.)

reduce the flow of foam beyond that region. Ceulen et al found that blocking the saphenovenous junction with either manual compression or ligation did not prevent but reduced the flow of 1% POL foam with radioactive pertechnetate into the femoral vein as the foam travelled through the deep venous system.[174]

Rapid healing of persistent venous leg ulcers with an underlying perforating vein treated with duplex UGFS appears to be effective in producing rapid healing of the ulcers.[175] Cabrera et al[123] reported that, at 6-month follow-up, 83% of their patients' ulcers healed after a single ultrasound-guided sclerotherapy treatment with their proprietary foam (Variglobin).

Treatment of a proximal perforating vein with UGFS has also been shown to cause resolution of the associated varicose vein.[176]

UGFS may also be particularly effective in treating the incompetent SSV. Schadeck[177] injected the SSV an average of 3.17 times over 5 years in 74 patients to maintain closure of the vein. Bullens-Goessens et al[178] found an enhancement in functional improvement after ultrasound-guided sclerotherapy of the SSV in 11 patients evaluated with air plethysmography.

DOPPLER-GUIDED INJECTION

This technique is of historical significance only and is not recommended because portable high resolution ultrasound devices are readily available. The concept of this abandoned

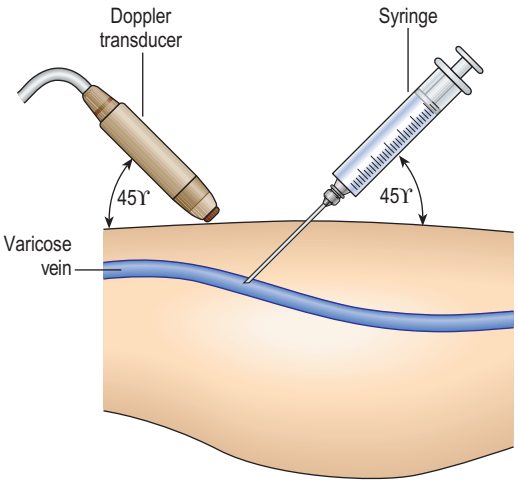


Figure 9.15 Schematic representation of the relationship between the Doppler transducer and syringe. Continuous-wave Doppler localizes the inflow at the needle tip. The continuous wave beam and the long axis of the needle are virtually perpendicular as the needle passes under the Doppler transducer. The needle and Doppler transducer must be separated by several centimeters at the skin surface for proper alignment and transmission of suction and injection sounds. (Redrawn from Cornu-Thenard A, De Cottreau H, Weiss RA. Dermatol Surg 1995;21:867.)

technique is that a handheld Doppler probe may guide accurate cannulation and injection of sclerosing solution into poorly visible varicose veins. The Doppler probe is used to determine the point of maximum reflux and is positioned approximately 1 cm distal or proximal to that point. While an assistant holds the Doppler probe in place, the needle or syringe is advanced toward the vein with slight negative pressure on the plunger. Puncture of the vessel is heard as a tinkling sound, and the syringe fills with venous blood. Injection is heard as a flushing sound, almost like flushing a toilet.

Cornu-Thenard[179] found that approximately 20% of varicose veins change their position by 1 cm or more when patients move from a standing to a supine position. Therefore, preinjection markings of varicose veins with the patient standing to localize veins that may disappear when the patient lies down are not reliable. Doppler evaluation is important when the patient is supine to ensure accurate needle placement. A multicenter study of this technique in 220 patients with approximately 1400 injections demonstrated successful cannulation in all but 18 injections.[180]

The advantage of Doppler-guided injection is its simplicity. A single operator with practice may perform this technique with one hand holding the needle and the other hand holding the Doppler probe (Fig. 9.15). The ideal vein to treat with this method is palpable standing, measuring 4 to 5 mm in diameter and impalpable supine.

ENDOSCOPIC INJECTION

Venous endoscopy has been reported as being useful when injecting the SFJ or perforator veins but, given the availability of superior duplex ultrasound technology, it is rarely performed.[33,181] Van Cleef[182] first presented this technique in 1989 for treatment of the GSV at the SFJ. This technique uses an angioscope inserted through an 11-French Seldinger introducing set (USCI-Bard, Billerica, MA) while the patient is either standing or in a reverse Trendelenburg position. Endoscopes should have a diameter of 0.85 mm. Irreversible spasm may occur if the introduction occurs with the patient supine.[33]

The saphenous vein is cannulated with a 16-gauge needle, with the dilator and 11-French sheath inserted over a guidewire after the needle is removed. The angioscope is advanced with visualization, helped by 5% dextrose solution infusion at 37°C and manual compression of the refluxing SFJ, while the patient is supine. The endoscope is brought to within 2 to 3 cm of the ostial valves and the sclerosing solution is injected through the infusion channel.

Manual compression of both the injection site and the angioscope insertion site is maintained until vessel spasm is complete. After 5 minutes, the venous lumen is irrigated and observed for endothelial destruction, which is noted as a change from the normal pearly-white color to a reddish gray. A compression dressing is then applied. At present, visualized endovenous changes have not been correlated with outcome. Sclerotherapy under endoscopic control is considered an experimental procedure.

INTRAVASCULAR ULTRASOUND-CONTROLLED INJECTION

Intravascular ultrasound (IVUS) provides a unique perspective for evaluating vessel walls before, during and after therapeutic interventions. Echographic data processing and computerized image manipulation can produce accurate luminal and transmural images of blood vessels. Electronically switched array devices use frequencies of 12 to 25 MHz in 4- to 12-French catheters to produce cross-sectional images of vascular segments. However, with present probes, a bright circumferential artifact known as a 'ring down' surrounds the catheter and prevents imaging of structures in the area immediately surrounding the catheter.[183]

Determining the luminal and vessel wall morphology of normal and minimally diseased vessels using IVUS produces a dimensional accuracy of 0.05 mm.[184–186] This device can visualize calcified and noncalcified arterial lesions and intimal tears or flaps and can distinguish between the media, intima and adventitial layers of the vessel wall. This technology has primarily been used in evaluating arterial lesions. Future devices may one day combine the benefits of angiography, angioscopy and IVUS in a single compact unit.

Raymond-Martimbeau[187,188] have reported injection through an IVUS probe. This technique allows injection to continue while the vein wall is resonated by the ultrasound probe until sclerosis is visualized by whitening of the entire vein wall (Fig. 9.16). The advantage of this technique is the assurance of complete destruction of the vein wall. The concentration or quantity of solution can be varied until effective endosclerosis is seen. This is rendered unnecessary by foam sclerotherapy.

Raymond-Martimbeau[187] performed a study of 25 incompetent sites diagnosed with IVUS and treated with sclerotherapy using liquid iodine sodium iodide in concentrations of 1% to 3% and volumes of 0.25 to 1 mL. In 21 cases (84%), partial echogenic intimal thickening was observed within 1 to 6 minutes (mean, 2.7 minutes). Circumferential intimal thickening became evident within 3 to 26 minutes (mean, 6.2 minutes). The lumen then filled with echogenic

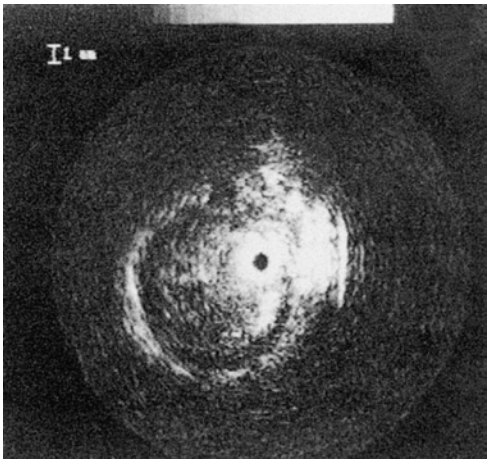


Figure 9.16 Intravascular ultrasound cross-sectional image from a segment of the great saphenous vein after injection of iodine sodium iodide. Note presence of intimal thickening and intimal destruction at the 2 o'clock position. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Raymond-Martimbeau P. Role of sclerotherapy in greater saphenous vein incompetence. In Bergan JJ, Goldman MP, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishing; 1993.)

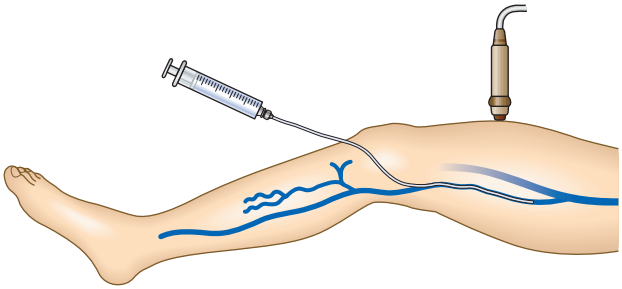


Figure 9.17 The infusion catheter enters the great saphenous vein at the knee level and its tip is positioned 2 to 3 cm below the saphenofemoral junction using ultrasound guidance. (Redrawn from Min RJ, Navarro L. Dermatol Surg 2000;26:410.)

material and decreased in diameter. Within 1 week, the treated segment was transformed into a fibrous cord that disappeared completely between 2 and 12 weeks. In four cases (16%), weak or no intimal thickening occurred and the vein recanalized within 2 to 12 weeks. These patients were then treated successfully in a second session. With the use of foam sclerotherapy the advantages of IVUS are diminished, although in the age of liquid sclerosants it was only useful in defining the success of treatment and in ensuring accurate placement of sclerosing solution.

TRANSCATHETER DUPLEX ULTRASOUND-GUIDED SCLEROTHERAPY

When liquid sclerosant ultrasound-guided sclerotherapy was challenging for treating GSV reflux at the SFJ junction, a technique of transcatheter duplex ultrasound-guided sclerotherapy was developed by Min and Navarro, who used endovenous transcatheter techniques of vessel occlusion under image guidance (Fig. 9.17).[189] Fifty-one GSVs in 50 patients were treated with this technique. With the use of ultrasound guidance and local anesthesia, the GSV was entered 15 to 45 cm (mean, 35 cm) below the SFJ. A 5-French infusion catheter was placed over a 0.035-inch diameter guidewire and positioned under ultrasound guidance 2 to 3 cm below the SFJ. An injection of 2 mL of STS 3% was made in this location, with additional 0.3-mL injections given at 3- to 5-cm intervals as the catheter was withdrawn. The treated leg was then compressed with a class II (30- to 40-mmHg) graduated compression stocking that was worn for a minimum of 7 days and the patient was instructed to walk immediately. A mean of 4.5 mL (2 to 5 mL) of STS 3% was given in each vein. All veins remained closed at 3- to 12-month (mean, 8 months) follow-up.

Transcatheter duplex ultrasound-guided sclerotherapy represents the use of Seldinger principles in cannulating the GSV for the safe delivery of concentrated sclerosant. This important step helped minimize inadvertent arterial injection with liquid sclerosant. The insertion of a catheter to deliver sclerosing solution is not a new procedure and was described by Rose in 1941.[190] Here, the catheter was introduced into the GSV intraoperatively to sclerose the distal GSV after ligation at the SFJ. Use of the ureteric catheter was discontinued in 1945, and the practice of simultaneous sclerotherapy was ended in 1946 with the introduction of a simplified method for ligation of the GSV proximally and distally.

To summarize the preceding discussion, sclerotherapy of the GSV may be accomplished best by the use of a foam sclerosant placed accurately with duplex-guided endoluminal catheters or high resolution with easily visualized needles monitored with continuous duplex ultrasound monitoring.

MECHANOCHEMICAL ENDOVENOUS ABLATION (MOCA)

The MOCA technique uses a rotating wire to induce mechanical injury to the venous endothelium with a simultaneous catheter-guided dispersion of a liquid sclerosant. Because heat is not generated, tumescent anesthesia is not required. Boersma et al examined 50 patients with SSV insufficiency treated with the MOCA technique. A rotating wire within the ClairVein catheter device (Vascular Insights, Madison, CT) was used to induce mechanical endothelial injury while dispersing 1.5% to 2% liquid POL (Aethoxysklerol, Kreussler Pharma, Wiesbaden, Germany). A 100% success rate was seen at 6 weeks and a 94% success rate at 1 year with no major complications. The maximum diameter SSV treated was 11 mm.[191]

VEINRX INFUSION CATHETER

Of historical interest, a proprietary industry-designed catheter received FDA 510(k) clearance in 2005 for infusion of physician-specified fluids, including thrombolytics. The catheter combines a distal occlusion balloon and a series of unique, sealable infusion ports that enable even and simultaneous distribution of sclerosant along the entire treatment length of the target vessel. Either liquid or foam sclerosant may be used with this catheter.

The VeinRx infusion catheter (VeinRx Inc, Miami, FL) was designed to temporarily occlude a proximal vessel segment with a distal expandable balloon and then deliver a predetermined dose of a physician-specified fluid along the lumen of the vessel.

As illustrated in Figure 9.18, the infusion catheter comprises a distal occlusion balloon, fixed infusion length catheter body with infusion holes and a trifurcated hub. Figure 9.19 is a line drawing that further illustrates the catheter design. The FloLock trifurcated hub is designed to connect the three main systems of the device (Fig. 9.20). A tubing extension incorporating a stopcock on one side of the hub is the port used to inflate and deflate the occlusion balloon. The Luer connection in the center of the hub is used to mount the syringe loaded with the desired sclerosant. Opposite the balloon port and nearest the blue button is a port for controlling the FloLock channel. The FloLock channel allows the physician to determine accurately whether the infusion ports are open or closed (Fig. 9.21), a feature previously unavailable in standard infusion catheters. This channel uses an inflatable elastomeric bladder to either close or open the infusion ports.

This feature is used to eliminate port obstruction before and during catheter placement, support prepurging and holding the purge in the catheter before and during placement and precise control of sclerosant during infusion. The device is provided in sterile packaging for single-patient use. The infusion catheter is manufactured with well-known and commonly used medical-grade materials.

The distal end of the catheter incorporates a compliant latex occlusion balloon. The balloon eliminates communication between the GSV and the SFJ and enables the sclerosant to produce maximal therapeutic action in the target vein. With the balloon inflated, the physician can deliver a predetermined amount of sclerosant through the catheter and into the GSV, with subsequent flow of sclerosant into incompetent perforators and tributaries. The sclerosant chemically ablates the targeted segment of the vein and has the potential for providing a complete treatment within a single procedure.

Figure 9.18 Photograph of foam extruding through multiple holes in the distal portion of the VeinRx catheter with inflation of the balloon. (Courtesy VeinRx, Inc., Miami, FL.)

There is also the possibility of a small amount of the sclerosant entering the deep venous system through communicating perforator veins. However, this potential is relatively insignificant when compared with femoral vein intrusion of sclerosants in the setting of direct-injection/ultrasound-guided sclerotherapy.

The importance of having a series of infusion ports along the lumen length is to optimize the treatment of the GSV by

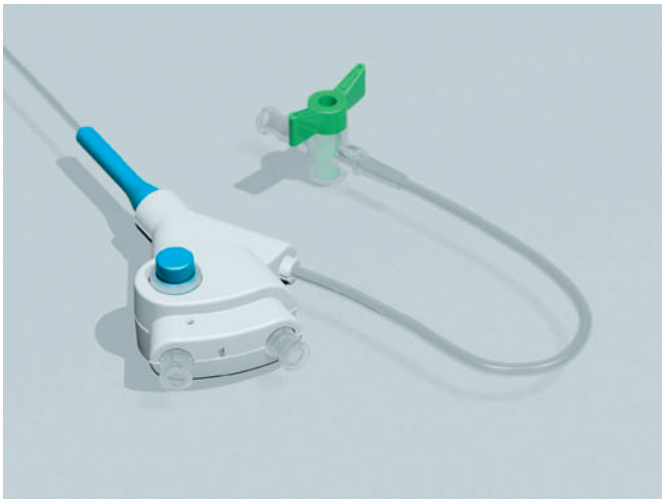


Figure 9.20 Photograph of the proximal end of the VeinRx catheter showing the infusion ports. (Courtesy VeinRx, Inc., Miami, FL.)

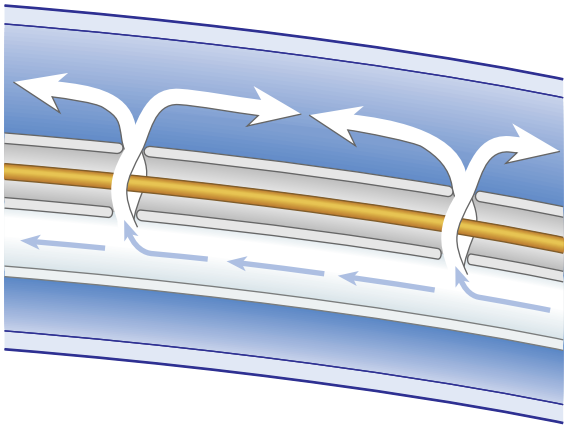


Figure 9.21 Diagram illustrating the effusion of solution from the distal ports on the VeinRx catheter. (Courtesy VeinRx, Inc., Miami, FL.)

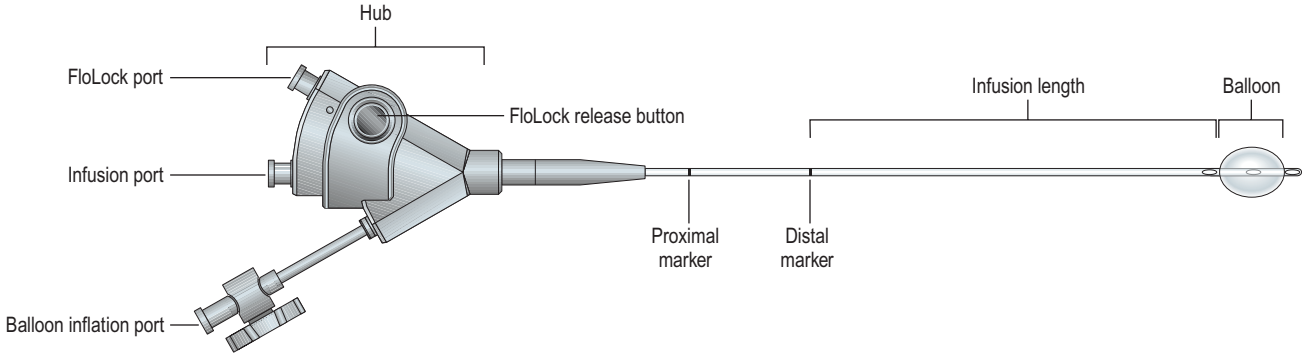


Figure 9.19 Diagrammatic representation of the VeinRx catheter. (Courtesy VeinRx, Inc., Miami, FL.)

localized delivery of the sclerosant. Sclerosant is uniformly delivered when all infusion ports are patent. This design also reduces the possibility of having excess sclerosant flow into large communicating veins near the target vein.

Device Preparation

The VeinRx infusion catheter comes in multiple infusion lengths. The catheter selected for a procedure is a function of the required vessel treatment length. This is determined preoperatively during ultrasound examination. Ultrasound examination is also required to determine the amount of sclerosant to be injected and the proper occlusion balloon inflation volume, which is a function of the vein diameter at the desired occlusion site, usually just distal to the SFJ. Before surgery, the balloon is inflated with sterile saline using a 10-mL syringe and inspected for leakage or damage.

The infusion lumen is prepared by purging the catheter using foam sclerosant constituted by passing the sclerosant back and forth between two 10-mL syringes for 10 or more times, using a ratio of one part sclerosant to four parts air. During proper functioning of the device, foam will exit from all of the holes in the infusion lumen.

The infusion ports are sealed by pressurizing the FloLock channel with a 1-mL syringe filled with approximately 0.75 mL of sterile saline. To insure that the bladder is properly inflated, the operator applies low-level pressure to the infusion syringe and visually confirms that no flow exits the infusion ports along the marked infusion length.

Delivery of Sclerosant

After the preparation described earlier and percutaneous access, the device should be introduced and advanced through the patient's vasculature with the leg in the horizontal and straight position. Using ultrasound guidance, the balloon is advanced to the most proximal treatment point, which is marked in advance. With the leg remaining horizontal and straight, the balloon is inflated. At this point, the foam sclerosant is injected through the device into the patient's target vein. The infusion rate should be approximately 5 mL over 10 seconds.

Upon completion of the infusion, the patient's leg should remain horizontal and straight with the balloon inflated for 4 minutes. This is known as the 'dwell time'. After the 4-minute dwell time, the balloon should be deflated and the device removed. After removal of the device, the introducer is removed and the entry site is manually compressed for 2 minutes and dressed using traditional wound closure techniques. Proper and constant pressure during this period is important to reduce the potential of ecchymosis at the entry site. This is followed by compression. This technique turned out not to yield any better results than standard foam sclerotherapy and is no longer manufactured.

RADIOLOGICALLY ASSISTED FOAM SCLEROTHERAPY

Radiologically guided foam sclerotherapy uses fluoroscopy of the vein with a contrast medium to highlight the vein. As the foam sclerosing agent is injected the contrast medium is displaced. The foam sclerotherapy is stopped as soon as the contrast medium in the varicosity is completely displaced.

Li et al examined 41 patients with leg varicose veins treated with 1% POL foam (Lauromacrogol 400, Xhanxi Tianyu Pharmaceutical Co., Ltd., Xi'an, China) under fluoroscopy (Varicography, Axiom-Artis dFA Nagiographic System, Siemens Medical Systems, Munich, Germany) in both the superficial varicosities and the GSV followed by 15 days of compression. At a medium of 9 months follow up, 89.8% of the patients were successfully treated with a 45.8% rate of skin pigmentation and a 30.5% rate of thrombophlebitis. There were no major complications and the treatment was deemed to be safe and effective.[192] However, the practical utilization of fluoroscopy with increased cost as well as radiation exposure to both patient and staff along with the lack of increased efficacy when utilizing foam sclerotherapy alone makes this technique only suitable for very select patients.

TREATMENT OF SPECIFIC PROBLEMS

TREATMENT OF LARGE-DIAMETER GREAT SAPHENOUS VEINS

The treatment of the GSV with foam sclerotherapy has been discussed and found to be effective depending on the method of foam injection, concentration and volume of solution. However, almost all of the previously cited studies set an upper limit for the diameter of the GSV to be no more than 8 mm.[193] One study used Variglobin 8%–12% (nonfoamed because nondetergent) to inject 500 GSVs with diameters between 6 and 12 mm measured 3 cm distal to the SFJ.[194] The authors reported a 22% failure rate irrespective of vein diameter. Barrett et al[106] reported outstanding efficacy in GSV with diameters greater than 10 mm injected with foamed STS. This was also found by Valsamis.[195] Williamsson et al examined 94 patients with GSV insufficiency treated with 10 mL of 3% POL (2mL POL in 8 mL air; Aethoxysklerol; Inverdia, Weisbaden, Germany) with CDFS as a single treatment. After 1 year 84% of the patients were satisfied and 70% had continued complete occlusion of the GSV. There were no major complications although 28% had continued pigmentation at 1 year.[196] Therefore, proper technique and the use of an appropriate concentration and/or type of sclerosing solution can allow successful treatment of large-diameter GSVs. The length of follow-up is also a critical factor in all of these studies.

Thibault [105] has described a technique for compressing the cannulated GSV with tumescent anesthesia placed in the surrounding facial sheath which may also lead to improved efficacy and reduce recurrences (see Fig. 9.13). However, Devereux et al compared catheter-directed foam sclerotherapy (CDFS) with the long angiography catheter (Cavafix Certo 355; FA Braun, Melsungen, Germany) with 2% POL foam (Easy-Foam kit liquid air 1.6:7.4; Laboratoire Kreussler Pharma, Paris, France) with and without tumescent anesthesia followed by compression for 4 weeks in 50 patients with 5–10-mm GSV. Both groups had an occlusion rate in the region of 74% at 12 months. It remains unclear if tumescent anesthesia with epinephrine could compress and constrict the veins for improvement of foam sclerotherapy.[197]

TREATMENT OF VULVAR VARICOSITIES

Vulvar varicosities can be treated effectively with sclerotherapy. Two problems in their treatment are sclerosis of the proximal point of reflux and compression of the treated vein. Because vulvar veins may arise from the internal iliac

(hypogastric), pudendal, obturator, uterine or ovarian veins deep within the pelvis, treatment directed at the most proximal point of reflux cannot be attempted directly. Instead, the most proximal visible varicosity is cannulated and sclerosing solution injected in a proximal manner. With this technique, 1 to 2 mL of liquid 0.5% to 1.0% STS is injected slowly. Distal varicosities are then treated. Alternatively, foamed 0.25 to 0.5% STS may be injected.

A pelvic support device has been developed to compress the vulvar veins (V2-supporter, Prenatal Cradle Inc, Hamburg, MI). This device is worn until veins have resolved. Five patients treated in this manner showed no evidence of recurrence in 1-year follow-up.[198] Adverse sequelae have not been noted. A 2-year follow-up of these five patients (and two others) also demonstrated no adverse sequelae and resolution of the varicose veins.[199]

Pelvic congestion syndrome with insufficient ovarian veins (IOV) is another potential cause of lower limb varicosities along with varies on the medial thigh, vulva and labia. Castenmiller et al treated 43 patients with IOV with embolization of the ovarian vein. In 12% of the patient's embolization of the ovarian vein resulted in a clearance of lower limb varicosities but only 13% had an improvement in their CEAP classification likely because of venous insufficiency of multiple venous structures other than IOV. However, an 88% improvement in vulvar varices was noted with coil embolization of the ovarian vein resulted in clearance of the vulvar varies in 88% of the patients.[200] However, coil embolization is much more invasive and expensive compared with foam sclerotherapy. In our experience, multiple treatment utilizing dozens of coils are usually necessary for occlusion. It is unclear if similar results could be achieved with a similar number of sequential foam sclerotherapy treatments.

Vulvar and lower limb varicose veins as a symptom of pelvic congestion syndrome (PCS) with insufficient ovarian veins (IOV) and is a potential reason for recurrence of varicosities following lower extremity vein treatments. Paraskevas reported the treatment of PCS through embolization of the ovarian veins followed by ultrasound-guided 1.5% STS foam (Fibrovein Australasian Medical and Scientific, Artamon, NSW, Australia) sclerotherapy of the pelvic tributaries with clinically symptomatic improvement.[201]

TREATMENT OF ULCERS

Foam sclerotherapy is also effective in the treatment of venous ulcers. Cabrera et al[123] investigated carbon dioxide-POL foam in 116 patients with venous stasis ulcers and found complete resolution at 6 months in 83% of patients. Either the saphenous veins, perforator veins or a combination were injected under ultrasound guidance. The mean time for complete resolution of an ulcer was 2.7 months. Long-standing ulcers (over 24 months), size greater than 2 cm, patient age over 65 years old, a history of venous surgery and incompetence of the deep venous system were negative prognostic indicators. Neto and colleagues[139] have shown excellent results in the treatment of ulcers because of severe chronic venous insufficiency utilizing echoguided foam sclerotherapy, with healing rates of 85% for CEAP 6 and 100% for CEAP 5 patients. In their follow-up period of 20 months, there was no ulcer relapse in CEAP 5 patients.

Bush advocates a terminal interruption of the reflux source (TIRS) to reduce venous hypertension at the local level allowing an ulcer to heal. In this method, with ultrasound guidance 1% STS foam is injected into a venous branch or branches in close proximity to the ulcer bed that have documented reflux and continuity with the primary source.[140] Bush demonstrated rapid healing of all 14 venous ulcers after TIRS, with an average time to healing of 6 to 8 weeks. Seven of the 14 patients had been followed for 5 years at the time of the report and remained ulcer free. Of the remaining 7 patients, 4 were ulcer free for more than 2 years, 2 were ulcer free at 1 year and the final patient had presented with multiple ulcers and was undergoing continued treatment on remaining ulcers.

The updated European guidelines recommend sclerotherapy of the varices in the region of venous ulcers to improve the healing rate.[49]

TREATMENT OF VENOUS MALFORMATIONS

Venous malformations (VMs), as described in Chapter 4, consist of variably sized vessels. Sclerotherapy has proven to be very useful in their treatment. In a study by Yamaki et al,[202] 28 patients with a variety of VMs on the face, neck, extremity and elsewhere were treated with duplex-guided sclerotherapy with liquid POL 3%. Eighty-two percent of the patients had effective resolution. Pain on injection in 82%, marked swelling in 75%, hemoglobinuria in 14%, and superficial epidermal necrosis in 10.7% were the reported adverse sequelae.

Foam sclerotherapy using the Cabrera foam on 50 patients with VM was beneficial in 92% after an average of 12 sessions with a mean of 30 months' follow-up.[205] Of the 46 responders, 18 showed complete disappearance of the VM and 15 showed a reduction of over 50% in size of the VM. Of the 39 patients who reported pain, it disappeared in 25 and was reduced in 14. Three cases of skin ulceration occurred. For more information on foam sclerotherapy in venous malformations, please see the earlier section on foam sclerotherapy.

Foam sclerotherapy can decrease the progression and size of VMs, including Klippel-Trénaunay syndrome.[90] In a study by Yamaki et al,[141] subjects with symptomatic VMs, including limited, infiltrating and complex-combined variants, received ultrasound guided foam or liquid sclerotherapy. The sclerosants investigated were 1% POL foam or liquid for treatment of the superficial component and 10% ethanolamine oleate for the deep components of the VM. As complete resolution of VMs would not be realistic in all patients in this study, patients received enough sessions until patient-perceived cosmetic satisfaction was obtained or when no further benefit was anticipated. A significant decrease in volumes of sclerosants (both POL and ethanolamine oleate) were found in the foam cohort. On 6-month follow-up duplex evaluation, increased rates of disappearance (defined as occluded and shrunken venous space) and partial recanalization (defined as partially recanalized and partially shrunken venous space) were greater in the foam group versus the liquid group (45% and 45% versus 25% and 15%).

Li et al[142] described a novel technique of foam sclerotherapy using a radiopaque agent (iopromide) to precisely treat VMs. A ratio of iopromide and 1% POL (1:2) was mixed to produce sclerosing foam by Tessari method before the mixed foam was injected into the VMs under digital

subtraction angiography (DSA). The injection was stopped when the foam completely filled the VMs. The authors conclude this new method of visualization for sclerosing the vessels will allow adequate dosage of foam for satisfactory efficacy and reduce the incidence of adverse reactions that may result from excess injection of sclerosant.

Lee et al[203] reported a 92% efficacy in treating 30 patients with a variety of VMs with absolute ethanol. Multiple sessions were required and 24 total adverse effects occurred in the 92 sessions given. Adverse effects consisted of nerve palsy in five, ischemic bullae in nine, tissue necrosis in two, tissue fibrosis in two and DVT in one. The authors proposed that this treatment helps to debulk and stabilize the VM, permitting simpler surgical correction. An additional report on 399 sessions in 87 patients by Lee and colleagues[204] showed similar results with long-term efficacy.

Absolute ethanol has also been studied as a sclerotherapy modality to treat voluminous VMs of the head and neck, where the lesion is ≥15 cm in maximum diameter or the lesion invades more than one anatomical space. Wang et al[143] conducted a retrospective review of 23 patients who received direct puncture ethanol sclerotherapy under DSA guidance for voluminous and extensive head and neck VMs. All patients were satisfied with the results of therapy, with only minor complications reported. Seventeen patients (73.9%) achieved excellent responses and 6 patients (26.1%) achieved good responses in magnetic resonance imaging assessments. Serious complications, such as acute pulmonary hypertension, cardiovascular collapse and pulmonary embolism, were not encountered allowing the authors to conclude the procedure is reasonably safe and offers good therapeutic results.

Manoli et al[206] compared the treatment of VM with both image guided percutaneous sclerotherapy with 96% ethanol ($n = 19$) and surgical excision ($n = 21$) followed by compression stockings for 3 months. A statistically significant reduction in pain was noted for both procedures with no serious complications in both groups. Patient satisfaction was a 7.9/10 with sclerotherapy and 8.8/10 for surgical excision. This was likely because the surgical excisions were completed in circumscribed or partially circumscribed malformations that could be treated in a single procedure. The cases treated with sclerotherapy were too large to be treated by excision (i.e. worse) and therefore more difficult to treat.

Intramuscular vascular malformations are rare cause of exertional leg pain that has been reported to account for approximately 0.8% of vascular anomalies.[207] Mautner et al[208] reported the use of ultrasound guided doxycycline sclerotherapy (2.5 mL of 100 mg/10 mL) with a series of 4 treatments resulting in a 95% reduction of lower extremity pain in a case study. Doxycycline was chosen as the sclerosant because of its safety profile and availability.

TREATMENT OF OTHER VENOUS CONDITIONS

A variety of other venous conditions have been reported to resolve with sclerotherapy. A report of complete resolution of a venous lake of the lip after two treatments with POL 1%, without adverse effects, has been reported.[209]

Hemangioma showing late involution was successfully shrunk with an injection of 5% ethanolamine oleate, allowing surgical excision.[210]

Multiple hereditary glomangiomas were treated with 0.2% to 3% STS, depending on the size of the lesion.[211] An average of two treatments where the lesions were injected with 0.5 to 1 mL of solution was required for lesion improvement.

Treatment of pyogenic granuloma with 5% monoethanolamine oleate in nine patients, who were all injected once, resulted in complete resolution of the lesion within 2 weeks.[212] An additional study on 15 lesions in 14 patients treated with 0.5% STS (0.15–2 mL) one to five times (mean, 2.2) showed complete resolution in 12 lesions.[213] No adverse effects were seen in any patient.

TREATMENT OF RECURRENCES

When unsuccessful or in case of recurrence, sclerotherapy does not modify the initial, pretherapeutic varicose pattern, which reappears as it was before or smaller. This is not the case with surgery, and, very often, recurrent varices after surgery (REVAS) are extremely difficult to manage.[214] Therefore, if surgery can be, in certain selected cases, considered as an alternative treatment after sclerotherapy failure, sclerotherapy is the usual and most appropriate recourse for recurrence after surgery of varicose veins. The progress in ultrasound guidance and, most of all, the use of foam sclerosing agents have revolutionized the approach to this difficult problem.

As stated in the REVAS consensus document,[214] all recurrences must be completely assessed by duplex to map all leaks and refluxes. After surgery of junctions, two types of recurrence can be observed:

- Neovascularization, where very small veins have grown through the hard connective tissue and lymph nodes and reinject lower varicose veins
- Inappropriate ligation, where an important saphenous stump has been left in place and where macro veins connect the femoral or popliteal vein to the varicose network.

Before onset of UGFS, both types were issues. Since, in the first case, direct injection was rendered difficult by the small diameters, and, in the second case, appropriate long-term control of reflux was doubtful. Now, both types of recurrence can be easily treated either by direct echo-guided puncture and foam injection or by remote access through more superficial tributaries. REVAS veins are usually prone to sclerose because the venous wall remodeling has been severe and because dysplasia allows easier sclerosis. Anyway, in all these cases, attention must be paid to an annual check-up of veins to take care of new recurrences as soon as possible.

For most patients, the difference between 'new veins' and 'recurrent veins' is not obvious at all and this misunderstanding is likely to create some difficulties in doctor–patient relationships. A simple diagram explaining evolution of varicose veins with or without treatment can be extremely useful (Fig. 9.22; also see Case Study 13 later in this chapter).

DOES THE MENSTRUAL CYCLE INFLUENCE SCLEROTHERAPY?

The actions of estrogens and progestins on venous distensibility were discussed previously (see Chapters 3 and 4).

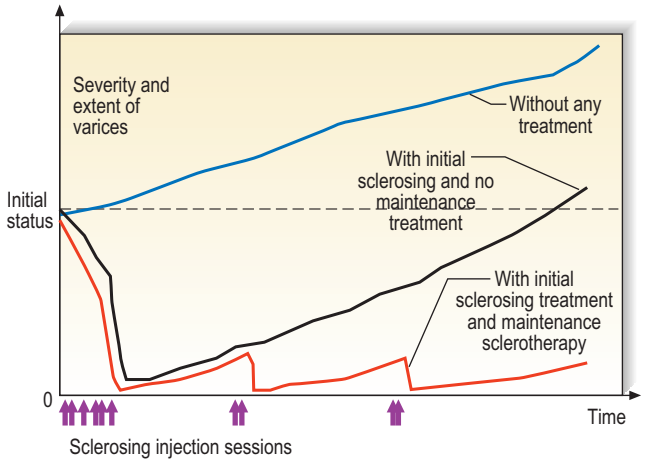


Figure 9.22 Evolution of varicose veins. Although we do not have a simple and accurate criterion of evaluation of the severity and extent of varicose veins, the concept is simple enough and patients can understand it easily. This diagram represents the evolution of the varicose status and the influence of active management. If it is true that there is some spontaneous trend toward worsening, the status is always better when patients are appropriately treated by sclerotherapy, especially with maintenance treatments (theoretical approach).

Theoretically, sclerotherapy should be performed when the venous system is in its most contracted state so that post-treatment thrombosis is minimized. Because limb volume and venous distensibility are at their least during and just after menses and at their highest during ovulation, the optimal window for sclerotherapy treatment is when estrogen levels are lowest.[215] However, until appropriate studies are performed to test this hypothesis, no absolute recommendation can be made.

RECOMMENDED SCLEROSING SOLUTION AMOUNTS AND CONCENTRATIONS FOR NONFOAM SCLEROTHERAPY

Although the exact concentration of sclerosing solution depends on the caliber and location of the varicose vein, the following suggestions can serve as an initial guide to therapy. Dilution of nonosmotic sclerosing solutions with sterile water will cause the sclerosing agent to sting with injection. Thus, dilutions should be performed with bacteriostatic normal saline solution, which will not impart an additional sting.

The *first principle* of determining solution amounts and concentrations is that the concentrations should be strongest at the highest point of reflux. With saphenofemoral reflux, the concentration should be strongest at the upper thigh and weakest at the ankle. With ankle or calf perforating veins, the concentration should be highest at the perforator. For example, Vin[216] recommends that 1 mL of STS 1.0% be used at the proximal thigh, 0.5 mL of STS 1.0% be used at the medial thigh and 0.3 mL of STS 0.5% be used at the medial knee to treat a moderately sized varicose vein.

The *second principle*, as described by Tournay in 1949, is: 'It is not the concentration of the sclerosing agent in the syringe that matters, but the concentration within the vein.'[217] The importance of this statement was discussed in Chapter 7. In short, for sclerotherapy to be effective, the entire vein wall must be damaged and the entire intraluminal volume of the segment of the vein must be destroyed. This is important because the smooth muscle portion of the vein wall theoretically can regenerate endothelium, and endothelial cells can migrate long distances to re-establish a functional conduit. Sackmann[218] expanded on this principle by demonstrating in polyvinyl tubes the local conditions of 'time and space' regarding contact of the sclerosing solution with the vessel wall were also important. He showed the zone of contact diminishes as the caliber of the vessel increases. In tubes with a diameter of less than or equal to 4 mm, the liquid flowed in a laminar fashion. In tubes with a diameter of greater than or equal to 8 mm, turbulent flow was produced. In tubes 6 mm in diameter, a mixed flow occurred, with a transition between a laminar and turbulent appearance (Fig. 9.23). In contrast, the caliber and position of the needle, the speed of injection and the viscosity of the solution did not seem to influence the time of contact of the sclerosing solution with the tube.

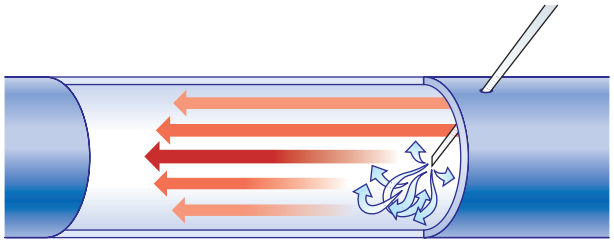


Figure 9.23 Turbulent flow is produced with injection of solution at the point of discharge of sclerosant from the needle cannula. (From Green D. Semin Dermatol 1993;12:88.)

Green[219] used Poiseuille's formula to describe resistance to fluid flow in a varicose vein:

$$R = 8\kappa n^{l}/\pi r^{4} \qquad [9.3]$$

where
R = resistance
κn = viscosity of the solution
l = length of the vein
r = radius of the vein.

From this formula it is apparent that the most important factor in determining resistance of flow is the vessel diameter (radius). At the point of injection into an empty vein, expected flow of sclerosing solution would be nonlaminar (see Fig. 9.23). This may account (along with increased localized concentration; see the following paragraph) for a greater incidence of vessel damage and blowout at the point of injection (see Chapter 8). Nonlaminar flow also occurs downstream of injection in an empty vein in which resistance is still high, because the pressure generated by the physician on the syringe plunger is much greater than intravascular pressure, which would approach zero in an empty vein, especially if the limb were elevated (Fig. 9.24).[220]

Guex[220] has worked out that the concentration of sclerosing solution can be calculated based on the diameter of the vein by the following formula:

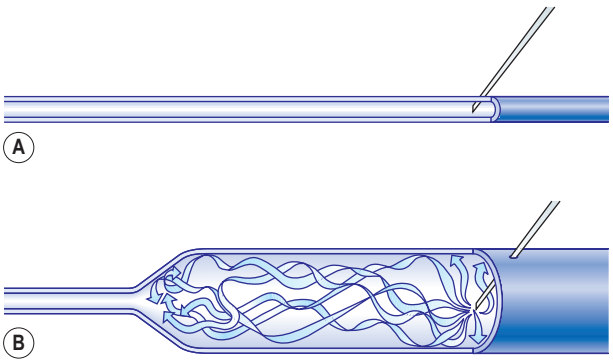


Figure 9.24 Nonlaminar flow occurs distal to the point of injection in an empty vein. **A,** Needle inserted into empty vein. **B,** The force of the advancing injected solution dilates the vein and produces turbulent flow. (From Green D. Semin Dermatol 1993;12:88.)

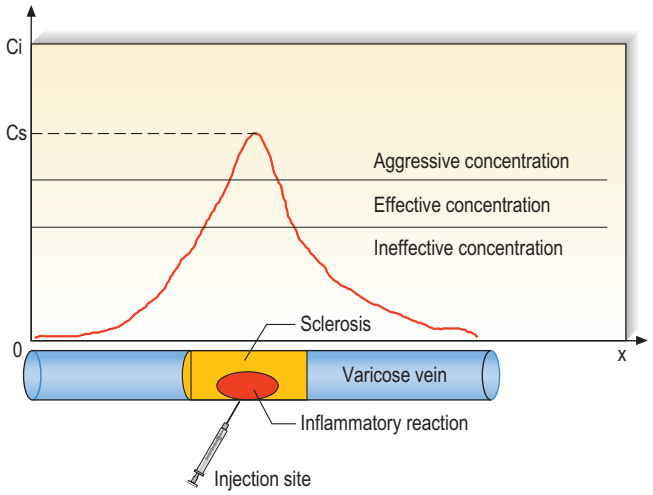


Figure 9.25 Injection at one site with a high concentration but low volume of sclerosing solution. Note localized excessive concentration. (From Guex JJ. J Dermatol Surg Oncol 1993;19:959.)

$$\mathrm{Cm} = v \times C \times n / \pi r^2 \qquad [9.4]$$

where
Cm = mean concentration of solution
v = volume of injected sclerosing solution
C = concentration of sclerosing solution
n = number of injections
r = radius of the injected vein.

Thus, if 0.5 mL is injected into a varicose vein 2 mm in diameter, the sclerosing solution will fill a 16-cm length of vein. In reality, the concentration of sclerosing solution at the injection site is maximal and decreases with distance from each point when small volumes of solution are injected (Fig. 9.25). The concentration of sclerosing solution along the entire course of the vein can be equalized either by injecting a larger volume in a single site or by injecting small volumes in multiple sites (Figs 9.26 and 9.27).

A study by Cornu-Thenard[221] suggests the following sclerosing concentrations for varicosities of various diameters:

- 4 mm = STS 0.25%
- 5 mm = STS 0.5%
- 6 mm = STS 1.0%.

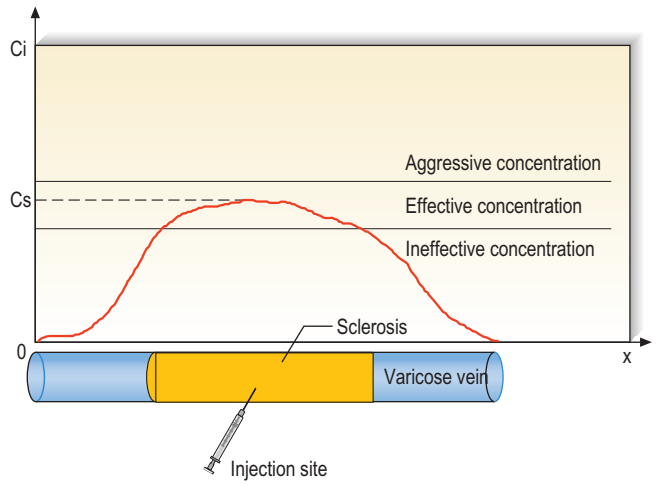


Figure 9.26 Injection at one site with large volume of a dilute concentration of sclerosing solution. Note that a longer segment of vein is sclerosed without any one point of excessive concentration. (From Guex JJ. J Dermatol Surg Oncol 1993;19:959.)

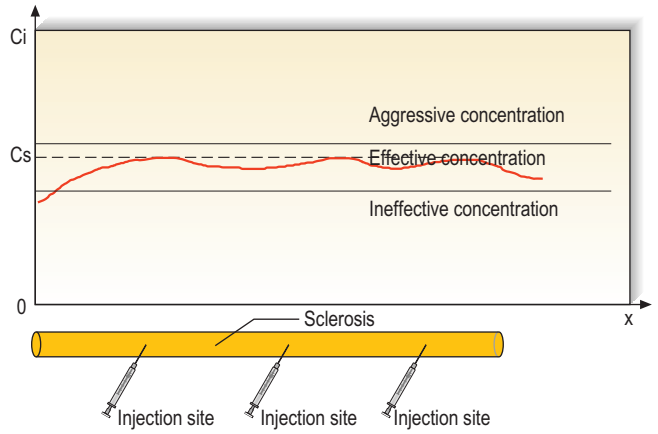


Figure 9.27 Multiple injections with low volumes of low concentrations of sclerosing solution. This technique theoretically provides the safest method for treating long lengths of vein. (From Guex JJ. J Dermatol Surg Oncol 1993;19:959.)

He recommends 0.5-mL injections are placed every 6 to 10 cm along the varicose vein. Additional recommended concentrations for injection of other sclerosing solutions into various types and diameters of vein can be found in Chapter 7.

The *third principle* is the amount of sclerosing solution injected into a single site should not be more than 1.0 mL (usually 0.5 mL). Venographic studies of direct injections into varicosities of the leg have demonstrated that if more than 1.5 mL of solution is injected at a single site, it is likely to spill over into the deep veins.[60,222] In addition, the patient should not move the leg for a few minutes so that the sclerosing solution can remain in contact with the varicose vein, because any movement of the leg will rapidly move the sclerosing solution into the deep venous system.

Some physicians do not limit the volume of sclerosing solution at a single site.[223] Green[223] reports infusing from 3 to 12 mL of STS into each injection site. Concentrations ranged from 0.75% to 3.0% depending on vein size. He reports treating more than 3000 patients in this manner

Table 9.8 Indicative Concentrations and Volumes for Polidocanol Foam

Vein	First Session (%)	Second Session (%)	Volume (cm^3)
Thigh GSV	1.5	3	Up to 8
GSV main tributary	0.5	1	Up to 4
SSV	1.5	3	Up to 4
Perforators	1	2	Up to 2
Nonsaphenous	0.5	1	2 per site

GSV, Great saphenous vein; SSV, small saphenous vein.

without encountering a single case of DVT. He also reports enhanced efficacy with this technique, having near 100% efficacy with follow-ups of up to 5 years. He uses class II compression for 2 to 8 weeks. Other details of his technique are not specified. Green claims that 'the widely varying success rates reported in the literature are usually a reflection of the technique of the practitioner and not any inherent limitation of the procedure.' The authors believe that this statement is somewhat correct but still caution against the use of excessive volumes of sclerosing solution in a single site, because many cases of DVT have been reported by other reputable physicians (see Chapter 8).

Histologic examination of peripheral veins may provide assistance in determining the optimal concentration of sclerosing solution. Corcos et al[224] have determined through biopsy of the dorsal pedal vein that the degree of intimal thickening, ectasia, muscular hyperplasia, medial fibrosis, fragmentation and dissociation of the internal elastic membrane and intimal fibrous plaques correlate with the concentration of sclerosing solution necessary to effect endosclerosis of varicose veins. This finding is supported by the theory that varicosis is a systemic disease (see Chapter 3).

The use of foam has very much simplified the approach of concentration and the current trend is to decrease the concentration in half when using foam as opposed to liquid sclerosing solution. Guex[72] has suggested the values shown in Table 9.8, which remain open to adaptation and discussion.

POSTSCLEROTHERAPY COMPRESSION

After injection of varicose or telangiectatic veins, the treated veins are immediately compressed to minimize significant thrombosis. The patient is instructed to walk immediately after the injection session to help prevent DVT and reduce venous reflux into the treated veins. Calf muscle movement produces a rapid blood flow in the deep venous system, which dilutes any sclerosing solution that may have migrated into the area.

Postsclerosis compression is perhaps the most important advance in sclerotherapy treatment of varicose veins since the introduction of relatively safe synthetic sclerosing agents in the 1940s. Primarily, compression eliminates a thrombophlebitic reaction and substitutes a 'sclerophlebitis' with the production of a firm fibrous cord.[14] The advantages of postsclerotherapy compression are discussed in detail in Chapter 6.

In addition to providing external compression to the treated vessel, one should try to minimize forces that act to distend the vessel. Because taking hot baths or saunas dilates the cutaneous venous network, they should be avoided for 2 to 6 weeks after sclerotherapy or until such time as the treated vessel is fully sclerosed. In addition, any activity that increases abdominal pressure may act to force blood in a retrograde manner through the SFJ or IPVs, producing venous dilation. Heavy weight lifting therefore must be discouraged, along with any exercises that use the abdominal musculature, unless the legs are elevated during abdominal exercise. One such activity that increases abdominal pressure by approximately 22 mmHg is running, with pressure apparently being produced to splint the trunk and pelvis.[225] Therefore, aerobic exercises, jogging and running should be limited for 1 to 2 weeks.

Patients should be examined 2 weeks after injection so any area of thrombosis can be evacuated early.[226] Each individual area should not be treated again sooner than 6 to 8 weeks after initial injection to allow adequate healing between treatments.

GENERAL CONTRAINDICATIONS TO TREATMENT

Knowing and applying contraindications to sclerotherapy is an important part of phlebological practice. The principle of precaution is increasingly applied when using a treatment or a drug: when its use has not been specifically determined, registered and officially approved, its use is unlawful. Official contraindications are very often unclear, false or inaccurate, outdated or worse. Contraindications should remain under medical control and managed by specialists.[227]

PREGNANCY

Besides the risk of absorption of the sclerosing solution by the fetus, pregnancy is associated with dilation of the entire venous system through multiple mechanisms that do not normalize until 3 months postpartum (see Chapter 3).[228,229] Therefore, although sclerotherapy can be and has been performed successfully by many physicians on pregnant women,[230–234] the increase in venous distensibility counteracts the desired contraction of the treated varicose vein (see Chapters 3, 4, and 8). Finally, varicose veins may decrease in size and disappear after delivery (see Chapters 3 and 4).[235] Thus, waiting may eliminate the need for the procedure.

One situation that may justify sclerotherapy during pregnancy is the presence of significant and painful vulvar varicosities, which develop in approximately 2% of pregnant women.[236] They usually occur by the second trimester and are more likely in multiparous women. Although they rarely thrombose, they are painful, especially with walking. Bed rest, leg elevation and localized compression are usually effective in alleviating symptoms, but sclerotherapy may be necessary in severe cases.

Venography has shown that vulvar varices arise from any combination of the following: obturator vein; internal

pudendal vein; inferior gluteal vein; external iliac, uterine and ovarian veins; obturator vein; presacral veins; common femoral vein; and the GSV.[237,238] Because of this variable and extensive system of reflux and the thin-walled, fragile nature of these veins, sclerotherapy is preferred over surgical excision or avulsion (see Case Study 7 later in this chapter).

Extrahepatic portal-vein obstruction (EHPVO) in pregnancy is a cause of portal hypertension that can result in life threatening variceal bleeds warranting treatment. Subbaiah et al[239] evaluated 9 prenatal cases of EHPVO treated with endoscopic variceal ligation and 8 pregnant women treated with endoscopic sclerotherapy. There was no statistical difference in pregnancy outcome and complications between the two groups. A 23.8% risk of abortion, 18.7% risk of preterm delivery and a 12.5% risk of small for gestational age fetus were found. Thrombocytopenia was found in 61.9% and anemia in 40% of the pregnancies. None of the patients who were treated prenatally had variceal bleeds and 1 patient diagnosed during pregnancy had a variceal bleed that responded to endoscopic sclerotherapy. Sclerotherapy can be lifesaving in EHPVO in pregnancy with a good pregnancy outcome.

INABILITY TO AMBULATE

Walking after treatment is very important because it ensures rapid dilution of the sclerosing solution, which may enter normal deep veins. In addition, stagnation of blood flow is avoided, and the possibility of excessive thrombosis lessened, by the liberation of thrombolytic factors during muscle contraction when walking. Walking also decreases physical distention of the vein caused by reflux.

A corollary to the contraindication just mentioned is the performance of sclerotherapy during surgical ligation. Although this procedure has been performed by many surgeons and was advocated by de Takats in 1930,[240] it was usually limited to a point distal to the SFJ on the GSV and therefore was performed on an ambulatory basis. In 1934, Faxon[241] modified this technique to include ligation at the SFJ with retrograde injection of the GSV. He achieved good results (although follow-up was poor) in his series of 117 cases except for one case of fatal PE, which was attributed to faulty technique by a resident surgeon. Conrad[242] reports great success with this technique when used in conjunction with ligation at the SFJ. Hubner[243] reported similar success without mention of complications in 413 patients followed for more than 1 year. Patients treated with POL 4% had an 83% success rate, whereas patients treated with Variglobin 4% had a 94% success rate. However, Hubner separates the two procedures by a few hours to a day because his patients had the ligation performed by a surgeon in a separate office and return to him for sclerotherapy. This latter scenario ensures that the patient is ambulatory for both procedures.

In spite of the successful results mentioned earlier, there are potential complications that call for separating the two procedures. First, many varicose veins will resolve after surgical treatment of the high-pressure reflux points, so subsequent sclerotherapy is minimized or not necessary.[244] Secondly, the surgical period is often one of minimal ambulation because of postoperative pain and the use of general or regional anesthesia. The delay in adequate ambulation may allow the sclerosing solution to migrate to the deep venous system where unwanted damage could occur (see Chapter 8).[236] The authors recommend postoperative sclerotherapy be delayed for 2 to 3 weeks.

HISTORY OF THROMBOPHLEBITIS AND DEEP VEIN THROMBOSIS

Patients with a history of certain venous diseases may be predisposed to the development of excessive thrombosis with injection of a sclerosing agent (that is, development of an excessive phlebitic reaction; see Chapter 8).

Patients with low-risk thrombophilia (activated protein C resistance, hyperhomocysteinemia especially, factor II, factor V Leiden) can be treated with sclerotherapy. A prospective study in progress will determine the best prophylaxis (see Chapter 8).

Regarding patients already treated with oral anticoagulation, the contraindication is more dependent on the disease treated by anticoagulation than on anticoagulation itself. Patients treated for atrial fibrillation can be sclerosed without inconvenience; most of the time, the course of their treatment is simpler than for normal patients.

Also, in rare patients, the dilated superficial system may serve as a conduit for carrying blood to the heart. Interruption of the superficial system may then increase venous insufficiency. Therefore, PPG, both with and without application of a superficial tourniquet or a trial of 30- to 40-mmHg graduated compression stockings, helps determine which patients will benefit and which may be harmed by sclerotherapy treatment.

Another simple test to determine if the varicosity resulting from DVT is a necessary conduit is a modification of the Perthes test (see Chapter 5). A tensiometer cuff is inflated to 110 mmHg, and the patient is asked to walk quickly for 5 minutes. If the patient complains of heavy pain, or if the leg becomes livid or both, the varicosity is necessary as a collateral channel. This test has allowed, without complication, surgery on 53 limbs with varicose veins in 52 patients with a prior DVT.[245]

ALLERGIC REACTION

Patients are rarely allergic to a sclerosing solution, but a different solution can usually be substituted. If the allergic reaction consists of generalized urticaria, with or without an erythematous papulosquamous appearance, French authors advocate continuing treatment with the offending sclerosing solution with the addition of antihistamines before and after treatment (see Chapter 8).[246]

Infrequently, patients develop periorbital edema and a maculopapular cutaneous eruption even with the use of unadulterated hypertonic saline solutions. In this case, 'allergic reaction' may be the result of histamine release by intravascular basophils or perivascular mast cells that are directly damaged by the sclerosing solution (see Chapter 7).[247] Under this circumstance, administration of antihistamines before and after the procedure appears safe while therapy is continued.

An anaphylactoid reaction has been reported after the use of STS (Fibrovein, STD Pharmaceutical Products Ltd., Hereford, UK) in one patient.[248] Anaphylactic shock has also been reported after an injection of STS (Trombovar;

Kreussler Pharma, Wiesbaden, Germany).[249] Hypersensitivity testing or avoidance should be used in patients with more severe allergic reactions.

PATIENTS TAKING DISULFIRAM

Patients taking disulfiram (Antabuse) should not be treated with POL or Sclerodex, because these sclerosing solutions contain ethyl alcohol.

PATIENTS TAKING TAMOXIFEN

As described in Chapter 8, tamoxifen is often responsible for extensive superficial phlebitis in patients treated by sclerotherapy, even of reticular or spider veins. We consider it to be a relative contraindication.

PATIENTS TAKING HORMONES

Hormonal replacement as discussed previously is not considered a contraindication to sclerotherapy. If a patient is at risk for venous thrombosis they should not be on hormonal replacement in the first place.

OTHER CONTRAINDICATIONS

WARM WEATHER

Treating patients in summer is not a contraindication, provided they can wear compression and do not sunbathe during the treatment.

TRAVEL

Administering sclerosing injections immediately before a long flight or trip (more than 4 hours) is not recommended as the patient is at slightly increased risk for thromboembolic events from the inactivity in flight. Additionally, it is not very prudent for a patient to be unavailable for examination immediately after treatment.

AGE

Many venous malformations are currently treated with sclerosing foam; young age does not forbid sclerotherapy. Conversely, the elderly are good candidates for sclerotherapy because they are often not candidates for surgery. Because their veins are especially dysplastic, they usually respond better to injections. We do not limit our treatments in these patients, except when life expectancy is short.

CASE HISTORIES

The following case histories demonstrate the authors' technique of sclerotherapy for different varicose veins (Box 9.1).

Box 9.1 Sclerotherapy of Varicose Veins

Sequence of Events

1. Physical examination
2. Noninvasive diagnostic examination
3. If findings are abnormal, consider duplex scanning, varicography or photoplethysmography
4. Eliminate the high-pressure inflow points
5. Saphenofemoral-saphenopopliteal junction
6. Incompetent perforators
7. Sclerotherapy of the largest diameter varicose veins
8. Sclerotherapy of perforator or reticular veins that feed 'spider' telangiectasia
9. Sclerotherapy of 'spider' telangiectasia

CASE STUDY 1 Incompetent perforator veins treated with Fegan's technique

A 35-year-old woman developed varicose veins during the second trimester of her second pregnancy and wore an over-the-counter light compression stocking during the remainder of her pregnancy. At delivery, she developed thrombophlebitis that was treated with hot packs only. She came for evaluation and treatment 6 months after delivery. Physical examination showed a 4- to 6-mm varicose tributary of the GSV originating at the medial mid thigh and extending to the medial calf with continuation across the anterior tibia (Fig. 9.28A, B). Venous Doppler examination revealed a continuous venous sound with distal augmentation at the level of the posterior tibial vein at the left ankle. There was no evidence of saphenofemoral reflux or other abnormalities. Photoplethysmography revealed a normal venous refilling time in the right leg and an abnormal refilling time in the left leg (20 seconds). The venous refilling time normalized with placement of a tourniquet at the level of the left upper calf and left lower thigh. Therefore, the physical and noninvasive examinations were consistent, showing incompetence of the mid thigh (Hunterian) perforator.

Because of the localized abnormality (IPVs) producing the varicose vein, Fegan's technique of perforator interruption was used. Sclerotherapy was performed with the injection of 0.5 to 1.0 mL of STS 1.0% at the mid thigh, medial superior calf and anterior distal tibial point of fascial depression. The needles were inserted with the patient standing, and the patient then assumed the supine position with the leg elevated to 45 degrees. After aspiration to confirm proper needle placement, the sclerosing solution was injected while proximal pressure was maintained. STD E-foam pads were placed over the entire course of the varicose vein and secured with Microfoam tape. A 30- to 40-mmHg graduated compression stocking was applied and worn continuously for 7 days, after which it was worn for an additional week only while the patient was ambulatory.

The patient was seen 2 weeks later, at which time physical examination revealed total resolution of the varicosity at the mid thigh (Fig. 9.28C) and persistence of a thrombosed varicosity at the anterior tibial level (Fig. 9.28D). It was drained, and the pressure stocking was prescribed for use while the patient was ambulatory for another week. On follow-up examination 6 weeks later, the vessel had resolved (Fig. 9.28E). One-year follow-up demonstrated total obliteration of the varicosity and posttreatment hyperpigmentation (Fig. 9.28F, G). This case illustrates Fegan's principle that interruption of the IPVs alone causes normalization of the entire varicose vein.

One year later (2 years after her initial sclerotherapy), the patient became pregnant with her third child and noted the development of new varicose and telangiectatic leg veins during her first trimester. Despite wearing 30- to 40-mmHg graduated support stockings for much of her pregnancy, she developed incompetence of the SFJ bilaterally, with new incompetent GSV

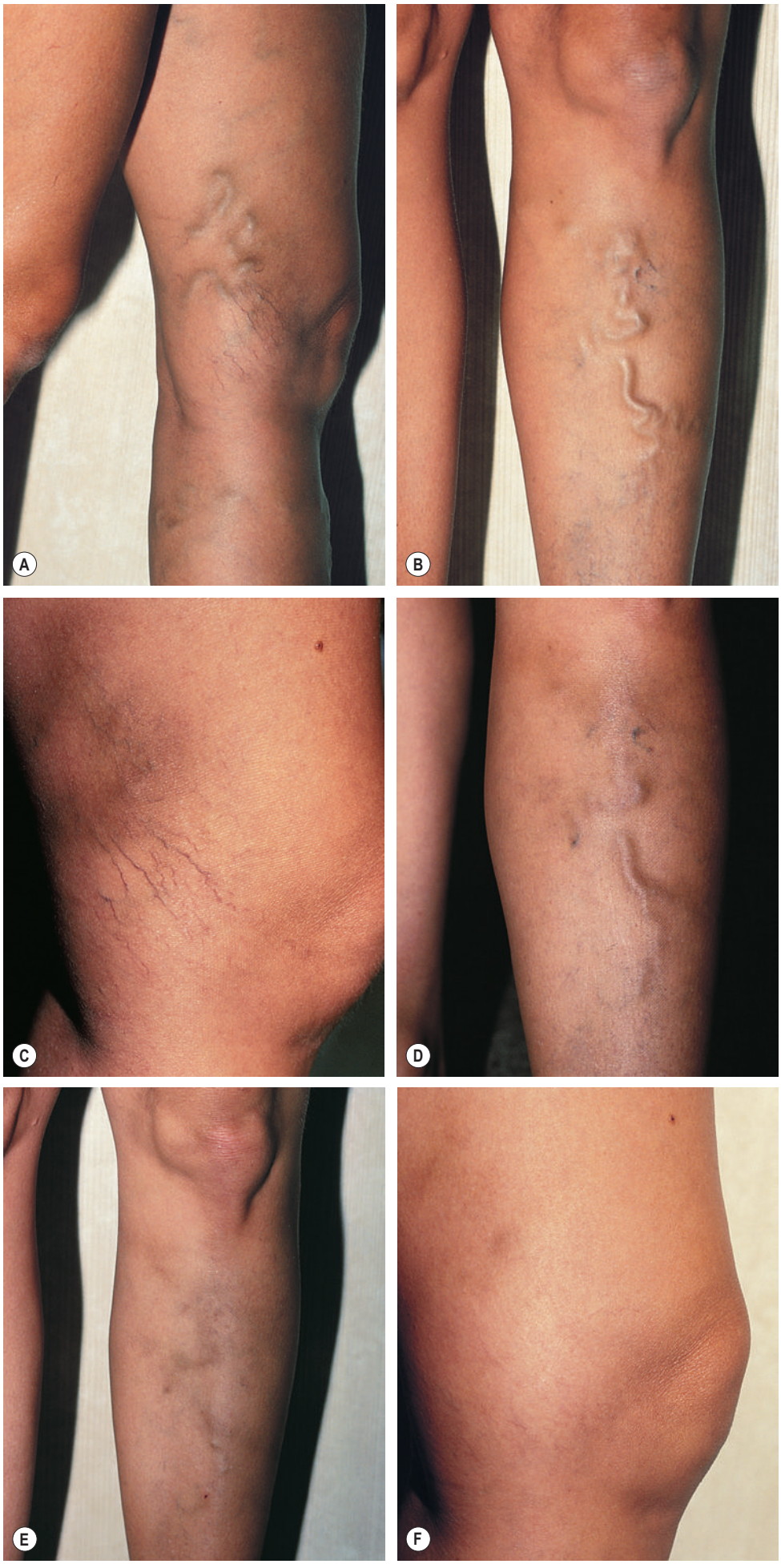


Figure 9.28 Case Study 1. **A,** Varicose tributary of the great saphenous vein originating at medial mid thigh and, **B,** extending to medial calf and continuing across the anterior tibia. **C,** Two weeks after sclerotherapy, total resolution of varicosity is shown at mid thigh, but, **D,** persistence of thrombosed varicosity is visible at anterior tibial level. **E,** Complete resolution 6 weeks after sclerotherapy. **F,** Lateral views of vein normalization 1 year after treatment.

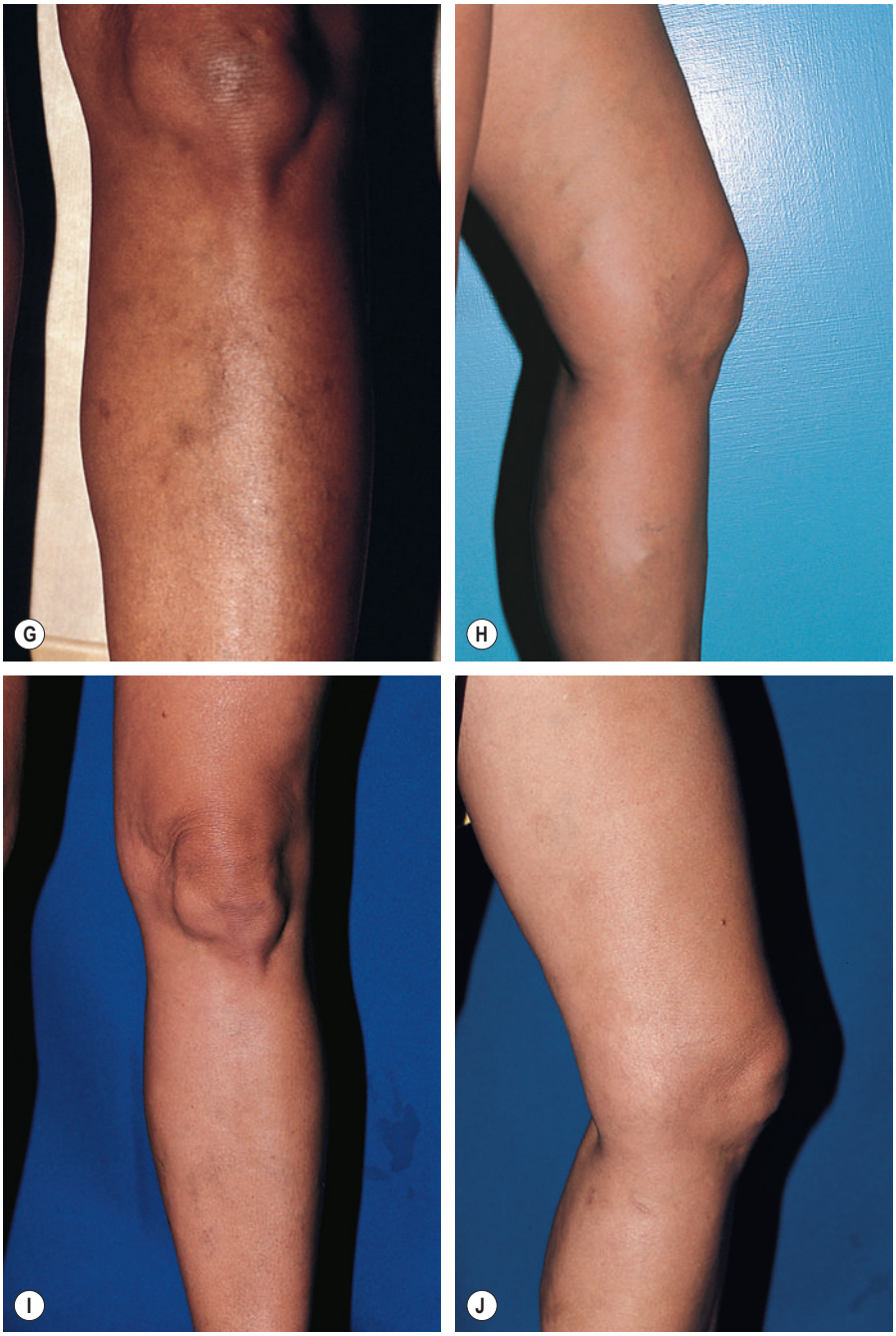


Figure 9.28, cont'd **G,** Anterior views of vein normalization 1 year after treatment. **H** and **I,** New varicose great saphenous vein (GSV) from an incompetent saphenofemoral junction. Note that previously treated veins remain sclerosed. **J,** Clinical appearance, 6 months after ligation and stripping of GSV followed by sclerotherapy of reticular veins.

bilaterally and new vulvar varicosities. Interestingly, the previously sclerosed veins just above the medial knee and on the anterior tibial surface did not reappear (Fig. 9.28H, I). Ligation and stripping were performed 18 months postpartum when breastfeeding was discontinued, followed 2 weeks later with sclerotherapy of reticular veins, with excellent results (Fig. 9.28J).

This patient illustrates many important points. Sclerotherapy is very effective in treating large varicose veins when the SFJs are competent. However, varicose veins represent a disease of the venous system that is often progressive. So, initial success may be met with new disease over time, especially if additional aggravating events (pregnancy) occur. Fortunately, treatment is both effective and cosmetic.

CASE STUDY 2 Incompetent perforator vein at the mid calf treated with modified Fegan technique

A 40-year-old woman noticed the gradual development of a varicose vein over 4 years without any predisposing factors. Physical examination showed a varicose tributary of the GSV 3 to 5 mm in diameter extending from the mid-anterior tibial surface to the medial calf and thigh and ending in the lower anterior thigh (Fig. 9.29A, B). Venous Doppler examination was remarkable only for an IPV at the right mid-medial calf.

As fascial depressions could not be felt, the classic Fegan technique could not be performed. Therefore, 25-gauge butterfly catheters were placed randomly into the varicosity at the level of

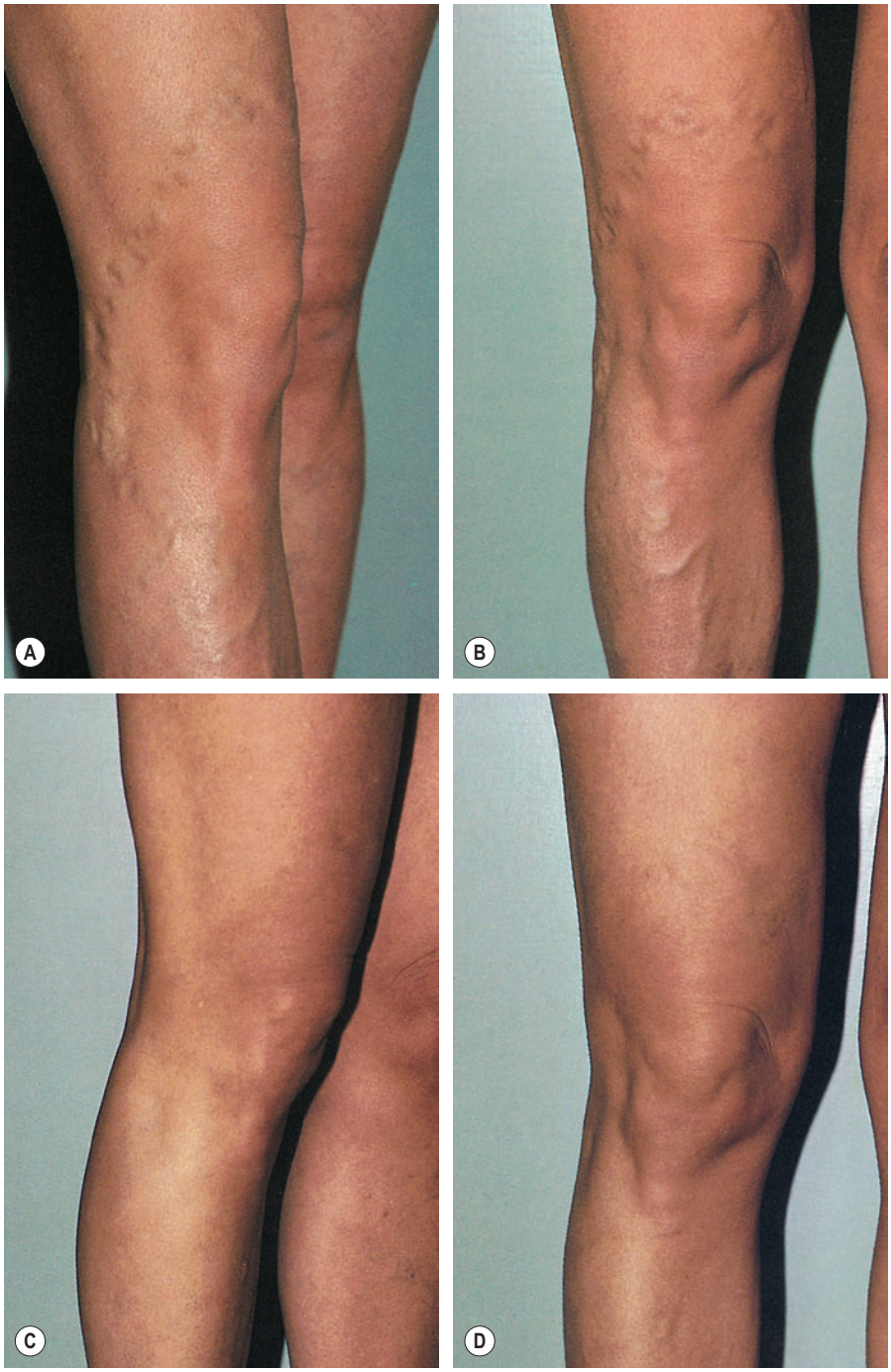


Figure 9.29 Case Study 2. **A,** Varicose tributary of great saphenous vein extending from mid-anterior tibial surface to, **B,** medial calf and thigh ending in lower anterior thigh. **C,** Mid-anterior tibial surface and medial calf and thigh and, **D,** lower anterior thigh views of vein normalization 11 months after treatment.

the anterior mid tibia, medial superior tibia and the lateral knee with the patient standing. After the patient assumed the supine position, STS 0.5% was injected into these sites after proper needle placement was confirmed with blood aspiration. A total of 0.5 mL was injected at the anterior mid tibia, 1 mL at the medial superior tibia and 2 mL at the lateral knee while pressure was maintained on the vein proximally. STD E-foam pads were placed over the entire vessel and were secured with Coban tape applied with moderate pressure. A 30- to 40-mmHg graduated compression stocking was applied, with two stockings worn on top of each other while the patient was ambulatory and one stocking worn at night for 1 week. During the second week, the dressing was removed, and the graduated support stocking was worn for another week only while the patient was ambulatory. The varicosity was completely resolved on follow-up examination at 2 weeks, and a few thrombi were drained. The photographs in Figure 9.29C, D were taken 11 months after treatment.

The latter technique used the principles of Fegan, except the entire area of presumed perforator incompetence was sclerosed. If Sigg's technique had been used, the sclerosing solution would have been more randomly injected throughout the entire course of the varicose veins. The classic Fegan technique could have been performed if the sites of IPVs were localized with duplex imaging. Duplex-controlled injections may have limited the quantity of sclerosing solution injection to very specific sites but probably would not have affected the clinical outcome.

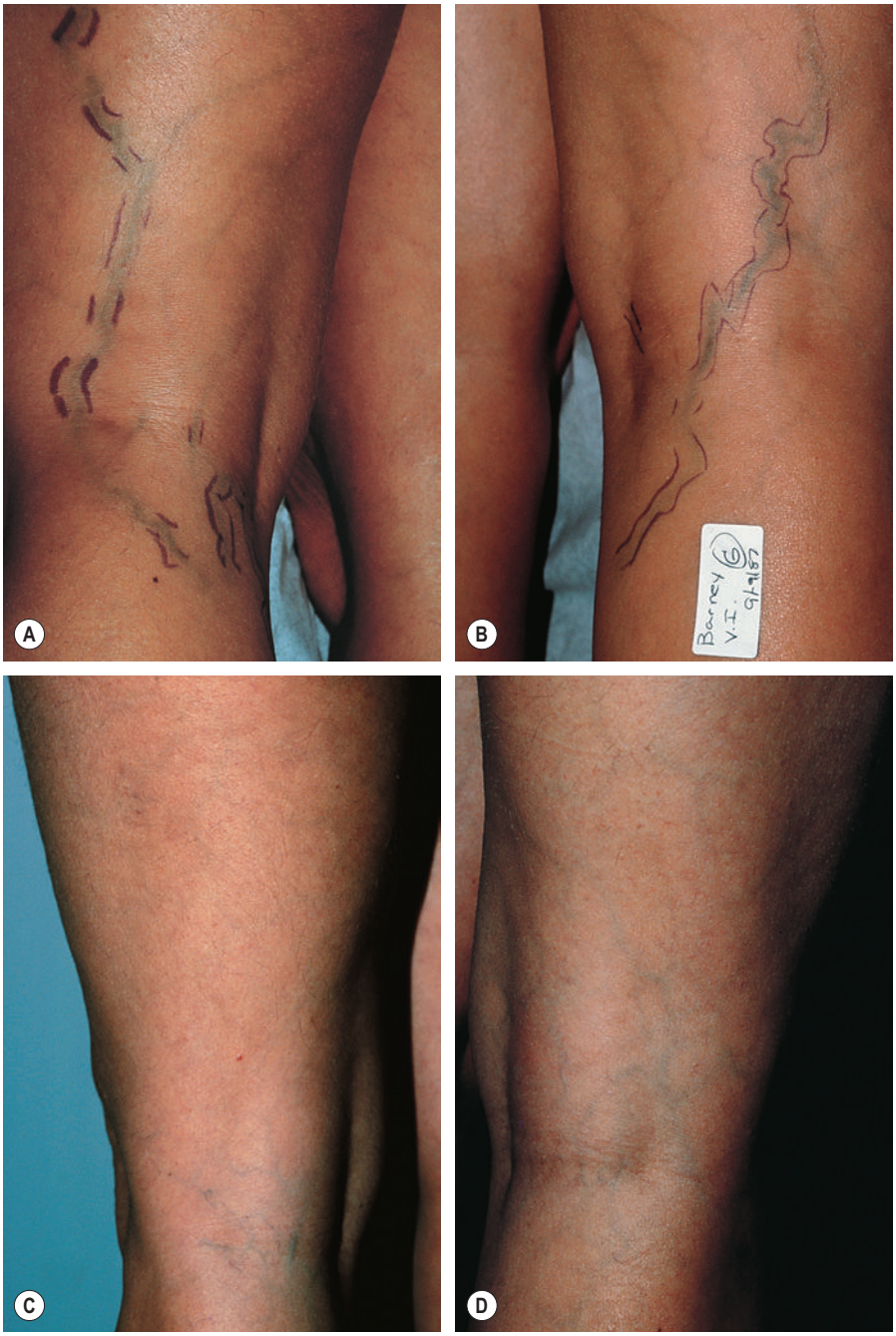


Figure 9.30 Case Study 3. Varicose reticular veins, **A,** from posterior mid thigh to, **B,** posterior mid calf. **C,** Posterior mid thigh to, **D,** posterior mid calf normalization of veins 1 year after treatment.

CASE STUDY 3 Reticular varicosities without perforator vein reflux treated with total-vein sclerotherapy (Sigg's technique)

A 34-year-old woman first noticed the appearance of varicose veins with her second pregnancy, 3 years before treatment. The veins were symptomatic after prolonged standing and were thought to have enlarged over the past year. Physical examination showed a set of 3- to 4-mm varicose reticular veins coursing from the posterior mid thigh to the posterior mid calf bilaterally (Fig. 9.30A, B). There was no evidence of incompetence in either the perforator veins or the SFJs on venous Doppler examination.

While the patient was lying horizontal on her abdomen, multiple injections of STS 0.5% were made into the varicose veins. Approximately 0.5 mL was injected into each site every 4 to 6 cm for a total of 8 mL of solution per leg. Continuous compression was maintained for 7 days only with 30- to 40-mmHg

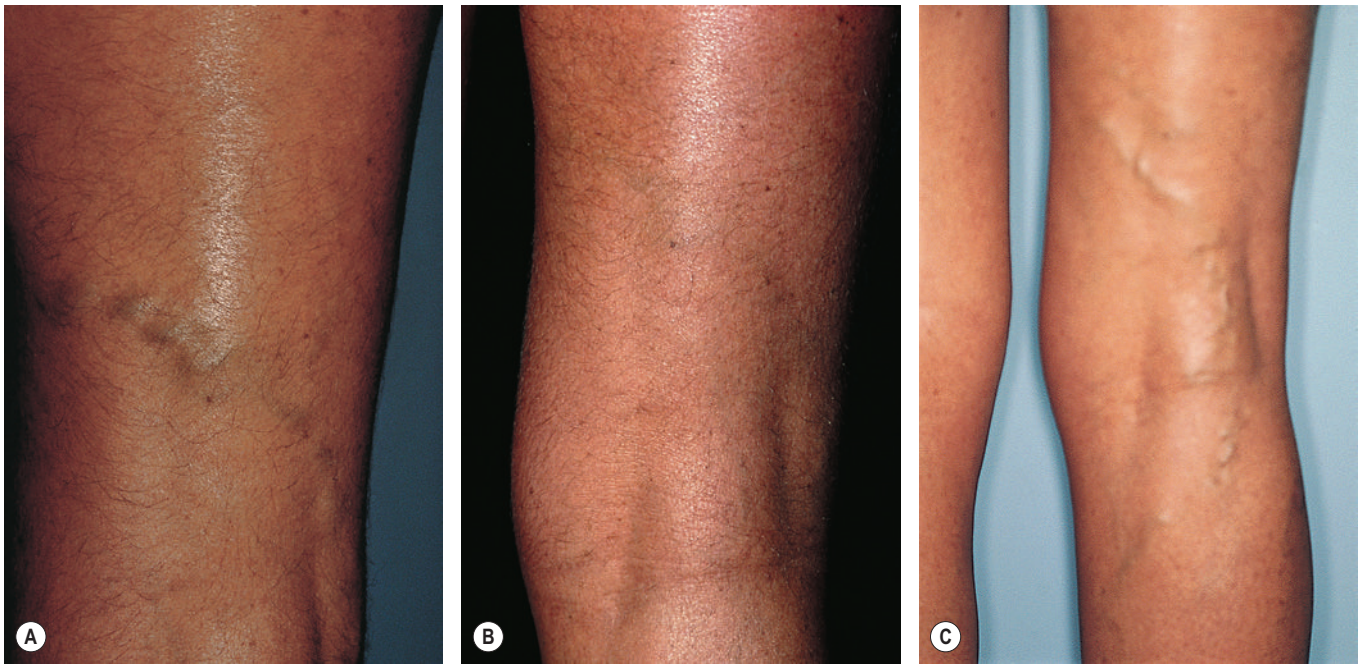


Figure 9.31 Case Study 4. **A,** Varicose vein from mid-posterior thigh to mid calf. **B,** Vein remains sclerosed 2 years after treatment. **C,** Recurrence of the treated vein as well as appearance of distal reticular veins 10 years after initial treatment.

graduated compression stockings overlying STD E-foam pads over the varicose veins. Follow-up examination did not disclose excessive bruising or pigmentation. No thrombosis occurred. Figure 9.30C, D, shows the appearance of the treated vessels at 1-year follow-up.

As points of venous reflux could not be found either at the SFJ or in perforator veins, it was assumed that the varicose vein was essential in nature. As it was serving no useful function, it was obliterated in its entirety. This forms the rationale for Sigg's technique.

CASE STUDY 4 Posterior thigh varicose GSV tributary associated with an incompetent SFJ treated with sclerotherapy alone using the air-bolus technique

A 36-year-old woman developed a varicose vein during her second pregnancy, 3 years before evaluation and treatment. The vein was symptomatic during prolonged standing, and she reported associated ankle edema. Physical examination showed a 5- to 8-mm diameter varicose vein coursing from the mid-posterior thigh to the mid calf (Fig. 9.31A). Venous Doppler examination demonstrated gross incompetence of the right SFJ and a positive Trendelenburg test in the lower thigh. The remainder of the examination was normal.

Surgical ligation and limited stripping were recommended, but refused by the patient. Therefore, sclerotherapy of the involved varicose vein was performed using an air-block technique. The air block was used in an attempt to concentrate the sclerosing solution in the injection site without dilution or inactivation of blood. Butterfly needles, 25-gauge, were placed in the vein at areas of fascial depression—two sites on the thigh and one site on the calf—while the patient was standing. These areas were found by venous Doppler ultrasound not to represent IPVs. With the patient lying horizontal with the leg elevated to 45 degrees, 1 mL of STS 1.0% was injected into each site after injection of 0.5 mL of air. STD E-pads were immediately placed and secured with Microfoam tape, and a single 30- to 40-mmHg graduated compression stocking was worn continuously for 2 weeks. Follow-up examinations at 2 and 6 weeks showed persistent resolution of the vein with a slightly palpable cord. A small amount of coagula was drained at 6 weeks. The vein remained fibrosed 2 years after treatment (Fig. 9.31B).

Treatment in the patient consisted of a modified Fegan and Sigg technique. The entire varicosity was obliterated using fascial depression areas as injection sites. The French technique with injection of sclerosing solution into the SFJ could have been used. However, this procedure was not performed because of the unavailability of Variglobin. Alternatively, STS 3% could have been injected under duplex control at the SFJ. Refer to the articles by Raymond-Martimbeau[36] and Schultz-Ehrenburg et al[42] for a description of these latter techniques.

The patient returned 8 years later (10 years after initial treatment) with recurrence of the varicose vein as well as new distal extensions to it (Fig. 9.31C). The vein had slowly recurred over the past year. Venous Doppler examination demonstrated Valsalva-positive reflux into the GSV through the SFJ. The patient will now undergo endovenous RF closure of the GSV with distal ambulatory phlebectomy.

The long-term follow-up is rarely reported in the literature. Most studies on the efficacy of varicose vein treatment have 1- to 2-year follow-up and at best 3- to 5-year follow-up. Clearly, this patient represents someone whose vein recurred 10 years after treatment. This was expected because the cause for the development of the varicose vein (incompetence of the SFJ) was never addressed in the initial treatment.

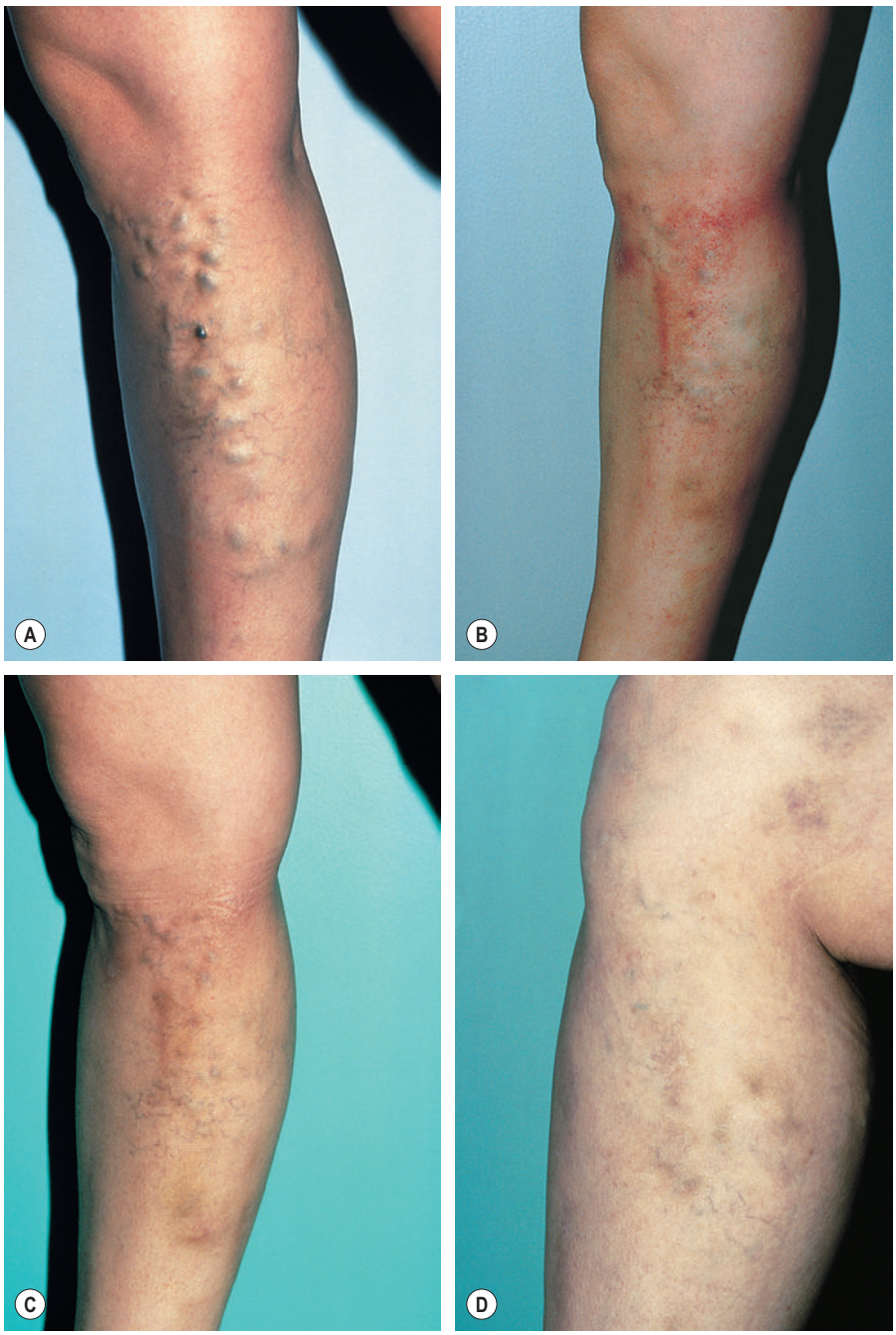


Figure 9.32 Case Study 5. **A,** Clustered varicose vein over right anterior and medial calf. **B,** Mild phlebitic reaction 2 weeks after treatment. **C,** Further treatment 4 weeks after first injection. **D,** Resolution of vein continues at 1 year after treatment.

CASE STUDY 5 Incompetent GSV varicose tributaries treated with total-vein sclerotherapy alone

A 31-year-old woman noted the onset of varicose veins over the right lower leg at 10 years of age. With each of her succeeding three pregnancies, the veins enlarged and became more painful while she was standing. Physical examination showed a clustered varicose vein 5 to 10 mm in diameter over the right anterior and medial calf (Fig. 9.32A). Venous Doppler examination demonstrated marked reflux of the right GSV throughout the varicosity.

The patient refused surgical ligation and limited stripping. Therefore, sclerotherapy with STS 1.0% was performed while the patient was horizontal. One milliliter of solution was slowly injected at each of nine separate locations, followed by application of STD foam pads and a double layer of 30- to 40-mmHg graduated compression stockings, which were worn continuously for 2 weeks while the patient was ambulatory. One stocking was removed while she was sleeping. A mild phlebitic reaction

was clinically apparent 2 weeks after injection (Fig. 9.32B), and compression was maintained for another 2 weeks. Four weeks after the first injection, multiple thrombi were drained from the medial calf, and two more injections of STS 1% (1 mL each) were made into persistent varicose dilations on the medial and anterior superior calf (Fig. 9.32C). At 1-year follow-up the leg remained pain free and showed persistent resolution of the treated veins (Fig. 9.32D). Venous Doppler examination disclosed an incompetent, 4-mm-diameter varicose vein just below the right anterior tibia and another incompetent varicosis over the inferior mid-posterior calf. These veins were successfully sclerosed with STS 1%. At 2 years follow-up, multiple new varicosities became apparent after resolution of sclerotherapy-induced hyperpigmentation. The patient has remained pain free and is very happy with the results of treatment. Her wish is to continue sclerotherapy treatment, even with the understanding that new or recurrent varicose veins may occur later.

This patient represents two common findings in the author's practice. First, many patients would rather undergo multiple (perpetual?) sclerotherapy treatments than limited surgical ligations or strippings. Second, the resolution of symptoms, which is very important to patients, may occur despite a reappearance of the varicose vein. It appears that incomplete treatment is enough to alleviate symptoms in many patients.

CASE STUDY 6 Incompetent perforator vein underlying ankle ulceration

A 27-year-old woman sought treatment after a 3-year history of cutaneous ulceration over the right medial mallear region (Fig. 9.33A). The patient had been seen previously by a physician from the infectious disease service and was prescribed multiple courses of systemic antibiotic treatments that did not produce significant change in the appearance of the ulceration. She was also evaluated by a physician in the plastic surgery department and had been treated with the placement of full-thickness pinch grafts, which did not heal. Physical examination was remarkable for pedal edema extending to the mid calf and associated truncal varicosities. Venous Doppler examination demonstrated a normal deep venous system and saphenofemoral and popliteal junctions and an IPV at the base of the ulcer (marked *X* in Fig. 9.33A). The perforator vein was injected through the ulcer. A 23-gauge butterfly needle was inserted into the perforator vein while the patient was standing, and the leg was elevated while the patient reclined. STS 1.0%, 1 mL, was slowly injected while the leg was blocked proximally and distally with hand pressure 3 cm in either direction. Immediately afterward, compression was applied with an STD foam pad under Microfoam tape and two 30- to 40-mmHg graduated compression stockings. The stockings were worn for 2 weeks. Double stockings were worn during the day, and the outer stocking was removed when the patient was supine.

Follow-up examination at 3 months showed complete healing of the ulceration and resolution of associated venous stasis changes (Fig. 9.33B). The patient remained free of ulceration 2 years after treatment.

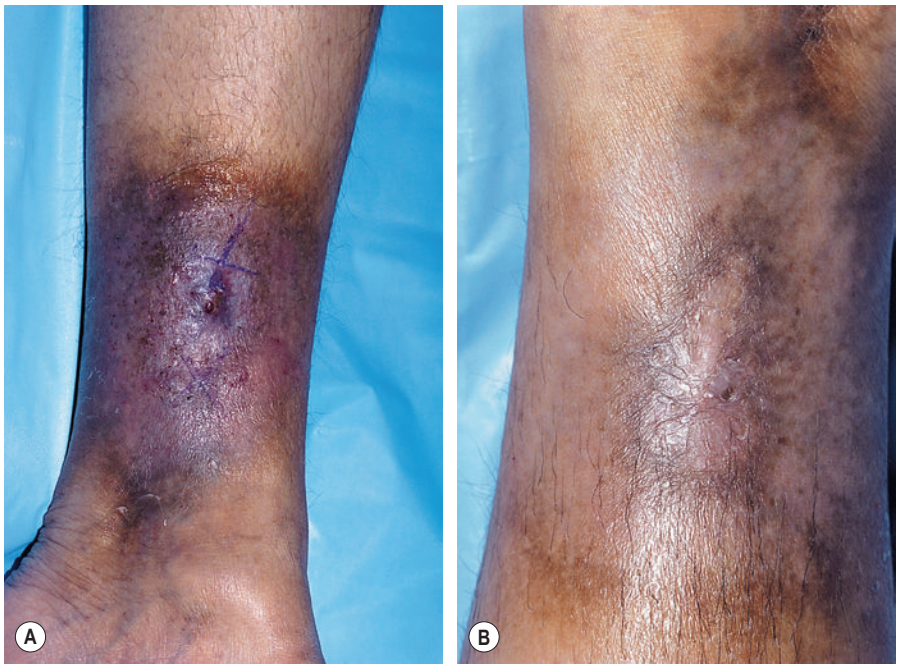


Figure 9.33 Case Study 6. **A,** Cutaneous ulceration over right medial malleolar region. **B,** Complete healing of ulceration and resolution of venous stasis changes 3 months after treatment.

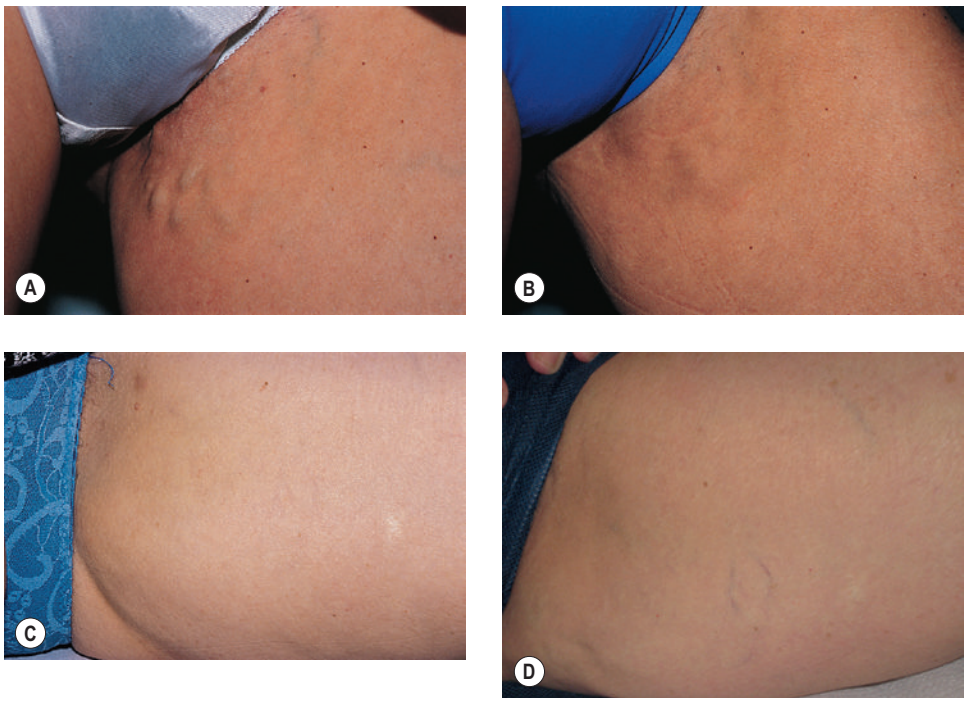


Figure 9.34 Case Study 7. **A,** Vulvar varices before treatment. **B,** Vulvar varices 2 months after treatment. **C,** Vulvar varices resolved 3 years after first treatment. **D**, 19 years from initial treatment the vulvar veins have remained sclerosed and the patient remains asymptomatic. **C** and **D**, The hypopigmented scar on the mid medial thigh is from a liposuction procedure performed 2 years after the initial and only sclerotherapy session.

CASE STUDY 7 Sclerotherapy of vulvar varicosities

A 40-year-old woman developed vulvar varices with her first pregnancy at age 18. She noted aching and pelvic fullness during her menstrual period and when standing for prolonged periods of time. Physical examination showed a prominent varicose vein 6 to 8 mm in diameter extending from the vulvar region into the GSV. The vein was incompetent throughout its entire length from the mid-posterior calf to the most superior aspect of the vulva, according to venous Doppler examination. Two IPVs underlying fascial defects were present at the medial knee and mid-posterior calf. There was no evidence of incompetence with the Valsalva maneuver. Her SFJ was competent according to venous Doppler examination. Scattered reticular veins 3 mm in diameter were noted on the anterior thigh. Scattered venules 0.4 mm in diameter were present on the anterior and lateral calf. The opposite leg was free of varicose or telangiectatic veins (Fig. 9.34A).

With the patient lying in a slight reverse Trendelenburg position, a total of 2 mL of STS 1.5% was injected into the two perforator veins at the medial knee and posterior calf. These areas were immediately compressed with an STD E-foam pad and Microfoam tape. A total of 4 mL of STS 1.0% was injected into the network of vulvar and superior thigh varicosities, and a figure-of-eight wrapover foam pad was used to compress the vulvar varices. This was followed by injection of 4 mL of STS 0.5% into the remaining reticular veins and venulectases. A 30- to 40-mmHg graduated thigh-high compression stocking was worn continuously for 7 days. When the patient returned 1 month later, all veins were sclerosed and without audible flow during venous Doppler examination. Multiple coagula were drained through 22-gauge needle punctures. Clinical appearance 2 months after treatment was excellent (Fig. 9.34B). Clinical appearance 3 and 19 years after treatment was still excellent, with the patient showing no evidence of recurrence in any of the treated veins (Fig. 9.34C, D).

CASE STUDY 8 Large varicose vein from incompetent perforator veins

After her second pregnancy, a 40-year-old woman developed varicose veins in the left lower leg, which increased in severity with her third pregnancy. Six years after her second pregnancy she developed pain in the left calf with associated leg swelling. The pain increased with exercising and resolved with leg elevation. She also complained of resting pain and a generalized tired feeling in the leg. There was a positive history of varicose veins in her mother. Photoplethysmography was normal, with a venous refilling time of 43 seconds and good calf muscle pump function. Venous Doppler examination demonstrated two IPVs at the left lateral knee and left medial posterior thigh without reflux from the SFJ. The vein measured 8 to 10 mm in diameter (Fig. 9.35A).

The patient was treated with a Fegan–Sigg technique. A 25-gauge butterfly needle was placed just distal to each of the two perforator veins, and the leg was elevated 45 degrees. A total

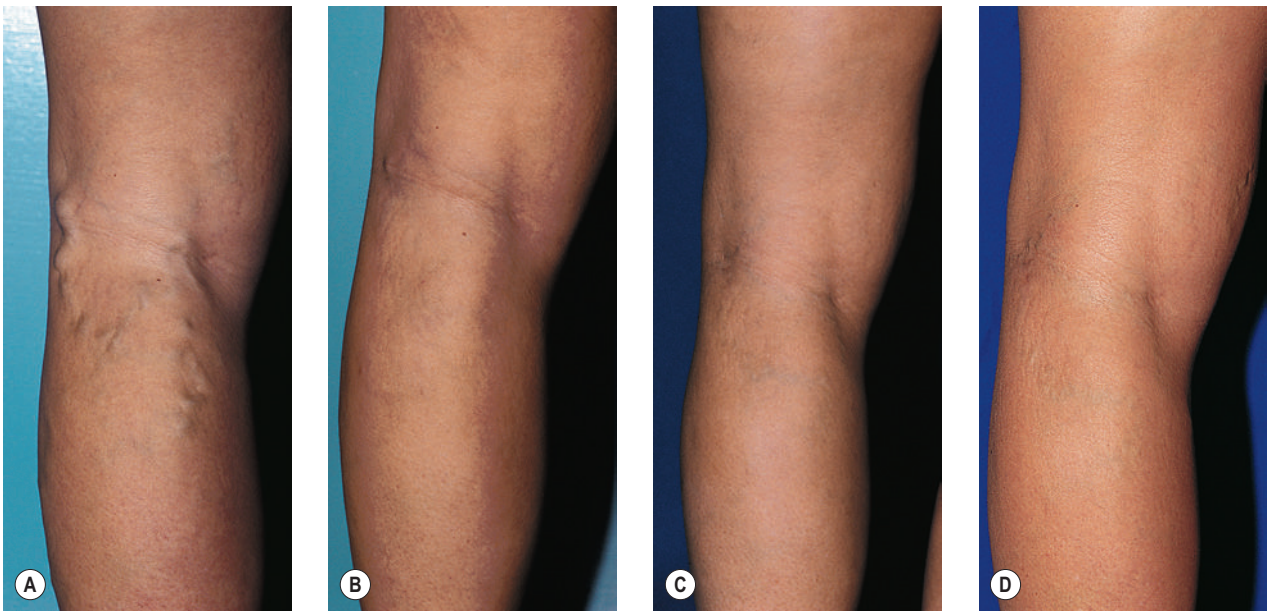


Figure 9.35 Case Study 8. **A,** Varicose veins before treatment. **B,** Varicose veins 6 weeks after treatment. **C,** Clinical appearance 2½ years after sclerotherapy treatment. **D,** No evidence of recurrence 8 years after initial treatment.

of 2 mL of STS 1% solution was injected, with the perforator points rapidly compressed with STD foam pads and Microfoam tape. An additional 1.5 mL of STS 1% was injected into distal aspects of the varicose vein in three separate sites. A double layer of 30- to 40-mmHg compression stockings was worn while she was ambulatory for 1 week, with the outer stocking removed when she was supine. A single 30- to 40-mmHg stocking was worn for an additional 2 weeks only while she was ambulatory. Thrombus was drained 2 weeks later, and an additional 1 mL of STS 1% was given to a nonsclerosed segment of the vein. Six weeks after the first injection session, the vein was entirely sclerosed and additional coagula were drained (Fig. 9.35B). She remained symptom free without evidence of recurrence 2½ years after the first injection session (Fig. 9.35C) and continues to remain symptom free without evidence of recurrence 8 years after the initial treatment (Fig. 9.35D).

CASE STUDY 9 Extensive varicosities of GSV and GSV tributaries

A 56-year-old woman noted the development of varicose veins during her second pregnancy at age 30. They were entirely asymptomatic, and she was seen initially for cosmetic treatment. There was a family history of varicose veins in her father. Physical examination showed a dilated GSV 6 mm in diameter with vulvar varices 4 mm in diameter and an anterior saphenous varicosity 6 mm in diameter. All varicose veins were incompetent throughout their length as demonstrated by venous Doppler examination but without Valsalva-induced reflux and without reflux across the SFJ (Fig. 9.36A, B).

With the patient supine, the entire varicose system was treated using a total of 11 mL of STS 1%. A double layer of 30- to 40-mmHg graduated compression stockings was worn during the day, with the outer stocking removed at night, for 1 week. A single 30- to 40-mmHg stocking was worn during the day for the second week. Six weeks later, reticular veins 2 to 3 mm in diameter were treated with a total of 4 mL of POL 0.75% and telangiectasia was treated with a total of 10 mL POL 0.5%. One year later, additional reticular veins were treated with 8 mL of POL 0.75% and telangiectasia was treated with 4 mL of POL 0.5%. Figure 9.36C, D shows the clinical appearance 2 years after initial treatment, with resolution of all varicose, reticular, and telangiectatic leg veins. Appearance 8 years postsclerotherapy (Figure 9.36E, F).

CASE STUDY 10 Development of SFJ incompetence after initial successful treatment of varicose GSV and tributaries

A 34-year-old woman was seen initially at age 27 years with the development of painful varicose veins during her first of four term pregnancies. The varicosities increased in size during each pregnancy, with the largest increase during her second pregnancy. The leg pain was throbbing, especially just before menses, with resolution 3 days into her menstrual period. Throbbing was relieved with leg elevation or by wearing graduated compression stockings. The family history included varicose veins in her mother, aunt and sister. Physical examination showed a 6-mm-diameter incompetent GSV with an incompetent mid

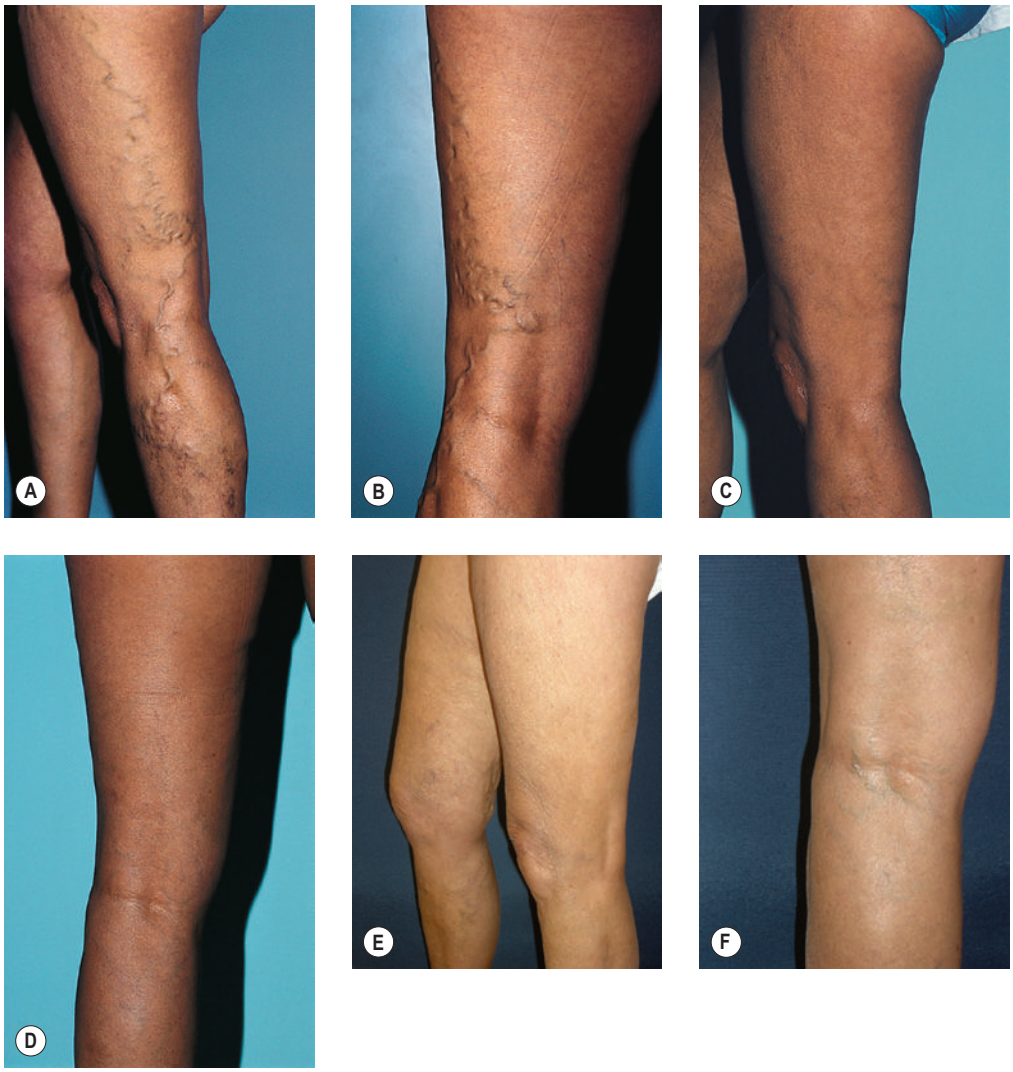


Figure 9.36 Case Study 9. **A,** Lateral aspect of varicose veins before treatment. **B,** Posterior aspect of varicose veins before treatment. **C,** Lateral aspect of varicose veins 2 years after initial treatment. **D,** Posterior aspect of varicose veins 2 years after initial treatment. **E,** Lateral aspect of varicose veins 8 years after initial and only sclerotherapy treatment demonstrating persistent resolution. **F,** Posterior aspect of varicose veins 8 years after initial and only sclerotherapy treatment. Note new 2 mm diameter reticular veins in a new location from the veins initially treated. These new veins were treated with STS 0.25% foam (1 : 4 with air dilution) with total resolution by patient report.

thigh (Hunterian) perforator vein without Valsalva-induced incompetence. The SFJ was competent (Fig. 9.37A, B).

With the patient supine, the varicose veins were injected with 2 mL of STS 1% just distal to the mid thigh (Hunterian) perforator vein, followed by a total of 16 mL of STS 0.5% to the remaining varicosities, with approximately 0.5 mL injected every 5 cm or so. A double layer of 30- to 40-mmHg graduated compression stockings was worn for 1 week while the patient was ambulatory, with the outer stocking removed when she was supine; a single stocking was worn for a second week when she was ambulatory. The patient became completely asymptomatic 1 month after the first sclerotherapy treatment (and remained so 3 years later). Nine months later, an additional 16 mL of STS 0.5% was injected into multiple varicose and reticular veins that had not resolved or were newly present, followed by an identical post-treatment compression regimen. One year after the second sclerotherapy treatment, all visible varicose and reticular leg veins resolved completely (Fig. 9.37C, D). Despite no new predisposing factors, new varicose veins were noted 3 years after the first sclerotherapy session. At this time, the SFJ was incompetent bilaterally to venous Doppler examination and the patient was referred for ligation and stripping of the GSV at the SFJ bilaterally (Fig. 9.37E, F).

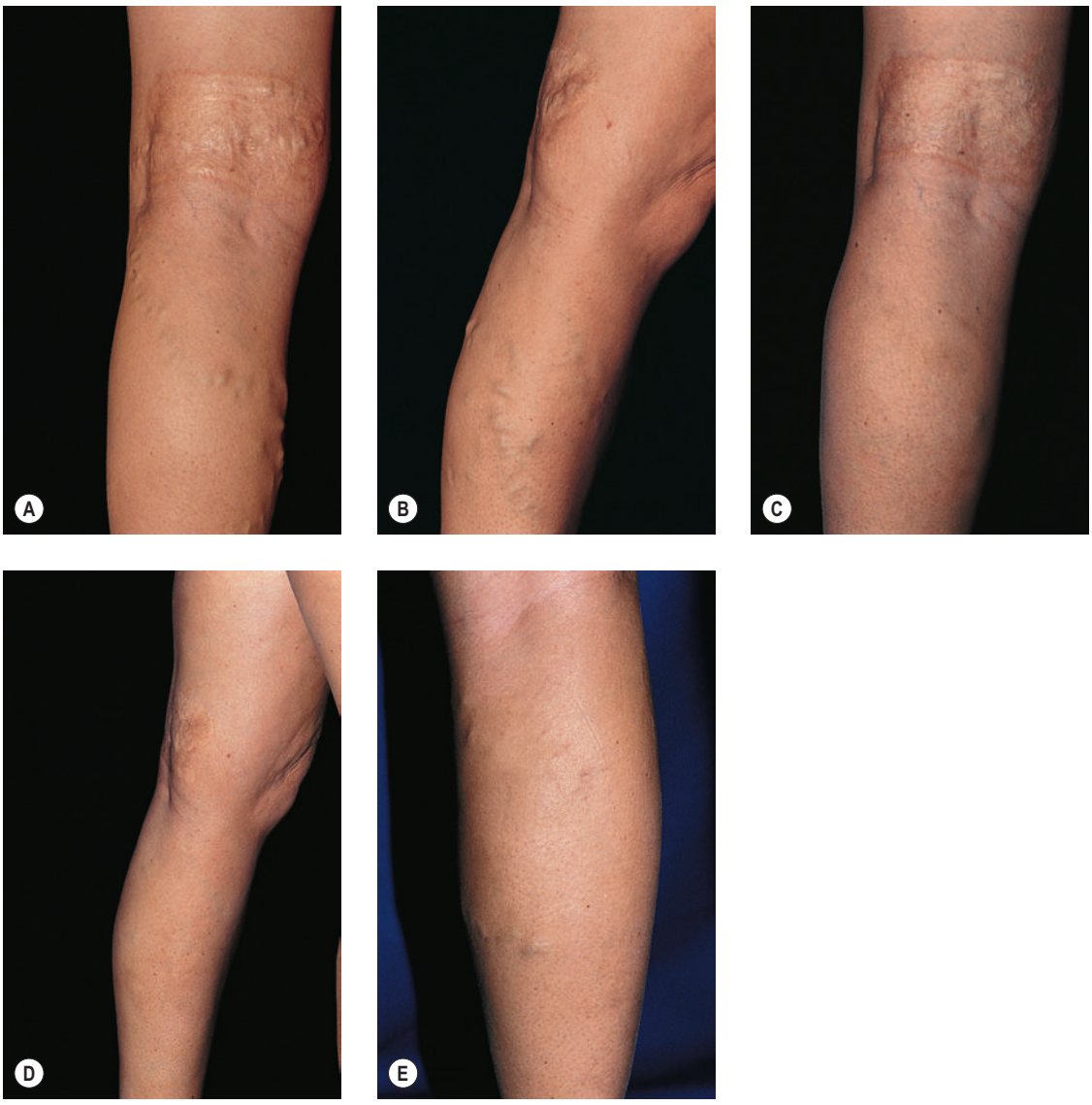
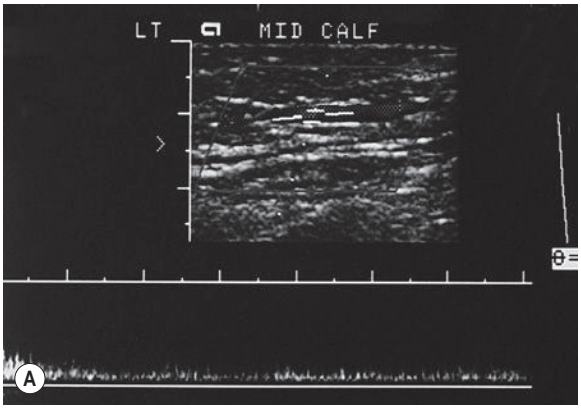


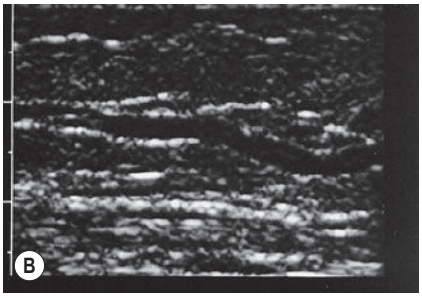
Figure 9.37 Case Study 10. **A,** Posterior aspect of varicose veins before treatment. **B,** Medial aspect of varicose veins before treatment. **C,** Posterior aspect of varicose veins 2 years after initial treatment. **D,** Medial aspect of varicose veins 2 years after initial treatment. **E,** Development of new varicose veins after initial treatment and resolution. The saphenofemoral junction is now incompetent bilaterally.

CASE STUDY 11 Symptomatic clinically unapparent varicose vein treated with duplex-controlled sclerotherapy

A 60-year-old woman was seen initially with a complaint of pain in the medial knee and calf area for the last 6 months. She had undergone ligation and stripping of the GSV from the SFJ 30 years previously for treatment of varicose veins that occurred during her only pregnancy. Clinical examination did not disclose visible varicose or reticular veins. A color-flow duplex Doppler examination showed normal common femoral and superficial femoral and popliteal veins without evidence of acute or chronic DVT. The deep venous system was without evidence of reflux. An atypical vein was present 5 to 6 cm distal to the area of the SFJ as a remnant or duplicate GSV that coursed down the medial aspect of the thigh, terminating in the area of symptomatology. The vein was markedly incompetent to Valsalva maneuver and thigh and calf compression, and communicated with numerous perforator veins along its course (Fig. 9.38A, B).

Under duplex guidance, 1 mL of STS 3% was injected into the medial thigh varicosity through a 22-gauge needle. Correct position was verified by open-needle insertion. The injection was given slowly until the vein thrombosed (Fig. 9.38C). An STD E-foam pad was placed with Microfoam compression, and additional injections were given to two additional perforator veins present in the area of greatest symptomatology. The entire procedure was performed with the patient supine. A double layer of 30- to 40-mmHg graduated compression stocking was worn while the patient was ambulatory for 2 weeks, with the outer stocking removed when the patient was supine. Four weeks later, examination showed complete fibrosis and resolution of all symptoms.





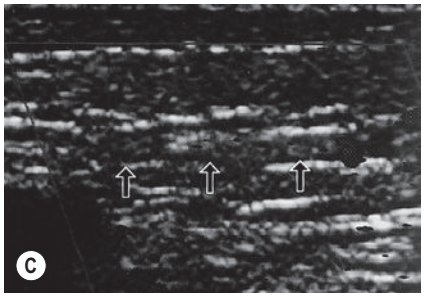
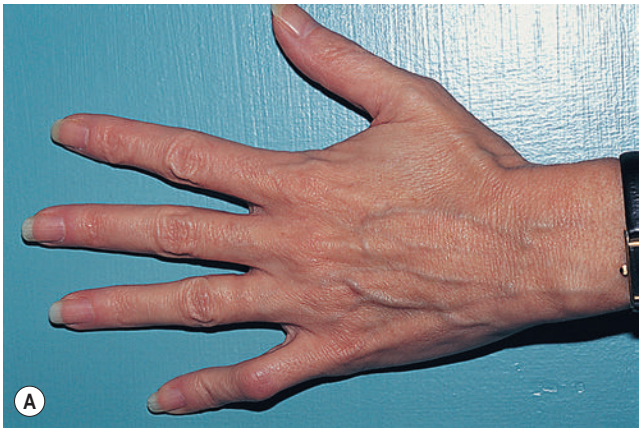


Figure 9.38 Case Study 11. **A,** Reflux is present in the symptomatic vein before treatment. **B,** Close-up duplex view of injection site before injection. **C,** Immediately after sclerotherapy, the injected vein is filled with echodense material and is noncompressible *(arrows)*.



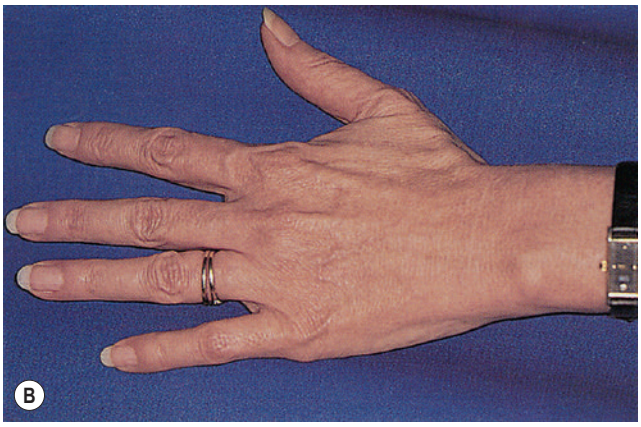


Figure 9.39 Case Study 12. **A,** Appearance of hand veins before treatment. **B,** Appearance of hand veins treated as detailed in the case history 9 months after treatment.

CASE STUDY 12 Treatment of dorsal hand veins

A 42-year-old woman complained of unsightly veins on the dorsal hands (Fig. 9.39A). She was advised of the normality of this appearance and the possible necessity for preserving these veins for insertion of intravenous catheters. Nevertheless, she insisted on their removal. Experience has demonstrated that strong sclerosing solutions of high concentration are necessary to eliminate these normal veins.[250] However, when the entire superficial venous network is sclerosed in a single session, hand edema is common and has been reported to occur in up to 82% of patients, resolving over 7 to 10 days.[251] To minimize edema, the author's method of treatment involves injecting half of the dorsal veins with STS 2% in one session (usually 2 to 4 mL). Three to four weeks later, the author injects the remaining veins with another 2 to 4 mL of STS 2%. Injections are performed with a 27- or 30-gauge needle with a nurse providing a tourniquet on the mid forearm until the injection is completed. The hand is then elevated, the dorsal aspect is padded with cotton balls and an Ace bandage is wrapped from the distal hand to the proximal forearm. The Ace wrap is left in place for 2 days, during which time the patient may vary the compression to avoid numbness of the fingers. Patients usually have near total resolution of the visible veins with this technique (Fig. 9.39B). Hand edema occurs in 20% of patients. To date, no episodes of pigmentation or telangiectatic matting have been seen. Although Duffy has reported superficial necrosis with probable extravasation of solution in one patient,[251] and numbness and paresthesia persisting for 2 weeks in another patient,[251] this procedure is remarkably free from adverse sequelae.

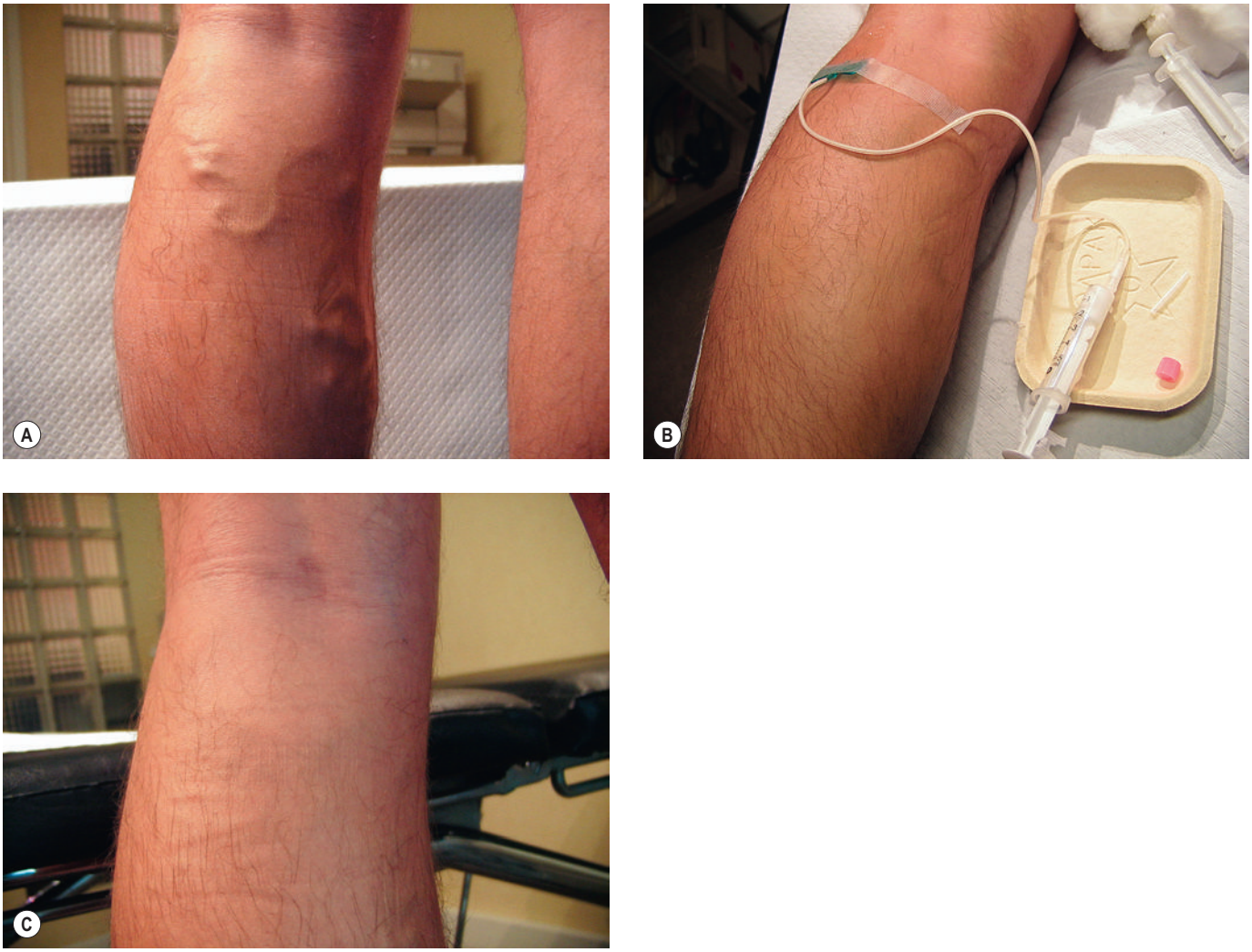


Figure 9.40 Case Study 13. **A,** Varicose cluster of the left popliteal fossa and medial upper third of the lower leg. **B,** Duplex-guided injection of polidocanol 0.5% through a butterfly needle. **C,** Appearance 1 month after treatment.

CASE STUDY 13 Duplex-guided injection

This 35-year-old male presented with a painful isolated varicose cluster of the left popliteal fossa and medial upper third of the lower leg (C2s Ep As Pr). Varicose veins were fed by a popliteal fossa perforating vein and drained into a GSV tributary (Fig. 9.40A).

The vein was treated with one injection of 4 cm^3 of POL 0.5% through a butterfly needle (Fig. 9.40B), and massaged with the ultrasound probe to fill up the whole varicose network. Compression was realized with knee-high class II medical stockings and a popliteal foam pad.

At 1 month, no visible varicose veins remained; several small indurations (3–4 mm, not visible on pictures) were palpable and were punctured (Fig. 9.40C).

CASE STUDY 14 VeinRx catheter foam sclerotherapy of the GSV

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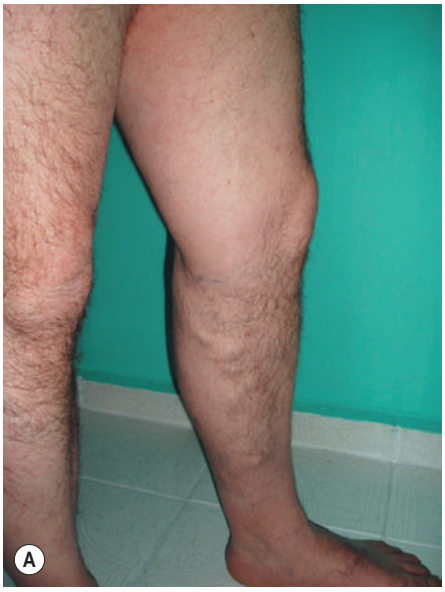
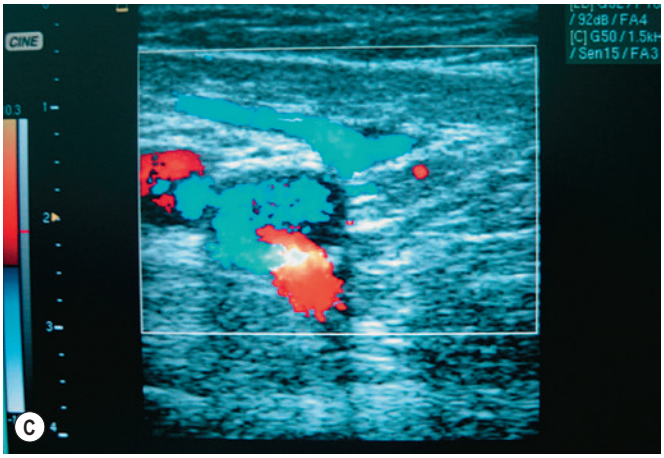
Santiago, Chile

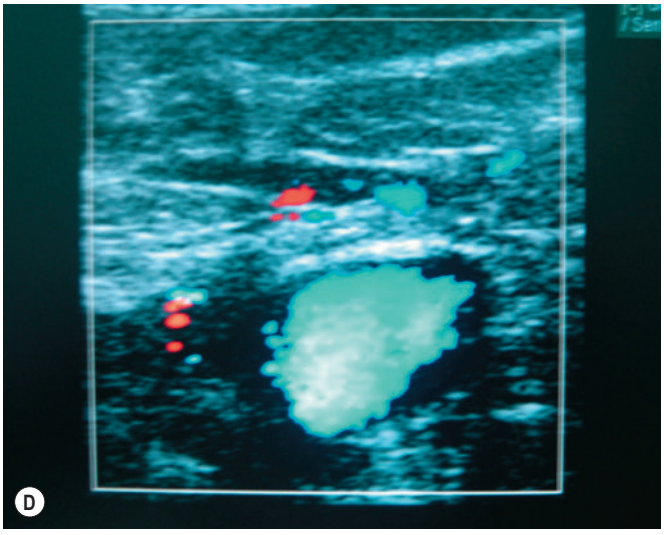
A 99-kg, 1.62-m, 49-year-old male presented with a varicose vein on the left lower leg, pain in the left leg, night cramps and ankle edema (Fig. 9.41A). His CEAP classification was C3 Ep As Pr; the venous clinical severity score (VCSS) was 5.

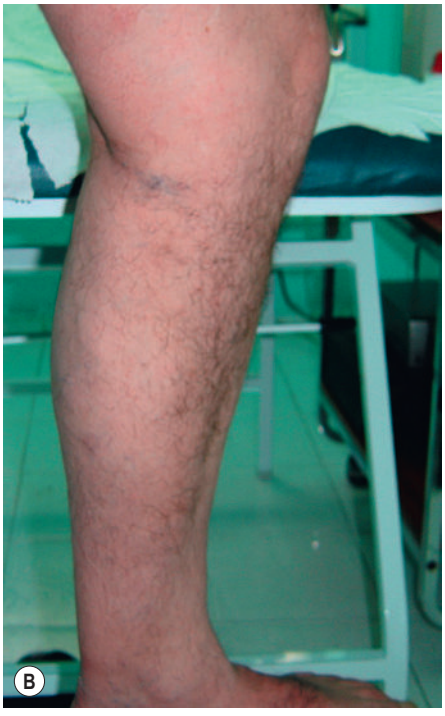
Ultrasound examination showed a normal deep venous system. The GSV was incompetent from the SFJ to the mid thigh. The GSV diameter at 2 cm from the SFJ was 11 mm, with a mean diameter of 14 mm. The length of the refluxing segment measured 28 cm (Fig. 9.41B).

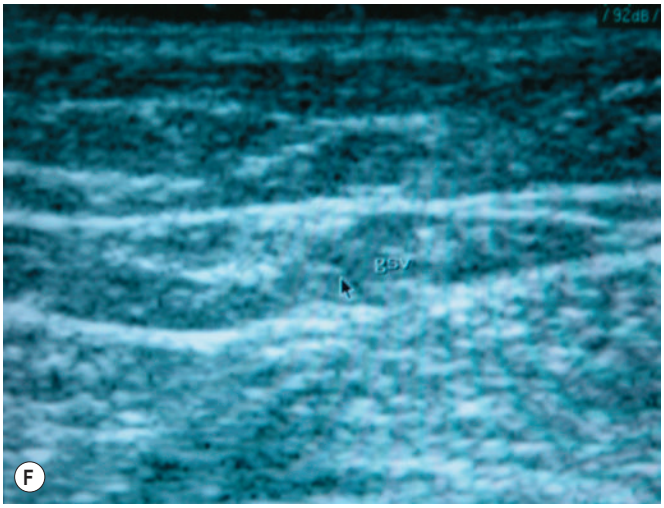
The procedure was performed under local anesthesia with 2 mL of lidocaine placed at the vein access site. Access to the GSV was made 34 cm from the SFJ. The VeinRx catheter was placed 1.5 cm distal to the SFJ. The leg was elevated 30 degrees for 2 minutes to allow for drainage of venous blood. The VeinRx catheter balloon was inflated with 2.6 cm^3 of saline 2 cm distal to the SFJ. Ten milliliters of 3% foam (made with the Tessari technique, 2 mL of 3% STS + 8 cm^3 of air) was infused into the catheter and allowed to stay in the GSV for 4 minutes. The











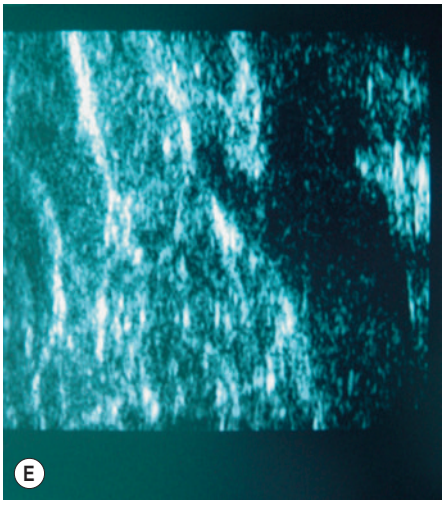


Figure 9.41 Case Study 14. **A,** Varicose vein on the left lower leg. **B,** The length of the refluxing segment measured 28 cm. **C,** Duplex examination 1 day after VeinRx catheter foam sclerotherapy, showing no evidence of thrombosis extension into the saphenofemoral junction or deep venous system. At 12 months, **D,** vein size was 1.2 mm, **E,** the epigastric vein was patent, and, **F,** the great saphenous vein showed firm sclerosis, with echogenicity similar to surrounding tissue.

intravascular balloon was deflated and a foam pad was placed over the treated GSV. A class II graduated compression stocking was then applied. One day after the procedure a duplex examination was performed and no evidence of thrombosis extension into the SFJ or deep venous system was noted (Fig. 9.41C). The GSV was noncompressible. Foam pads were removed and the compression stocking was worn for another 6 days and nights, then for 7 days only during daytime. The patient was evaluated with duplex ultrasound at days 1 and 7 and at months 1, 3, 6 and 12. No complications occurred. Minor ecchymosis at the access site for 1 week resolved spontaneously. Complete sclerosis of the desired segment occurred. Vein size was 1.2 mm (almost not visible) at 12 months (Fig. 9.41D).

The ultrasound images are from 12 months post treatment: you may see the epigastric vein patent (Fig. 9.41E) and the GSV with firm sclerosis and echogenicity similar to surrounding tissue (a little more dense) (Fig. 9.41F). The femoral vein is patent.

CASE STUDY 15 Varicose veins and venous ulcers treated with sclerosant microfoam

DDI Wright, JC Cabrera

Elderly patients with leg ulcers frequently remain uninvestigated and untreated, as the prospect of surgery in the presence of open ulcers is discounted and often not acceptable to the patient. Microfoam sclerotherapy offers an effective and acceptable alternative in appropriate cases.

A 64-year-old woman presented with bilateral leg ulcers open for 1 and 2 years (right and left, respectively). She had bilateral varicose veins which had been severe for in excess of 20 years (Fig. 9.42A). Previous treatment was confined to compression and local antiseptics.

Duplex scanning revealed bilateral GSV incompetence from groin to ankle and incompetent perforating veins near the left ulcer. The SPJs were competent, but distally both small saphenous veins were incompetent. The deep venous systems were normal.

Initial treatment consisted of 19 mL of 1% POL microfoam (1% POL mf) injected under ultrasound guidance through a 20-gauge cannula into the right GSV and an additional 4 mL injected directly into varicose veins. Two weeks later, the left GSV was injected with 15 mL of 1% POL mf in the same manner, and further injections of 15 mL to the varicose veins and IPVs were administered. At review 1 month later, recanalization of the proximal segment of the right GSV was observed and reinjected with an additional 6 mL of 1% POL mf. By this visit, all ulcers had healed and the varicose veins were occluded.

Photographs taken 3 months later show the healed ulcers and greatly reduced varicose veins (Fig. 9.42B). Two years later, recanalization of both GSV with narrow lumens was detected, but the ulcers remained healed. A further 12 mL of 1% POL mf was injected into recanalized segments. There were no complications following any of the treatments. At last review, 43 months after the first treatment, the ulcers remained healed, no varicosities were visible and there was no reflux.

This case illustrates that microfoam sclerotherapy can be a simple, effective and durable treatment for patients with venous hypertension and ulceration caused by superficial vein and perforator incompetence. Minor recanalization can be retreated and normal venous function restored.

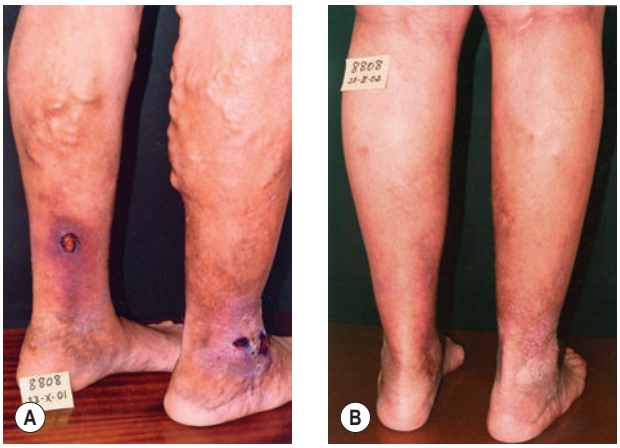


Figure 9.42 Case Study 15. **A,** At presentation, multiple bilateral ulcers. **B,** 4 months after treatment with sclerosant microfoam, the varicose veins are reduced and the ulcers closed.

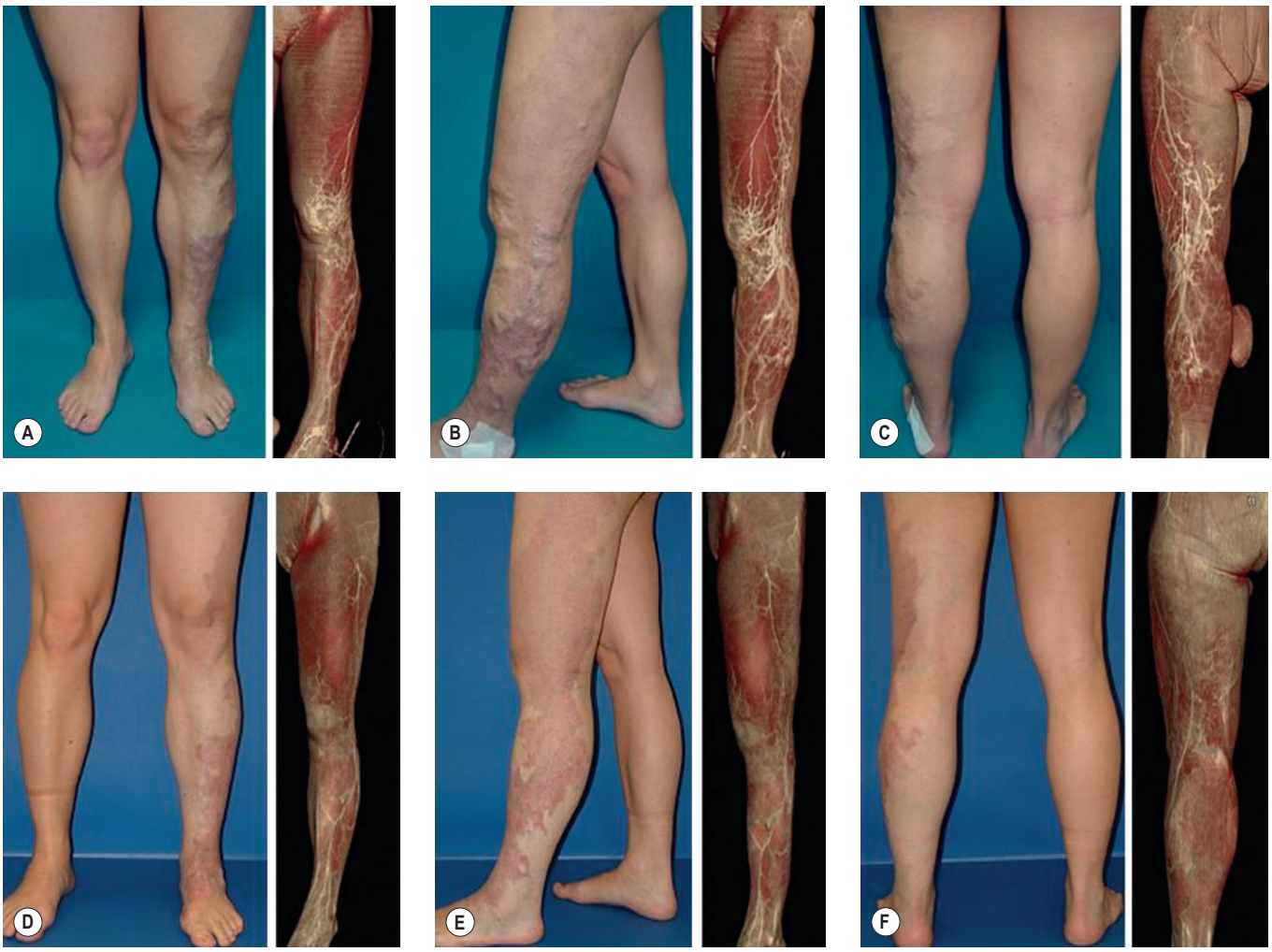


Figure 9.43 Case Study 16. Clinical and multidetector-row computed tomography venography images from a 25-year-old women with Klippel-Trénauny Syndrome. Upper row, initial images; lower row, follow-up images. **A** and **D,** Anterior views (left); **B** and **E,** lateral views; and **C** and **F,** posterior views. (Extracted and used with permission from Arch Dermatol 2009;145:1147.).

CASE STUDY 16 Microfoam sclerotherapy in Klippel-Trenaunay Syndrome (KTS) and a patent foramen ovale (PFO)

P Redondo, G Bastarrika, A Sierra, A Martinez-Cuesta, J Cabrera

A 25-year-old women presented with KTS manifested as widespread venous varicosities and a segmental port wine stain affecting the left leg with associated intralesional pain. Multidectector-row computed tomography (MDCT) revealed that the aberrant vessels originated from the superficial venous system with a normal deep venous system. Duplex ultrasound demonstrated incompetence in the superficial system. She was then treated with polidocanol microfoam (POL mf) injected into the marginal, great saphenous and peripheral small veins via 20-, 23- and 25-guage needles, respectively, under ultrasound guidance with limb elevation for 15–20 minutes followed by graduated compression with a Struva 23-mmHg stocking for 7 to 15 days (Medi-Bayreuth, Bayreuth, Germany). Eight separate treatment sessions over 12 months with injection of 20 to 80 mL of POL mf at 0.25 to 2% concentration was required. A migraine headache after the second session resulted in a work-up which demonstrated bubbles in the middle cerebral artery. Magnetic resonance imaging at 24 hours showed no evidence of cerebral damage and all subsequent treatments were without incident. Examinations 6 months after the final sclerotherapy session with MDCT revealed significant clinical improvement and reduction in the number and size of the percutaneously treated aberrant veins (Fig. 9.43).

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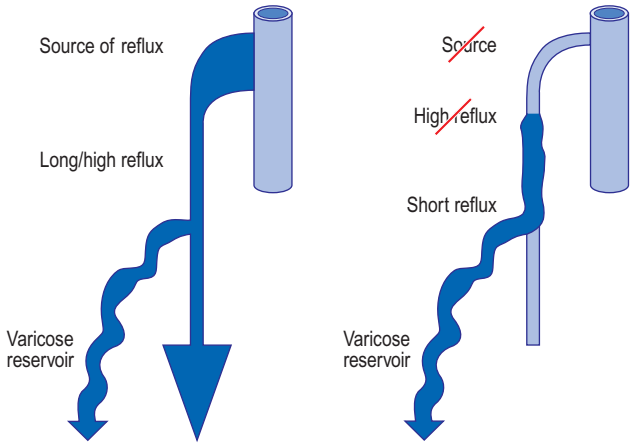
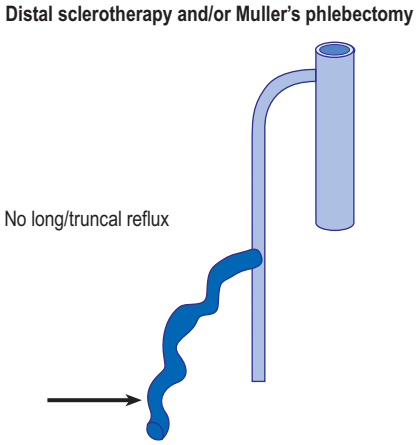
CHAPTER 9: APPENDIX

SCHEMATIC PRINCIPAL TYPES OF VARICOSE NETWORKS, SCHEMATIC TREATMENTS

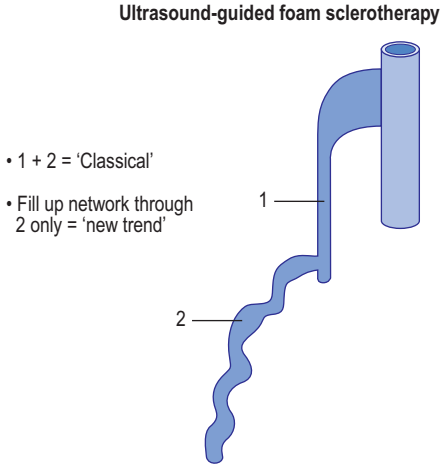
Appendix 9.1



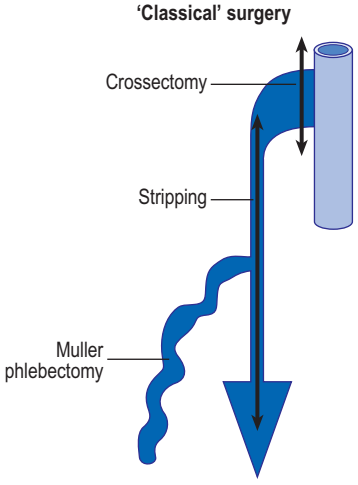
Appendix 9.2



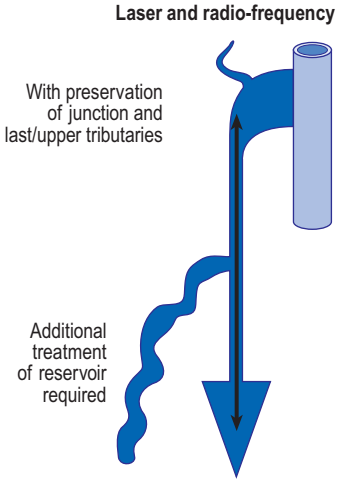
Appendix 9.3



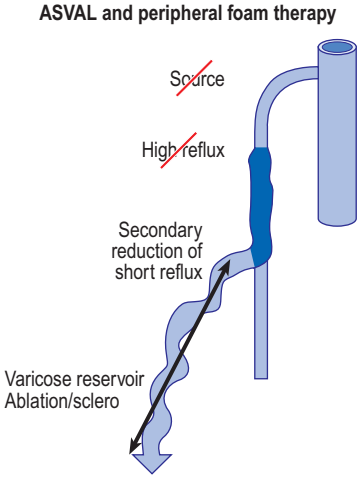
Appendix 9.4



Appendix 9.5



Appendix 9.6



10

Role of Surgery in the Treatment of Varicose Veins

Oscar Maleti | Marzia Lugli | Michel R. Perrin

BACKGROUND

Surgery for treating varicose veins (VVs) has been advocated for centuries. The first descriptions were attributed to Aulus Cornelius Celsus from the Roman era, which included hook extraction of varicose veins, double ligation and phlebectomy. Modern surgery is based on hemodynamic treatment, which started at the beginning of the nineteenth century when T. Rima performed a high ligation (HL) of the upper great saphenous vein (GSV), although F. Trendelenburg is credited as the first to perform the procedure in 1890. Complementary saphenous trunk stripping came some years later with W.L. Keller in 1905 (internal stripping), C. Mayo in 1906 (external stripping) and W.W. Babcock in 1907 (flexible stripper). Various alternative techniques to conventional HL plus trunk stripping were proposed in the second half of the twentieth century.

The first to suggest interruption of perforators to treat VVs was probably C. Remy in 1901.

Duplex ultrasound (DUS) investigation was the cornerstone to our changing knowledge and attitude in the management of VVs; nevertheless it must be emphasized that there is presently no consensus regarding the best procedure for the operative treatment of VVs when taking into account their various patterns of clinical and hemodynamic presentation.

BASIS AND AIM OF SURGERY

In theory, VV surgery, as with other operative methods (e.g., thermal and chemical ablation), aims to suppress or reduce reflux in the standing position (orthostatism) in the incompetent, enlarged and tortuous superficial veins.

In practice the aim is twofold:

- To eliminate reflux originating from the deep venous system (DVS) into the superficial venous system (SVS) by suppressing abnormal leak points. Reflux occurs because of the incompetent valves.
- To remove the incompetent superficial veins, which are visualized as varices.

THE DIFFERENT SURGICAL PROCEDURES

Procedures depend on the different concepts of VV disease progression and evolution in addition to the principles of correction of hemodynamic anomalies, which are currently controversial and are reviewed subsequently. The procedures discussed can be performed alone or in combination:

- Resection of all the refluxing veins.
- Resection of the incompetent 'reservoir'.
- Ligation of the leak points between the DVS and SVS at the saphenofemoral junction (SFJ), saphenopopliteal junction (SPJ) and perforator.
- Redirecting reflux from the SVS into the DVS.

The different procedures will not be described in detail; however, the advantages and inconveniences of the different surgical methods will be underlined.

SURGERY WITHOUT SAPHENOUS TRUNK PRESERVATION

Conventional surgery includes GSV and/or small saphenous vein (SSV) termination ligation flush to the corresponding deep vein, plus saphenous trunk stripping with or without phlebectomy of incompetent tributaries and/or incompetent perforator interruption.

PRINCIPLE AND CONTROVERSIES

This method is based on the VV descending progression hemodynamic concept that was established at the beginning of the twentieth century. It was believed that reflux always started at the SFJ and/or the SPJ, as a result of the terminal valve incompetence, and extended progressively in a distal direction within the saphenous trunk and into the suprafascial accessory or tributary veins in which the varices developed. Consequently SFJ and/or SPJ ligation completed by trunk stripping and/or phlebectomy of tributary varices was the 'cure all' method. However, the systematic use of DUS for investigating VVs has shown that this concept was wrong in many cases:

- Reflux and dilatation are frequently segmental in any location of the saphenous and nonsaphenous systems.
- Onset of the VV can occur in any segment of the superficial veins without incompetence of the SFJ, SPJ and saphenous trunk itself.[1–8]
- The VV reservoir volume favors magnitude and extension of reflux. Compression of an incompetent tributary vein termination can reduce or suppress reflux in the saphenous trunk when they are not dilated beyond 6 to 8 mm in diameter (Fig. 10.1)

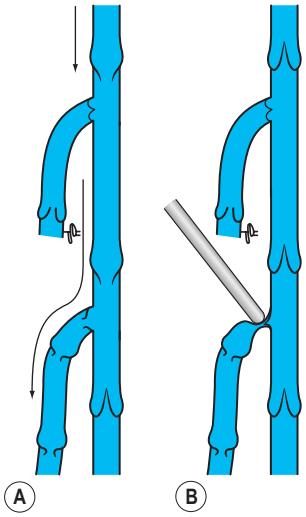


Figure 10.1 Reservoir reduction capacity allows reduction or suppression reflux in the main trunk. **A,** Reflux of the main trunk drains in an incompetent tributary. This siphon effect increases reflux volume in the main trunk. **B,** Compression at the termination of the incompetent tributary suppresses reflux in the main trunk. (Adapted from Perrin M. Insuffisance veineuse superficielle: notions fondamentales. EMC [Elsevier Masson SAS, Paris], Techniques chirurgicales—Chirurgie vasculaire, 43-161-A, 2007.)

- Furthermore we have learned that leak points between the DVS and the SVS can disappear after ablation of the VVs even though they have not been treated. After VV ablation 80% of previously incompetent perforator veins became competent.[9,10]
- More surprisingly, incompetent terminal valves can recover their normal function after ablation of the refluxing varices.

All of these findings have enhanced development of new surgical procedures that will be described later.

TECHNICAL INFORMATION

- Ligation of the SFJ and SPJ can be performed by using a 4- to 6-cm transverse incision without cosmetic prejudice, particularly when the incision is made within the groin crease (Fig. 10.2).
- Saphenous trunk stripping is most frequently performed using the endoluminal technique, with invagination or pin stripping, and is credited with causing fewer neurologic complications (Figs 10.3–10.5).
- Extension of trunk resection depends more on operator conviction than on the extent of reflux.
- Incompetent tributary phlebectomy is performed through a very small skin incision, usually 2 to 3 mm in length.
- Surgical perforator ablation can be performed directly by skin incision overlying the perforator in the absence of overlying skin pathology. In the presence of lipodermatosclerosis, subfascial endoscopic perforator surgery is strongly recommended, at least for medial leg perforator veins.

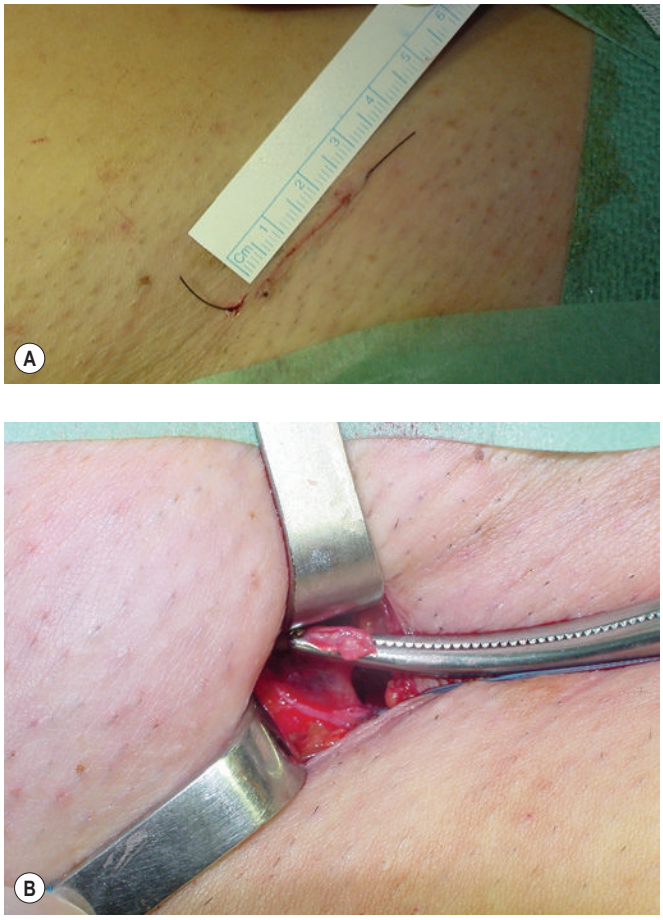


Figure 10.2 **A, B,** In patients who are not obese it is possible to perform flush ligation through a two centimeter-long incision.

CONVENTIONAL SURGERY VARIANTS

Saphenous Trunk Stripping with Preservation of Saphenofemoral Confluence, with or Without Incompetent Tributary Phlebectomy and/or Incompetent Perforator Interruption

Nonflush ligation at the SFJ and/or SPJ was described until recently as a technical mistake responsible for in situ recurrence in all cases as reflux through the incompetent terminal valve persisted. But preoperative ultrasound investigations have proven that in GSV varices the terminal valve is competent in approximately half the patients.[11,12]

In this situation it looks obvious that high flush tie is not recommended as tributaries of the saphenofemoral confluence can drain in a physiologic way into the common femoral vein. Besides neovascularization, elimination of normal physiologic reflux is the main cause of recurrence after flush ligation,[13] but rarely identified after confluence conservation.[14]

When the terminal valve is incompetent, nonflush ligation was thought to promote recurrence as previously stated. However, one prospective study has demonstrated that this concept is wrong. In this large series neither postoperative outcome nor clinical and diagnostic evaluation found a difference in terms of recurrence if the terminal valve was competent or not.[14]

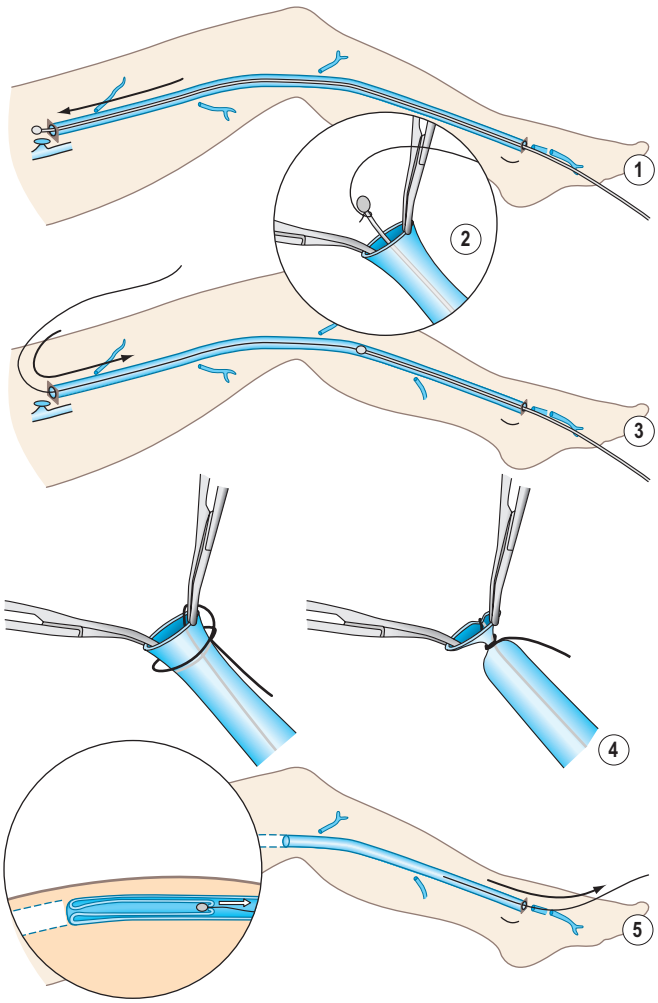


Figure 10.3 Invagination stripping. *1,* The vein is catheterized from the ankle to the groin. *2,* A thread is fixed on the stripper. *3,* The rigid stripper is pulled up from the ankle to the groin. *4,* The thread is fixed on the vein at the groin. *5,* Pulling on the thread allows the removal of the vein by the invagination technique. (Adapted from Perrin M. Chirurgie à ciel ouvert de l'insuffisance veineuse superficielle. Principes. Techniques. Résultats. EMC [Elsevier Masson SAS, Paris], Techniques chirurgicales—Chirurgie vasculaire, 43-161-B, 2007).

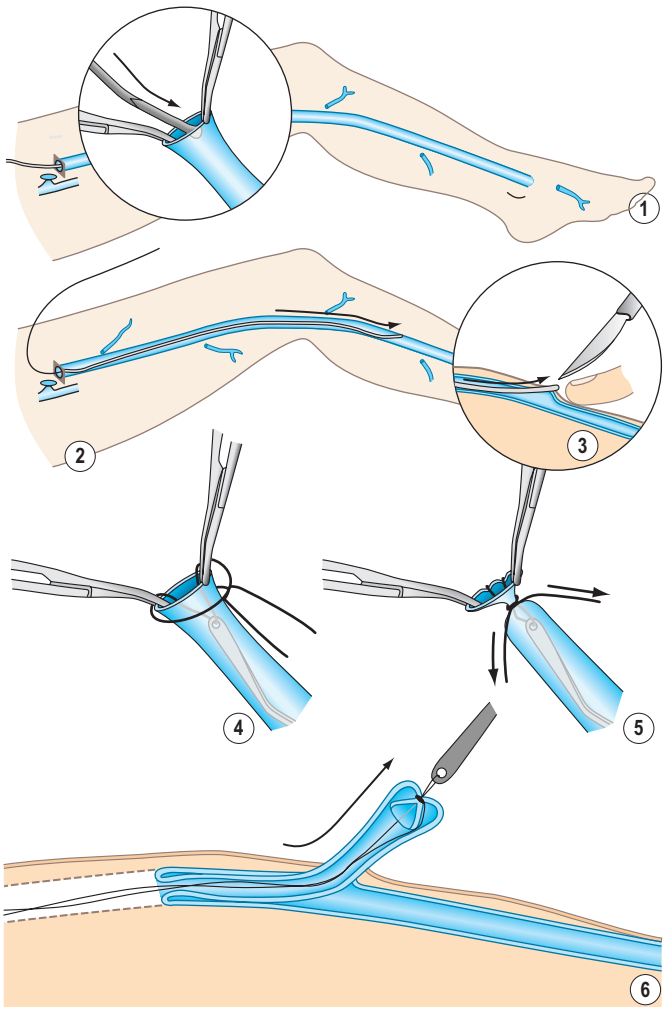


Figure 10.4 Pin-stripping. *1,* The great saphenous vein is catheterized from the groin to the upper third of the lower leg with the pin-stripper. *2, 3,* The pin-stripper distal extremity is pushed through the vein wall and the skin. *4, 5,* A thread is passed through the pin-stripper eyelet. Then the thread is interlocked with the vein; the tie must be done on the thread and not on the pin-stripper. *6.* Both stripper and invaginated vein are extracted through the distal incision. (Adapted from Perrin M. Chirurgie à ciel ouvert de l'insuffisance veineuse superficielle. Principes. Techniques. Résultats. EMC [Elsevier Masson SAS, Paris], Techniques chirurgicales—Chirurgie vasculaire, 43-161-B, 2007).

The explanation for this may be that suppression of the reservoir represented by an incompetent saphenous trunk and tributaries allows the terminal valve to recover its competence.

Cryostripping

The only difference with cryostripping in comparison with classical surgery is the ablation modality of the saphenous trunk. After HL, the saphenous trunk is catheterized downward with the cryoprobe until reaching the lower limit of the vein to be stripped. The generator is activated and when the vein is attached to the cryoprobe (by freezing to it) the vein is broken off easily. No distal ligation is needed and the vein attached to the probe is progressively pulled up and extracted through the groin incision (Fig. 10.6).

Cryostripping is said to cause less postoperative bruising and hematoma along the path of the saphenous trunk than conventional stripping, but this procedure has not been confirmed by others to be superior to current techniques.

SURGERY WITH SAPHENOUS TRUNK PRESERVATION

This is less invasive than other procedures, including vein stripping. The most aggressive part of vein stripping is the trunk excision. Supporters claim that the preserved saphenous trunk might be used as an arterial substitute either for coronary surgery or as a bypass in femorocrural obliteration. Unfortunately there are no data on the real need for, or value of, the saphenous trunk as an arterial substitute after such surgery. Another argument in favor is the preservation of venous flow drainage, as ablation of the superficial system

enhances varicose vein recurrence. The different procedures are depicted in Figure 10.7.

ISOLATED FLUSH LIGATION OR LIMITED RESECTION

Isolated flush ligation or limited resection of the SFJ and/or SPJ is termed 'crossectomie' in Western Europe. This procedure is rarely performed as an isolated procedure since older studies demonstrated very poor outcome after this procedure. It has been proposed in association with sclerotherapy[15] of the saphenous vein at thigh level to imitate the flush ligation and stripping. The target of associated sclerotherapy, obtained by means of a catheter inserted through the proximal incision performed for high ligation, is to reduce problems like pain and hematoma correlated to stripping. However, the risk of recanalization of the treated segment is particularly elevated; probably the employment of foam can reduce this recurrence.

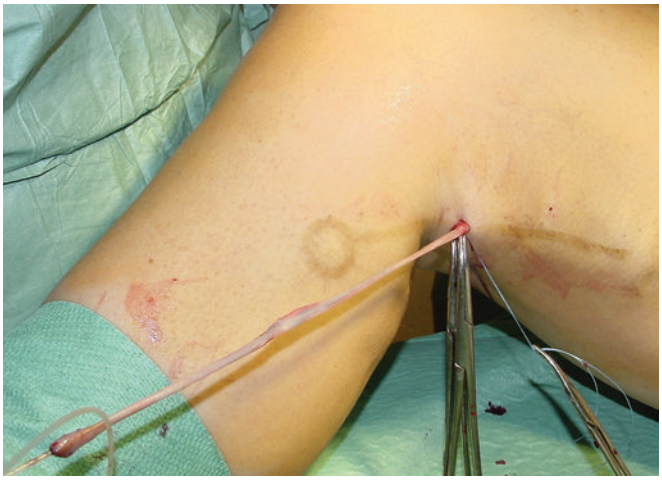


Figure 10.5 Stripping by invagination with flexible stripper.

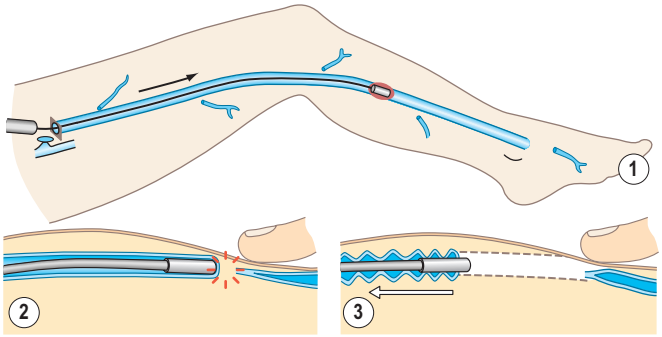


Figure 10.6 Cryostripping. *1,* The saphenous trunk is catheterized downwards with the cryoprobe until it reaches the lower limit of the vein to be stripped. *2, 3,* While still applying the freezing, the stripper is progressively pulled out by traction from bottom to top. The great saphenous vein remains attached to the cryoprobe. (Adapted from Perrin M. Chirurgie à ciel ouvert de l'insuffisance veineuse superficielle. Principes. Techniques. Résultats. EMC [Elsevier Masson SAS, Paris], Techniques chirurgicales—Chirurgie vasculaire, 43-161-B, 2007).

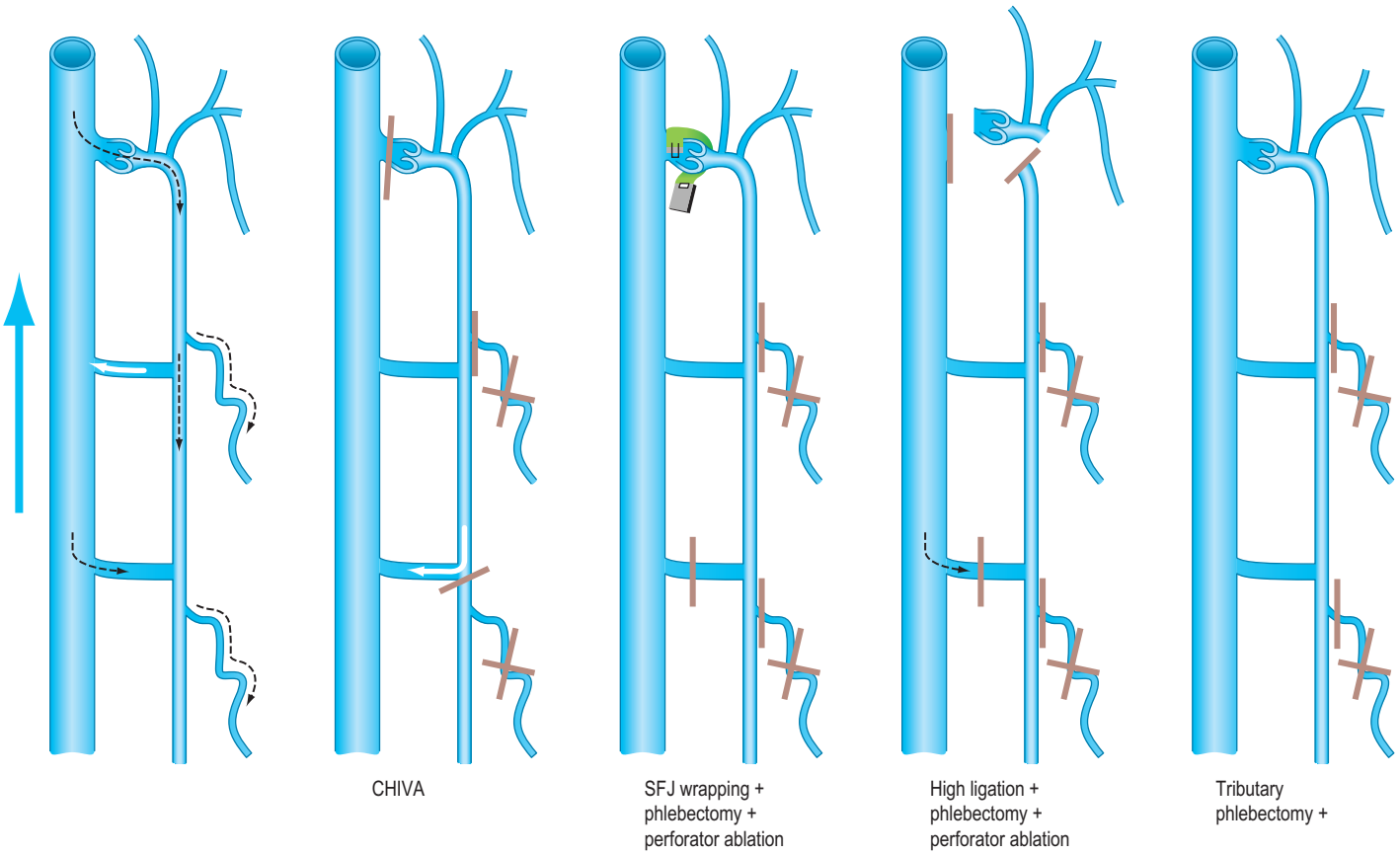


Figure 10.7 Schema of the trunk-preserving procedures.

SFJ AND/OR SPJ LIGATION PLUS INCOMPETENT TRIBUTARY PHLEBECTOMY WITH OR WITHOUT INCOMPETENT PERFORATOR INTERRUPTION

Suppression of leak points between the DVS and the SVS combined with reservoir ablation is supposed to restore competence of the saphenous trunk.[16–19] This procedure was promoted during the last two decades, but is presently rarely performed, probably because the myth of compulsory HL has been discredited for its lack of clinical efficacy.

SFJ WRAPPING OR VALVULOPLASTY PLUS INCOMPETENT TRIBUTARY PHLEBECTOMY WITH OR WITHOUT INCOMPETENT PERFORATOR INTERRUPTION

The remark made about the previous procedure—on the one hand the relationship between SFJ incompetence and the development of VVs, and on the other hand the fact that suppression of the refluxing SFJ is no longer compulsory—should explain the loss of interest in these techniques.

SFJ Wrapping

The hemodynamic principle here is that by wrapping the SFJ using an external stenting technique (instead of the HL described earlier), the supposed restoration of competence to the valve restores valvular function.[20–22]

The upholders of this method have underlined that the terminal or subterminal valve has to be assessed carefully by B-flow ultrasound preoperatively, for only selected valves can benefit from wrapping. These are valves that are not irreversibly damaged and can have their competence restored with a decrease in their diameter.

Valvuloplasty or Valve Repair

Valvuloplasty is another way to restore either terminal or subterminal valves. Repair is made by using either the assistance of external valvuloplasty angioscopy[23] or a direct surgical approach.[24–26]

AMBULATORY PHLEBECTOMY

Muller described this technique in 1956 and published it 10 years later.[27] The method consists of extracting VVs in an outpatient setting under local anesthesia using small punctures and hooks. This procedure is described in detail elsewhere,[28–30] but it is worth mentioning here that phlebectomy is performed by using fine-pointed blades, mini-incisions and crochet hooks or specialized phlebectomy hooks (Fig. 10.8).

Muller used this procedure in isolation or in combination with trunk stripping to avulse tributary varices, as reported in 1996.[31]

A powered phlebectomy device, the Trivex system (InaVein LLC, Lexington, MA), was introduced by G. Spitz in1966. Briefly, the system contains a shaver and a transilluminator coupled with an irrigator (Fig. 10.9).

VARICES PHLEBECTOMY

Varices phlebectomy with conservation of the refluxing saphenous trunk is named in French *'ablation sélective des varices sous anesthésie locale'* (ASVAL; selective ablation of varices under local anesthetic).[32] This process gathers and unifies techniques of phlebectomy that were previously scattered and insufficiently systematized, and is based on the demonstrated fact that varicose disease most often begins at lower leg level (see previous discussion). According to ASVAL principles, the suppression of varicose reservoirs (especially extrafascial varicose clusters) can, at least to a certain extent, improve or restore to normal (centripetal) the reflux in saphenous trunks, thus preserving them.[33]

CHIVA METHOD

CHIVA is the acronym of the French *'Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire'*.[34] The pathophysiological basis of CHIVA relates to a 'hemodynamicocentric model' of venous insufficiency (VI).[35]

According to CHIVA all the VI symptoms are the result of an obstacle to the flow and/or valvular incompetence, which increases the transmural pressure (TMP). Excessive TMP dilates the veins (varices) and impairs drainage (edema, lipodermatosclerosis and ulcer). The hemodynamic diagnosis consists of checking and correcting the causes of VI to normalize the TMP and consequently its clinical symptoms. According to the VI hemodynamic pattern, CHIVA involves fractioning the hydrostatic pressure, disconnecting the shunts and preserving the draining veins to cure all the symptoms of VI at the same time and avoid recurrence. Open Deviated Shunts Type II (varices + segmental saphenous trunk reflux) and Closed Shunts Type III (varices + segmental saphenous trunk reflux + SFJ reflux [SFJR]) are frequent patterns of VI because of superficial valve incompetence. In these specific cases, CHIVA divides the refluxing tributaries at their junction with the saphenous trunk. These divisions result in trunk reflux suppression and varices 'remodeling' to normal size, whereas the drainage is preserved to avoid short-term side effects and long-term recurrences (in the case of Shunt III SFJR, redo because of a trunk re-entry) (Figs 10.10–10.13).

INVESTIGATIONS TO BE DONE BEFORE VARICOSE VEIN SURGERY

A thorough physical examination is important; it allows the clinical class (using the comprehensive classification system for chronic venous disorders: clinical, etiology, anatomy, pathophysiology [CEAP]) to be identified. Both symptom type and severity must be carefully recorded.

Systematic DUS before surgery for varicose veins is crucial. From a classification standpoint DUS is used to complete CEAP sections E, A and P. In practical terms it allows creation of a precise map that will be very useful during surgery (Fig. 10.14).

This examination is required and is sufficient in clinical practice for primary and isolated superficial VI (SVI). For secondary SVI or SVI associated with abnormalities other than associated perforator incompetence, complementary tests should be performed depending on the clinical context.

The assessment performed in preparation for surgical treatment of varicose veins should provide answers to the following questions:

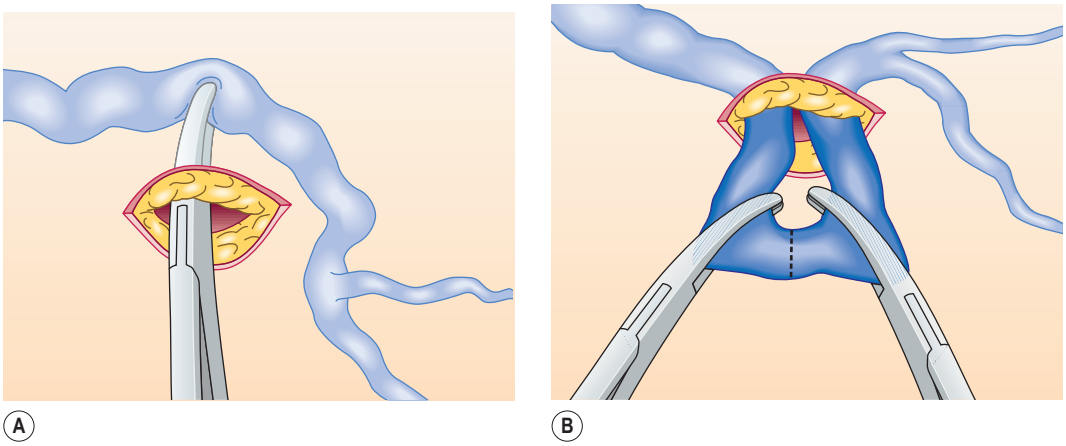


Figure 10.8 Grasping of previously marked varicosities. **A,** The incision is a 2- to 3-mm stab made with a No. 11 blade. **B,** After the varicosity is exteriorized, it is divided and each end is carefully avulsed to remove as much varix as possible. **C,** With the limb elevated 30 degrees, 2-mm cutaneous incisions can be made, the varicosity can be brought to the surface by the hook technique, and after division of the vein each end can be avulsed selectively. Placement of subsequent incisions depends on the length of varicosity excised. **D,** This photograph, taken 10 days after surgery, shows the location of a distal medial calf incision through which the great saphenous vein has been stripped from the groin to this level.

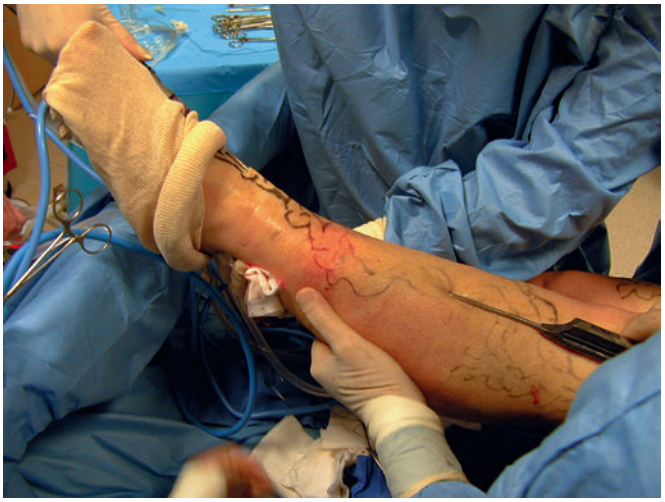


Figure 10.9 Intraoperative view of the transilluminated powered phlebectomy procedure. Note the subcutaneous transillumination.

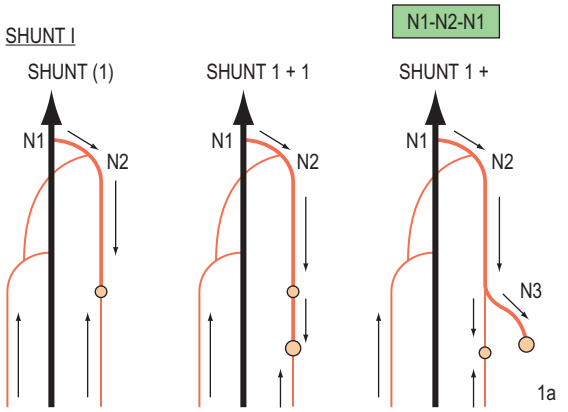


Figure 10.10 Types of 'private circulation' or veno-venous shunts according to CHIVA nomenclature. Type I shunt with re-entry on the saphenous trunk, and variations. *N1,* deep vein network; *N2,* superficial vein surrounded by the superficial fascia (great saphenous vein, small saphenous vein, proximal part of the accessory anterior saphenous vein, Giacomini vein); *N3,* superficial venous system not surrounded by the superficial fascia. (Courtesy Dr Franceschi.)

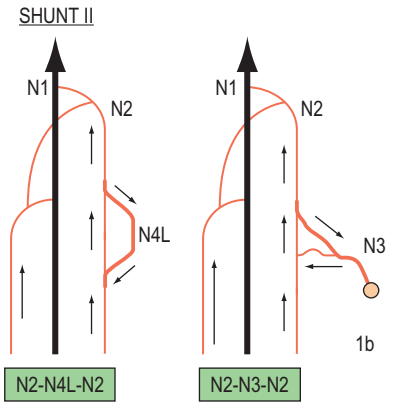


Figure 10.11 Types of 'private circulation' or veno-venous shunts according to CHIVA nomenclature. Type II shunt without reflux from the deep circulation, with compartmental regurgitation N2>N4>N2> or N2>N3>N2. *N1,* deep vein network; *N2,* superficial vein surrounded by the superficial fascia (great saphenous vein, small saphenous vein, proximal part of the accessory anterior saphenous vein, Giacomini vein); *N3,* superficial venous system not surrounded by the superficial fascia; *N4,* superficial communicant vein longitudinal *(N4L).* (Courtesy Dr Franceschi.)

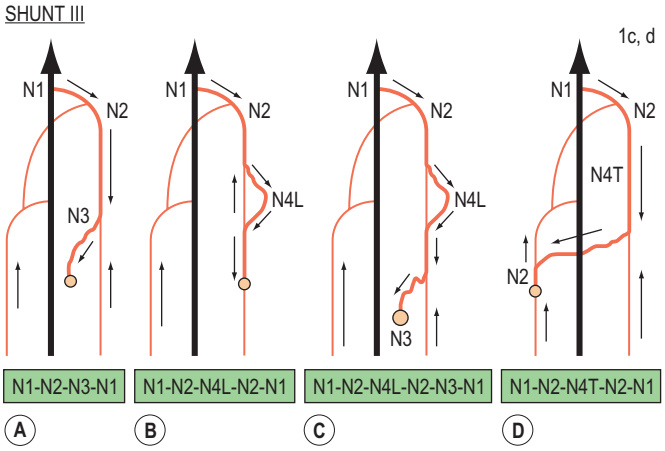


Figure 10.12 Types of 'private circulation' or veno-venous shunts according to CHIVA nomenclature. Type III shunt with re-entry located on an extrasaphenous perforator, and variations. *N1,* deep vein network; *N2,* superficial vein surrounded by the superficial fascia (great saphenous vein, small saphenous vein, proximal part of the accessory anterior saphenous vein, Giacomini vein); *N3,* superficial venous system not surrounded by the superficial fascia; *N4,* superficial communicant vein longitudinal *(N4L)* or transversal *(N4T).* (Courtesy Dr Franceschi.)

- Are the symptoms described by the patient connected to his or her varicose veins?
- Are there signs that can be used to classify the varicose veins into the category of complicated varicose veins (significant edema, skin changes, hemorrhage, superficial thrombophlebitis)?
- Are the varicose veins primary, secondary or congenital?
- Where are the leaks between the DVS and SVS (junctions and perforating veins)?
- Which veins are varicose (GSV: trunk, tributaries; SSV: trunk, tributaries; other nonsaphenous veins)?

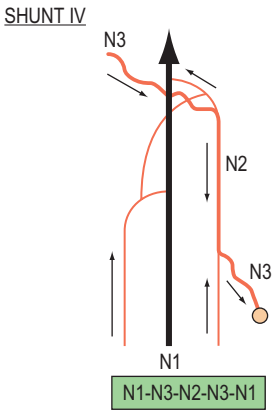


Figure 10.13 Types of 'private circulation' or veno-venous shunts according to CHIVA nomenclature. Type IV shunt with reflux from the pelvic circulation. *N1,* deep vein network; *N2,* superficial vein surrounded by the superficial fascia (great saphenous vein, small saphenous vein, proximal part of the accessory anterior saphenous vein, Giacomini vein); *N3,* superficial venous system not surrounded by the superficial fascia. (Courtesy Dr Franceschi.)

- What is the DVS status?
- Is there an associated disease that may affect the therapeutic indication?
- Is surgical treatment the best option?
- If the surgeon has made up his or her mind, have the anatomical variations been identified?
- What does the patient expect from surgery?

PATIENT INFORMATION

The information to be given depends of course on the technique scheduled, but in all cases the following information must be provided:

- Advantages and disadvantages of the different surgical methods must be explained, in addition to the postoperative course (return to normal activity, convalescence duration) and possible complications.
- Whether the surgery will be performed on an ambulatory basis or not.
- How much the patient will be charged.

In addition, a written document is handed over to the patient (Appendix 10.1).

ANESTHESIA AND HOSPITALIZATION

ANESTHESIA

Regardless of the technique used, surgery may be performed under local anesthesia (LA). Tumescent anesthesia is strongly recommended for all patients. This innovation has revolutionized varicose vein surgery.[36,37]

The addition of epinephrine (adrenaline) does decrease ecchymosis, and Goldman has shown that in appropriate

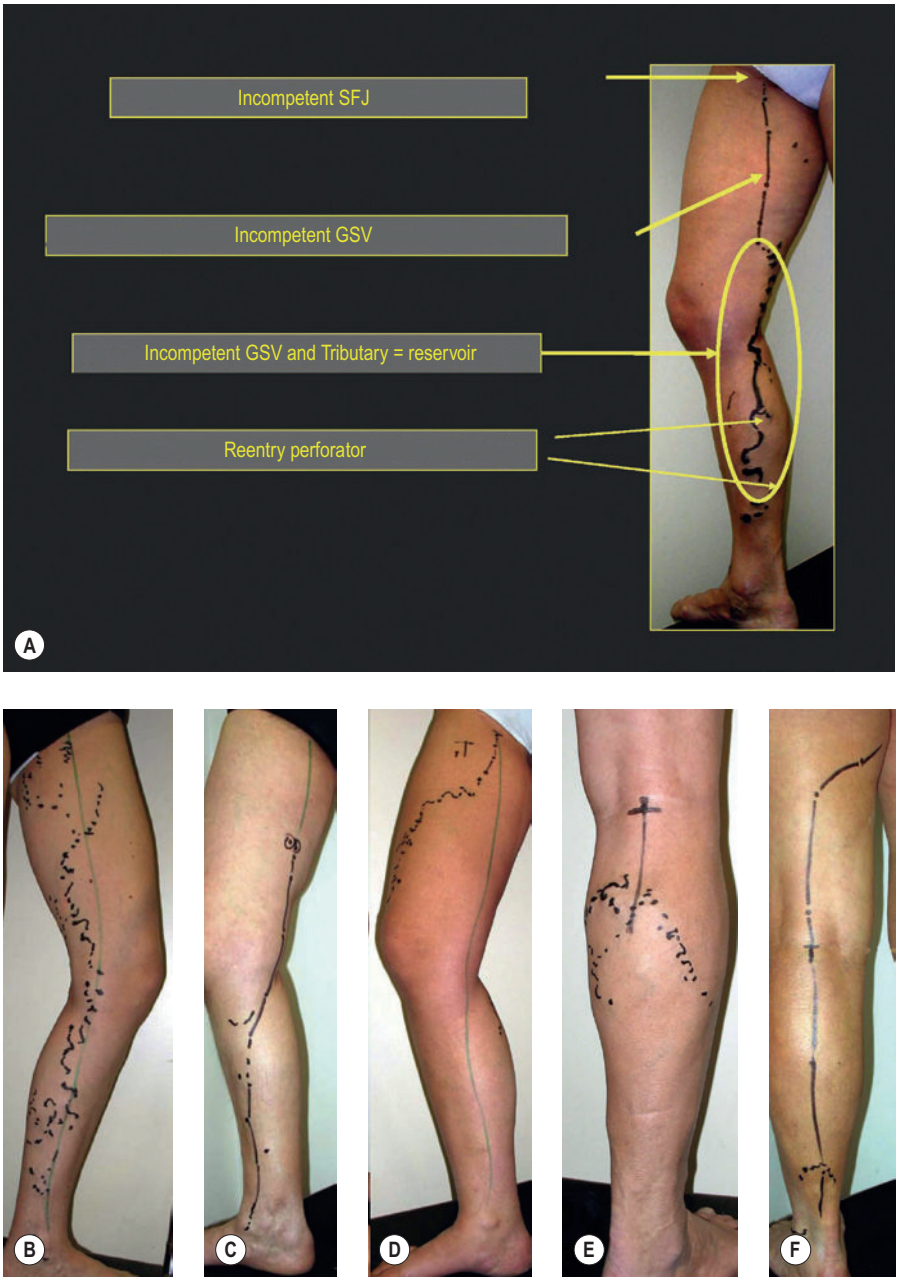


Figure 10.14 Surgery preoperative mapping. **A,** Incompetent saphenofemoral junction (SFJ) and great saphenous vein (GSV) until half-way down the thigh (line —— • ——). Below GSV is competent and a medial-posterior tributary is refluxing, draining in lower leg re-entry perforators. **B,** SFJ and GSV competent (*continuous line in blue*). Refluxing nonsaphenous veins (*dotted line in black*). **C,** SFJ and GSV proximal part competent (*continuous line in blue*). Incompetent femoral canal perforator feeding the GSV (*continuous line in black*). **D,** SFJ and GSV competent (*continuous line in blue*). Incompetent anterior accessory great saphenous vein (*dotted line in black*). **E,** SPJ and proximal small saphenous vein (SSV) incompetent (*continuous line in black*) and the SSV tributary (*dotted line in black*). Competent distal SSV (not mapped). **F,** Incompetent SSV not connected with the popliteal vein but with the GSV. (Courtesy Dr Creton.)

concentrations epinephrine is safe when used in a tumescent anesthetic technique during ambulatory phlebectomy. It does reduce the incidence of hematoma and hyperpigmentation.[38,39]

Flush ligation under echo-guided local anesthesia is also performable in obese patients (Fig. 10.15).

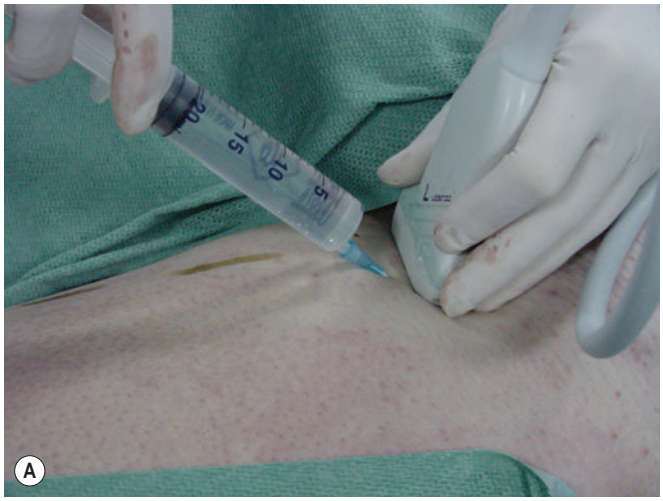
HOSPITALIZATION

Surgery for varicose veins is increasingly performed on an ambulatory basis. Only in elderly patients undergoing classical surgery or those characterized by a particular social or pathological context are hospitalized for 24 hours. Hospitalization is therefore determined by the patient's desires, local traditions or socioeconomic conditions.

POSTOPERATIVE CARE AND CONVALESCENCE

DRUG TREATMENT

After classical surgery minor analgesics may be proposed on the day of the procedure, which may be supplemented with anti-inflammatory treatment for 8 days. Tumescent anesthesia usually provides adequate pain control, which lasts for 1 to 2 days. Any patient complaining of pain must be evaluated to determine the cause. Postoperative antithrombotic prophylaxis with low molecular weight heparin (LMWH) is indicated in at-risk patients (history of thromboembolic disease, positive family case history, known thrombophilia, etc.). Ambulatory phlebectomy or other mini-invasive



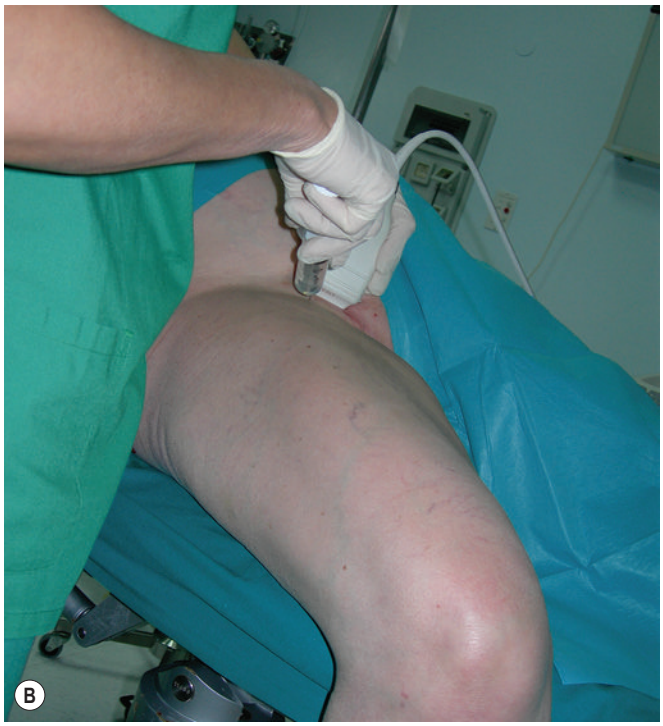


Figure 10.15 Echo-guided local anesthesia **(A)**. Position of the leg to perform echo-guided local anesthesia at groin in obese patients **(B)**.

techniques (ASVAL, CHIVA) performed under the same conditions do not require antithrombotic prophylaxis because of the absence of perioperative muscle atony and immediate mobilization of the patient at the end of the procedure.

POSTOPERATIVE ELASTIC COMPRESSION

Such treatment should be systematically initiated on the day of the procedure. It has been credited with analgesic effects, prevents edema and most likely the occurrence of thromboembolic complications that may affect the SVS and DVS. Depending on the case and customary practice, stockings or bandages are used. This compression is usually prescribed for 1 to 2 weeks in the absence of skin changes.

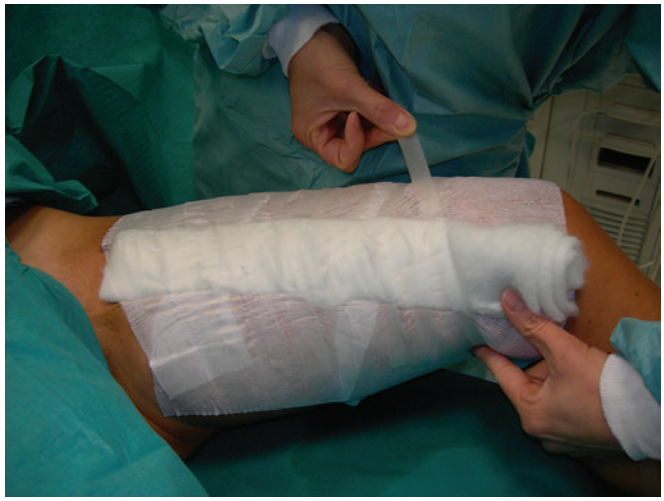


Figure 10.16 Eccentric compression by means of crossed-tape technique.

For ambulatory phlebectomy and other mini-invasive techniques, the duration of elastic compression (with bandages and then stockings) is usually 1 week. Poorly applied compression may lead to complications. Eccentric compression by mean of the crossed-tape technique (Fig. 10.16) applied for few days, is particularly useful in reducing postoperative complications.[40]

RECOVERY AND CONVALESCENCE

Recovery depends on the surgery performed and the level of patient activity; from 2 weeks for extensive excisional surgery to a maximum of a few days for so-called conservative surgery. The norm is rising with movement on the day of the procedure, depending on the procedure performed; with mini-invasive and LA procedures immobility time is shortened. Exercise time is progressively increased during recovery. In principle, surgeons should provide patients with a document showing all postoperative instructions (Appendix 10.1).

SURGICAL COMPLICATIONS

PERIOPERATIVE COMPLICATIONS

Perioperative complications associated with surgery are exceptional when the surgery is performed by a qualified operator. However, vascular injuries from damage to the principal arterial and venous trunks or nerves have been reported mainly after conventional surgery, sometimes with dramatic consequences.[41,42] Lastly, anesthesia regardless of its mode of delivery, may cause accidents, but tumescent LA provides fewer complications.

POSTOPERATIVE COMPLICATIONS

Postoperative complications may be cutaneous, vascular, lymphatic, neurologic or of a more general nature.

HEMATOMA

Hematomas are commonly seen following trunk stripping. They are often worrisome to the patient, who should be notified in advance and reassured that they disappear and have no lasting consequences. Compression can partially prevent hematomas and reduce the pain they engender, and the local application of cold compresses may also be recommended. Local drainage may be indicated after the blood clots have resolved (usually 2 weeks postop).

LOCAL INFECTIOUS COMPLICATIONS

Local infections are rare and usually occur following redo surgery in the groin. Antibiotic therapy is indicated depending on the clinical status and culture results.

LYMPHATIC COMPLICATIONS

Early occurrence of lymphatic complications can lead to lymphatic accumulations and/or lymphorrhea at the inguinal incision or at any incision point because of injury during surgery to the lymphatic vessels or nodes. The patient should be referred to the surgeon. The lymphatic vessels may be damaged during phlebectomy in certain areas (dorsum of the foot, crest of the tibia). A lymphatic pseudocyst develops and often requires multiple weekly treatments such as puncture and drainage compression, and in severe cases manual lymphatic drainage may be necessary. In cases of late onset, the complications lead to lymphedema that may be treated as such. This lymphedema is very rare and mainly occurs after redo surgery at the groin.

NEUROLOGIC COMPLICATIONS

Neurologic complications[43–45] are more frequent after trunk stripping, are mainly associated with perioperative injury, and rarely occur when elastic compression is applied to patients under general anesthesia. Lesions to the motor nerves are extremely rare but may be permanent. In contrast, lesions to superficial sensory nerves, estimated at between 10% and 40%, may lead to disorders such as anesthesia, paresthesia, dysesthesia and rarely neuralgia. The patient often only becomes aware of these neurologic disorders a few days after the procedure and they usually disappear within a few weeks, but sometimes after several months. They are rarely permanent.

VENOUS THROMBOEMBOLIC COMPLICATIONS

Local anesthesia and early mobilization have certainly reduced the frequency of such complications. Analysis of two prospective series with systematic DUS examination showed that after ancillary surgery occurrence of DVT was 0.4% to 5.3% and pulmonary embolism was 0.2% to 0%,[46,47] demonstrating that most of the DVTs were distal and asymptomatic. However, it should be noted that in the first series the patients ($n = 377$), who were treated by HL plus saphenous trunk stripping and tributary phlebectomy and/or ligation of the perforating veins, were operated on under general anesthesia followed by early mobilization and postoperative compression, but patients at risk for DVT were not systematically given preventive anticoagulation. In the second series various open surgery procedures were performed, but under LA. Although no randomized controlled trials (RCTs) comparing the two modes of anesthesia are presently available, it appears that venous thromboembolic complications are more frequent with general anesthesia.

In practice, on the slightest suspicion, the patient must be reassured and a venous DUS and/or lung scan urgently requested to diagnose or exclude possible deep vein thrombosis (DVT) and/or pulmonary embolism.

COSMETIC COMPLICATIONS

Cosmetic complications appear later. Unsightly scars are rare if the operator respects the accepted rules for cutaneous incisions. Aggravation of pre-existing telangiectasias, occurrence of a neotelangiectatic network ('matting') or of pigmentation, particularly on the medial aspect of the thigh, are not uncommon along the pathway of the stripping. The following cutaneous complications have also been reported along the line of incision:

- Localized hypertrichosis
- Scleroderma-like dermatitis
- Vitiligo

These complications may also occur near phlebectomy incisions.

REDO SURGERY

The modality and indication for repeat surgery will be discussed later. Nevertheless it must be underlined that redo-surgery, particularly at the SFJ and SPJ, generates a complication rate higher than primary surgery.

POSTSURGICAL FOLLOW-UP

Whichever VV operative treatment is undertaken, follow-up is strongly recommended and must be understood both by patient and physician. One must keep in mind that varices are a chronic and progressive disease and in most cases surgery cannot completely cure the patient. Postoperative DUS allows one to assess the presence of persistent reflux, and treatment may prevent further recurrence, although no RCT is available to recommend this practice.

RESULTS FROM SURGERY

Outcome is difficult to evaluate, owing on the one hand to the various anatomic and physiologic lesions or disorders, and on the other hand to symptoms and clinical signs that differ from one patient to another. These facts help to explain why there is no universally appropriate classification available for VVs.

Certain evaluations only take into consideration the investigation results (DUS, plethysmography, etc.), whereas others also include evaluation of the signs (presence or absence of varicose veins) and/or symptoms (persistence or disappearance). Lastly, pre- and postoperative patient quality of life (QoL) can be an interesting evaluation tool.

In a comprehensive review including 118 references the authors' conclusions were[48] that surgical treatment seems to:

- Relieve symptoms and improve disease-related QoL
- Have a role in the secondary prevention of venous ulcer
- provide a cosmetic improvement, which is almost certainly operator-dependent
- Be associated, as stated earlier, with minor complications that are relatively common, and major neurosensory or vascular complications that are very rare
- Be associated with a definite but variable risk of recurrence

Some prospective RCTs comparing the various surgical techniques themselves or comparing chemical or thermal ablation with surgery are available, but for most there is no long-term follow-up.

SURGERY WITHOUT PRESERVATION OF THE SAPHENOUS TRUNK

CONVENTIONAL SURGERY

Numerous publications about this technique are available; this procedure has been used almost exclusively for a century.

Natural Evolution of the Disease Versus Conventional Surgery

A set of 149 patients with uncomplicated but symptomatic VVs, who had chosen whether or not to be treated 6 months earlier, were assessed by a questionnaire.[49] Surgery significantly reduced the total number of symptoms reported by the patients at follow-up ($P < 0.02$). However, none of the symptoms reported during specific activities were significantly lessened by surgery compared with no treatment.

Conservative Treatment Versus Open Surgery

Three RCTs have been conducted concerning patients with noncomplicated varicose veins.

The outcome is displayed in Table 10.1.[50–53]

In $C_{5–6}$ patients four RCTs compare open surgery plus compression versus isolated compression. The outcome is shown in Table 10.2.[54–60]

OUTCOME OF CONVENTIONAL SURGERY IN OBSERVATIONAL STUDIES

Only two prospective observational studies will be analyzed here. The patients were treated at centers highly skilled in venous surgery, investigated in depth pre- and postoperatively by DUS and there was no patient loss at 5 years follow-up.[61,62]

In the first study, which included 93 patients (113 extremities $C_{2–6}$) the recurrence rate according to the REVAS (recurrent varices after surgery) definition[63] was 25% (28/113), of which 72% were symptomatic (20/28). Nevertheless the clinical score was an improvement on the preoperative one ($P < 0.001$). The main cause of REVAS was neovascularization at the SFJ.

In the second study with 92 patients (127 extremities: $C_2 = 58$; $C_3 = 11$; $C_4 = 34$; $C_5 = 5$; $C_6 = 19$) all patients were assessed postoperatively to identify incorrect surgery. The REVAS rate was 47% and mainly related to neovascularization at the SFJ or/and SPJ, but only two ulcers recurred (2/19 = 10.5%). Clinical recurrence was more likely in limbs with worse preoperative venous function, assessed by air plethysmography (APG), and reflux present at three or more sites. After surgery, correction to normal venous filling index was less frequent in limbs with recurrence. Gradual deterioration in APG measures of reflux was identified in 66% at 5 years. Unfortunately no correlation was established between long-term DUS and APG anomalies with patient satisfaction or severity of symptoms.

RCTs on Conventional Surgery Versus Other Operative Treatment

The results of these trials are shown in Table 10.3[64,65] (HL + conventional stripping vs HL + cryostripping); Table 10.4[66–74] (HL + saphenous stripping [S] vs radiofrequency ablation [RFA]); Table 10.5[75–91] (HL + S vs endovenous laser ablation [EVLA]); Table 10.6[16–18,92,93] and Table 10.7[94,95] (HL + S vs surgery preserving the GSV); Table 10.8[96–107] (HL + S vs foam sclerotherapy); Table 10.9[108–110] (HL + S vs EVLA vs ultrasound guided foam sclerotherapy [USGFS]); Table 10.10[89,111] (HL+S vs RFA vs USGFS); Table 10.11[112] (open surgery [OS] vs endovenous microwave ablation [EMA]); Table 10.12[72] (OS vs cryostripping vs RFA); Table 10.13[113–117] (OS with various types of tributary phlebectomy); Table 10.14[118–120] (EVLA vs cryostripping).

CLASSICAL SURGERY VARIANTS

Saphenous Trunk Stripping with Preservation of the Saphenofemoral Confluence with or without Incompetent Tributaries Phlebectomy with or without Incompetent Perforator Interruption

A retrospective cohort study of 151 patients (175 lower limbs $C_1 = 1.5\%$, $C_2 = 82.1\%$, $C_3 = 6.7\%$ and $C_{4-6} = 9.7\%$) were treated as mentioned earlier knowing that 68.1% were symptomatic. The preoperative DUS showed that both saphenofemoral confluence (SFC) and saphenous trunk were incompetent. At a mean of 24.4 months postoperatively (median 27.3 months, range 8 to 34.8), persistent SFC reflux was observed in only two cases (1.8%) and an SFC neovascularization in one case (0.9%). Recurrence of VVs appeared in seven cases (6.3%), but in conjunction with SFC reflux in only one case. Posttreatment 83.9% of limbs were converted to CEAP clinical class 0 to 1 and significant symptom improvement was observed in 91.3% of cases with an esthetic benefit in 95.5%.[14]

There is no RCT comparing this method to other operative treatments.

Cryostripping

Table 10.3 shows the outcome of the RCTs comparing cryostripping with conventional surgery.[64,65]

SURGERY WITH SAPHENOUS TRUNK PRESERVATION

ISOLATED FLUSH LIGATION OR LIMITED RESECTION OF THE SFJ AND/OR SPJ

Various observational studies as well as RCTs have demonstrated that this procedure results in a poor outcome in the long term.

Text continued on p. 336

Table 10.1 Open Surgery Versus Nonoperative Treatments in C_{2s} Patients

Operative procedure	Reference*	Summary
Open surgery versus conservative treatment	Michaels JA, Brazier JE, Campbell WB, et al. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. Br J Surg 2006;93:175. Michaels JA, Campbell WB, Brazier JE, et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). Health Technol Assess 2006;10:1.	246 patients with severe noncomplicated varices (C_{2s}) and reflux in the saphenofemoral and/or the saphenopopliteal junction reflux Group I (n = 122): conservative treatment (Life style advice + compression) versus Group II (n = 124): open surgery (OS) **Results at 2 years of follow-up:** Group II (OS)>Group I regarding: • HRQoL improvement (P = 0.083) • Symptoms relief (aching, heaviness, itching, swelling, cosmetic concerns, $P < 0.05$) • Anatomical extent of the veins ($P < 0.01$) **Conclusion:** Standard surgical treatment of varicose veins by saphenofemoral ligation, stripping and multiple phlebectomies is a clinically effective and cost-effective treatment for severe varicose veins. Injection sclerotherapy also appears to be cost-effective, but produces fewer overall benefits with a higher incremental cost-effectiveness ratio than surgery for patients with superficial venous reflux. In minor varicose veins without reflux, sclerotherapy is likely to provide a small average benefit with acceptable cost-effectiveness.
	Ratcliffe J, Brazier JE, Campbell WB, et al. Cost effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized control trial. Br J Surg 2006;93:182.	246 patients presenting with noncomplicated varices (C_{2s}) with saphenofemoral and/or saphenopopliteal junction reflux Group I: Conservative treatment (life style advice) versus Group II: OS **Results at 2 years of follow-up:** Group II (surgery) offers a modest health benefit for relatively little National Health Service cost compared to conservative treatment.
Open surgery versus compression therapy	Sell H, Vikatamaa P, Albäck A, et al. Compression therapy versus surgery in the treatment of patients with varicose veins: a RCT. Eur J Vasc Endovasc Surg 2014;47:670.	153 patients Noncomplicated varices (C_{2s}) Group I (n = 77): conservative treatment (CT) versus Group II (n =76): open surgery (OS) **Results at 2 years of follow-up:** Group I: VCSS decreased from 4.6 to 3.5, and VSDS decreased from 7.7 to 7.0, but HRQoL was unchanged Group II: VCSS decreased from 4.8 to 0.6, P = 0.01; and VSDS decreased from 8.2 to 0.9, P = 0.0001; whereas HRQoL improved significantly

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.

CT, conservative treatment; HRQoL, health-related quality of life; OS, open surgery (saphenofemoral and/or saphenopopliteal junction ligation + stripping, +/– perforator ligation +/– tributary phlebectomy); VCSS, venous clinical severity score; VSDS, venous segmental disease score.

Table 10.2 Open Surgery including CHIVA + Compression Versus Isolated Compression in C_{5-6} Patients

Operative procedure	Reference*	Summary
Open surgery +/– SEPS and compression therapy versus isolated compression therapy in C_5–C_6 or C_6 patients	Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2005;363:1854.	500 lower limbs classified C_6 Group I: OS + compression therapy versus Group II: isolated compression therapy **Results at 24 weeks of follow-up:** 40 patients lost to follow-up *Venous ulcer healing:* healing rates similar in both groups **Results at 1 year of follow-up:** *Venous ulcer recurrences:* recurrence rate reduced by 28% in Group I versus 12% in Group II; hazard ratio, 2.7; 65% CI 1.78 to 4.27; $P < 0.0001$
	Guest M, Smith JJ, Tripuraneni G, et al. Randomized clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. Phlebology 2003;18:130.	76 patients assigned C_6 of the CEAP Group I ($n = 39$): Four-layer bandaging versus Group II ($n = 37$): OS + Four-layer bandaging **Results at 24 weeks of follow-up:** *Venous ulcer healing:* no difference between the two groups in terms of healing rate (adjusted hazard ratio 0.69, $P = 0.41$), HRQoL (adjusted hazard ratio 0.79, 95% CI –0.45 to 1.39 using generic (SF–36) and specific (CXVUQ) tools

	Gohel MS, Barwell JR, Earnshaw JJ, et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study)–haemodynamic and anatomical changes. Br J Surg 2005;92:291.	214 lower legs with saphenous reflux +/– deep venous reflux
		Group I ($n = 112$): compression therapy
		versus
		Group II ($n = 102$): OS + compression therapy
		Results at 1 year of follow-up:
		Hemodynamics
		• Venous refill time better improved in Group iii II compared with Group I; $P < 0.001$
		• Deep venous reflux abolition
		  • 10/22 when segmental
		  • 3/17 when axial

	van Gent WB, Hop WC, Van Prag MC, et al. Conservative versus surgical treatment of venous leg ulcers: A prospective, randomized, multicenter trial. J Vasc Surg 2006;44:563.	70 patients, and 200 venous ulcers (C_6) Group I ($n = 97$ ulcers): open surgery +/– SEPS (50%) + compression therapy versus Group II ($n = 103$ venous ulcers): compression therapy **Results at 29 months (mean 27) of follow-up:** *Venous ulcer healing:* Group I, 72% versus group II, 53%; $P = 0.11$ *Venous ulcer recurrences or medial ulcers*: better results in group I compared with group II; $P = 0.02$
	Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy versus compression plus surgery in chronic venous ulceration (ESCHAR). Randomized controlled trial. Br J Surg 2007;335:83.	500 lower legs classified C_5-C_6 Group I: OS + compression therapy versus Group II: compression therapy. **Results at 3 years of follow-up:** *Venous ulcer healing* in C6 patients Nonsignificant difference between the two groups ($P = 0.73$) **Results at 4 years of follow-up:** *Venous ulcer healing and recurrence in patients with isolated superficial reflux:* Ulcer free time longer in group I vs group II; $P = 0.007$ Recurrence rates lower in group I vs group II; $P < 0.01$ *Venous ulcer recurrence in patients with combined deep segmental reflux:* Recurrence rates lower in group I vs group II; $P = 0.04$ *Venous ulcer recurrence in patients with combined deep axial reflux:* No significant difference between groups in recurrent rates; $P = 0.33$

Continued on following page

Table 10.2 Open Surgery including CHIVA + Compression Versus Isolated Compression in C_{5-6} Patients (Continued)

Operative procedure	Reference*	Summary
CHIVA + compression therapy versus compression therapy in C_6 patients	Zamboni P, Cisno C, Marchetti F, et al. Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. Eur J Vasc Endovasc Surg. 2003;25:313.	45 patients C_6 , and 47 venous ulcers Group I (patients, *n* = 21; ulcers, *n* = 23): CHIVA + compression therapy versus Group II (patients, *n* = 24; ulcers, *n* = 24):compression therapy **Results at 3 years of follow-up:** *Venous ulcer healing:* Group I, 100% at 31 days (mean) versus Group II 96% at 63 days (mean); *P* < 0.02 *Venous ulcer recurrences:* Group I, 9% versus Group II 36%; *P* < 0.05 *HRQoL (SF 36):* Group I with better HRQoL > Group II (*P* < 0.05)
	Zamboni P, Cisno C, Marchetti P, et al. Hemodynamic CHIVA correction versus compression for primary venous ulcers: first year results. Phlebology 2004;19:28.	45 patients and 47 lower limbs with primary VV (C6) Group I (*n* = 23): CHIVA + compression therapy versus Group II (*n* = 24): compression therapy) **Results at 1 year of follow-up:** *Venous ulcer healing:* Group I, 100% at 29 days (mean) versus Group II 96% at 61 days (mean); *P* < 0.02 *HRQoL (SF–36):* Group I with better QoL > Group II (*P* < 0.05)

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
CHIVA, Ambulatory conservative hemodynamic management of varicose vein; EVLA, endovenous laser ablation; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); HRQoL, health-related quality of life; SEPS, subfascial endoscopic perforating vein surgery; VV, varicose veins.

Table 10.3 Open Surgery Versus High Ligation + Cryostripping

Operative procedure	Reference*	Summary

Open surgery
versus
cryostripping
	Menyhei G, Gyevnar Z, Arato E, et al. Conventional stripping versus cryostripping: a prospective randomised trial to compare improvement in quality of life and complications. Eur J Vasc Endovasc Surg 2008;35:218.	Group I (*n* = 86): OS
		versus
		Group II (*n* = 79): HL + cryostripping
		Results at 6 months of follow-up:
		• No difference between group I and II in terms of:
		  • Postoperative pain
		  • Clinical results
		• Less hematoma in group II compared with group I (*P* = 0.01)

	Klem TMAL, Schnater JM, Schütte PR, et al. A randomized trial of cryostripping versus conventional stripping of the great saphenous vein. J Vasc Surg. 2009;49:403.	Group I (*n* = 245): OS versus Group II (*n* = 249): HL + cryostripping **Results at 6 months of follow-up:** No difference between the 2 groups

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
HL, High ligation; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy).

Table 10.4 High Ligation + Stripping Versus Radiofrequency Ablation

Operative procedure	Reference*	Summary
Open surgery versus RFA	Hinchliffe RJ, Uhbi J, Beech A, et al. A prospective randomised controlled trial of VNUS Closure versus surgery for the treatment of recurrent long saphenous varicose veins. Eur J Vasc Endovasc Surg 2006;31:212.	16 patients presenting bilateral REVAS with persistent GSV trunk. One leg: RFA with VNUS closure bipolar catheter on one lower limb versus Other leg: redo-groin surgery (RGS) + S Anesthesia: no standardization **Results at 10 days of follow-up:** • Procedure shorter with VNUS compared with RGS ($P = 0.02$) • Less postoperative pain with VNUS compared with RGS ($P = 0.02$) • Less bruising with VNUS compared with RGS ($P = 0.03$)
	Kianifard B, Holdstock JM, Whiteley MS. Radiofrequency ablation (VNUS closure) does not cause neovascularisation at the groin at one year: results of a case controlled study. Surgeon 2006;4:71.	GSV incompetence Group I ($n = 55$): VNUS closure bipolar catheter versus Group II ($n = 55$): OS No information on the type of anesthesia **Results at 1 year of follow-up:** *Neovascularization* No neovascularization in group I compared with 11 in group II ($P = 0.028$)
	Lurie F, Creton D, Eklof B, et al. Prospective randomized study of endovenous radiofrequency obliteration (Closure procedure) versus ligation and stripping in a selected patient population (EVOLVES Study). J Vasc Surg 2003;38:207.	GSV incompetence 86 lower limbs Group I ($n = 44$): VNUS closure bipolar catheter versus Group II ($n = 36$): OS Anesthesia: no standardization **Results at 4 months of follow-up:** • Return to normal activity shorter in group I compared with group II ($P = 0.02$) • Return to work shorter in group I compared with group II ($P = 0.05$) • Better HRQoL in group I compared with group II
	Lurie F, Creton D, Eklof B, et al. Prospective randomized study of endovenous radiofrequency obliteration (Closure) versus ligation and vein stripping (EVOLVeS) Two-year follow-up. Eur J Vasc Endovasc Surg 2005;29:67.	65 patients with GSV incompetence Group I ($n = 46$ at year 1, 36 at year 2): VNUS Closure bipolar catheter versus Group II ($n = 40$ at year 1, 29 at year 2): OS (HL and S) Anesthesia: no standardization **Results at 2 years of follow-up:** • Similar clinical and DUS results in both groups (at least equal in group I to those of group II, after HL + S) • Better HRQoL in group I compared with group II
	Rautio T, Ohinmaa A, Perala J, et al. Endovenous obliteration versus conventional stripping operating in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. J Vasc Surg 2002;35:958.	GSV incompetence Group I ($n = 15$): VNUS closure bipolar catheter versus Group II ($n = 13$): OS General anesthesia **Results at 2 months of follow-up:** • Less postoperative pain in group I compared with group II ($P = 0.017–0.036$) • Shorter convalescence in group I compared with group II ($P < 0.001$) • Cost saving for society in employed patients in group I compared with group II
	Perala J, Rautio T, Biancari F, et al. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. Ann Vasc Surg 2005;19:669.	GSV incompetence Group I ($n = 15$): VNUS closure bipolar catheter versus Group II ($n = 13$): L + S General anesthesia **Results at 3 years of follow-up:** • No difference between groups in terms of clinical results

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Table 10.4 High Ligation + Stripping Versus Radiofrequency Ablation (Continued)

Operative procedure	Reference*	Summary
	Stötter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping and cryostripping in the treatment of great saphenous vein. Phlebology 2006;21:60.	GSV incompetence Group I (n = 20): VNUS closure bipolar catheter versus Group II (n = 20): HL + invagination S versus Group III (n = 20): HL + cryostripping General anesthesia **Results at 1 year of follow-up:** • No difference in the physician-assessed clinical status between the three groups • More satisfaction in group I compared with group II and III regarding operative procedure (P = 0.001) and the cosmetic appearance (P = 0.006)
	Subramonia S, Lees T. Radiofrequency ablation vs conventional surgery for varicose veins-a comparison of treatment costs in a randomized trial. Eur J Vasc Endovasc Surg 2010;39:104.	GSV incompetence Group I (n = 47): VNUS closure bipolar catheter versus Group II (n = 41): OS General anesthesia *Results* • Procedure duration longer in group I compared with group II (P < 0.001) • Hospital cost more expensive in group I compared with group II • Earlier return to work in group I compared with group II (P = 0.006)
	Elkaffas KH, Elkashef O, Elbaz W. Great saphenous vein radiofrequency ablation versus standard stripping in the management of primary varicose veins–a randomized clinical trial. Angiology 2010;62:49.	GSV and SFJ incompetence of 180 lower limbs Group I (n = 90): VNUS closure bipolar catheter versus Group II (N = 90): OS RFA with local anesthesia, and OS with general anesthesia *Results* • Lower overall complication rate in group I compared with group II • Shorter hospitalization in group I compared with group II (P = 0.001) • More expensive procedure in group I compared with group II (P = 0.003) **Results at 2 years of follow-up** • No difference between groups in term of VV recurrence rate

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
DUS, duplex ultrasound; GSV, great saphenous vein; HL, high ligation; HRQoL, health-related quality of life; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); RFA, radiofrequency ablation; REVAS, recurrence of VV after surgery; S, stripping; SFJ, saphenofemoral junction; VV, varicose veins.

Table 10.5 Open Surgery Versus Endovenous Laser Ablation

Operative procedure	Reference*	Summary
Operative surgery versus EVLA	De Medeiros CA, Luccas GC. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. Dermatol Surg 2005;31:1685.	Patients with GSV incompetence Group I (n = 20): 980 nm diode laser, bare fiber, stepwise laser withdrawal versus Group II (n = 20): open surgery Spinal anesthesia for both procedures **Results at 9 months (mean) of follow-up:** • No difference between groups regarding postoperative pain • Group I (EVLA) • Less swelling and bruising in group I (EVLA) compared with group II (P-value not known) • Better outcome in group I (EVLA) compared with group II (P-value not known)

Table 10.5 Open Surgery Versus Endovenous Laser Ablation (Continued)

Operative procedure	Reference*	Summary
	Vuylstecke M, Van den Busche D, Audenaert EA, Lissens P. Endovenous laser obliteration for the treatment of primary varicose veins. Phlebology 2006;21:80.	Patients with GSV incompetence Group I (n = 118): 980 nm diode laser bare fiber, stepwise laser withdrawal versus Group II (n = 124): open surgery General anesthesia for both procedures **Results at 1, 8 weeks and 9 months of follow-up:** • Less postoperative in group I (EVLA) compared with group II • Sick leave shorter in group I (EVLA) compared with group II ($P < 0.001$) • Total cost fewer in group I (EVLA) compared with group II
	Ying L, Sheng Y, Ling H, et al. A random, comparative study on endovenous laser therapy and saphenous veins stripping for the treatment of great saphenous vein incompetence. Zhonghua-Yi-Xue-Za-Zhi 2007;87:3043.	Patients with GSV incompetence Group I (n = 40): 980 nm diode laser, bare fiber pulse mode versus Group II (n = 40): OS General anesthesia for both procedures **Results at 1 year of follow-up:** • Fewer bleeding in group I (EVLA) compared with group II ($P < 0.01$) • Less postoperative pain in group I (EVLA) compared with group II ($P < 0.05$) • Hospitalization shorter in group I (EVLA) compared with group II ($P < 0.05$) • No difference between groups regarding APG results
	Rasmussen LH, Bjoern L, Lawaetz M, et al. Randomized trial comparing endovenous laser ablation of the great saphenous vein with ligation and stripping in patients with varicose veins: short-term results. J Vasc Surg 2007;46:308.	Patients with GSV incompetence Group I (n = 62): Diode 980 nm diode laser, bare fiber, stepwise laser withdrawal versus Group II (n = 59): OS General anesthesia for both procedures **Results at 1, 2 and 6 months of follow-up:** • No difference between groups in terms of efficacy and safety • Less postoperative pain and bruising in group I (EVLA) compared with group II ($P = 0.05$).
	Darwood RJ, Theivacumar N, Dellagrammaticas D, et al. Randomized Clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous veins. Br J Surg 2008;95:294.	Patients with GSV incompetence Group I: EVLA with local tumescent anesthesia, 980 nm diode laser, bare fiber, stepwise laser withdrawal (n = 42), continuous laser withdrawal (n = 29) versus Group II (n = 32): OS with general anesthesia **Results at 3 months of follow-up:** No difference between groups (EVLA and OS) in terms of reflux abolition and HRQoL (specific questionnaire) Group I (EVLA) Earlier return to normal activity in group I (EVLA, both laser groups) compared with group II ($P = 0.005$)
	Kalteis M, Berger I, Messie-Werndl S, et al. High ligation combined with stripping and endovenous laser ablation of the great saphenous vein: Early results of a randomized controlled study. J Vasc Surg 2008;47:822.	Patients with GSV incompetence Anesthesia: incomplete information Group I (n = 47): diode 810 nm diode laser, bare fiber, stepwise laser withdrawal + HL versus Group II (n = 48): OS **Results at 1, 4 and 16 weeks of follow-up:** • Less bruising in group I (EVLA) compared with group II ($P = 0.001$) • Longer period of time until return to work in group I (EVLA) compared with group II ($P = 0.054$) • No difference between groups regarding HRQoL (CIVIQ)

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Table 10.5 Open Surgery Versus Endovenous Laser Ablation (Continued)

Operative procedure	Reference*	Summary
	Theivacumar NS, Darwood MJ, Gough MJ. Neovascularization and recurrence 2 years after treatment for saphenofemoral and great saphenous reflux: a comparison of surgery and endovenous laser. Eur J Vasc Endovasc Surg 2009;38:203.	Patients with GSV incompetence Group I (n = 69 lower limbs): 980 nm diode laser, bare fiber, pulse mode, with local tumescent anesthesia versus Group II (n = 60 lower limbs): OS with general anesthesia **Results at 2 years of follow-up:** • Recurrence rates similar in both groups • Neovascularization less frequent in group I (EVLA) compared with group II (P = 0.001)
	Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. J Vasc Surg 2010;52:1234.	Patients with GSV incompetence Group I (n = 100): 980 nm diode laser, bare fiber, stepwise mode versus Group II (n = 100): OS General or spinal anesthesia for both procedures **Results at 12 days of follow-up:** • No difference between groups in postoperative pain, use of analgesics and return time to normal activities • More hematoma in group II (OS) compared with group I • More bruising in group I (EVLA) compared with group II **Results at 1 and 2 years of follow-up:** • No difference between groups in terms of symptoms, VCSS or HRQoL • One GSV reopening in group I (EVLA) and none in group II (P < 0.051)
	Pronk P, Gauw SA, Mooij MC, et al. Randomised controlled trial comparing saphenofemoral ligation and stripping of the great saphenous vein with endovenous laser ablation (980 nm) using local tumescent anaesthesia: One year results. Eur J Vasc Endovasc Surg 2010;40:649.	Patients with GSV incompetence Local tumescent anesthesia for both procedures Group I (n = 62): 980 nm diode laser, bare fiber, continuous laser withdrawal + postoperative sclerotherapy for persistent varices versus Group II OS (n = 68): HL + pin-stripping + tributary stab avulsion Local tumescent anesthesia for both procedures **Results at 1 to 14 days of follow-up:** After 2 weeks more postoperative pain in group II compared with group I (P < 0.01) After 2 weeks more hindrance in mobility and daily activities in group II compared with group I (P > 0.01) **Results at 1 year of follow-up:** No significant differences between groups in terms of DUS recurrence
	Rasmussen LH, Bjoern L, Lawaetz M, et al. Randomized trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. Eur J Vasc Endovasc Surg 2010;39:630.	Patients with GSV incompetence Group I (n = 62): 980 nm diode laser , bare fiber, pulse mode versus Group II (n = 59): OS Local tumescent anesthesia for both procedures **Results at 2 years of follow-up:** No significant differences between groups in terms of: • Clinical or DUS recurrence • Clinical severity scores (VCSS; AVQQ) • Quality of Life (SF 36)

Table 10.5 Open Surgery Versus Endovenous Laser Ablation (Continued)

Operative procedure	Reference*	Summary
	Carradice D, Mekako AI, Mazari FAK, et al. Randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011;98:501.	Patients with GSV incompetence + incompetent saphenofemoral junction Group I (n = 140): 810 nm diode, bare fiber, continuous laser withdrawal, continuous power delivery 14 W, under local tumescent anesthesia versus Group II (n = 140): HL + inversion stripping under general anesthesia Tributaries phlebectomy + perforator ligation in both groups **Results at 1 week and 1 year of follow-up:** Significant improvement after treatment in both groups regarding VCSS & QUALY gain (P < 0.001) • Less pain in group I (EVLA) compared with group II (P < 0.001) • Better HRQoL improvement (SF-36) in 6 out 8 domains in group I (EVLA) compared with group II (P = 0.004) • Shorter return to work in group I (EVLA) compared with group II (P < 0.001)
	Carradice D, Mekako AI, Mazari FAK, et al. Clinical and technical outcomes from a randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011;98:1117.	Patients with GSV incompetence + incompetent saphenofemoral junction Group I (n = 140): 810 nm diode, bare fiber, continuous laser withdrawal, continuous power delivery 14 W under local tumescent anesthesia versus Group II (n = 140): HL + inversion stripping under general anesthesia Tributaries phlebectomy + perforator ligation in both groups **Results at 1 week to 1 year of follow-up:** • Better initial technical results in group I (EVLA) compared with group II (93% *vs* 92.4%; P = 0.005) **Results at 1 year of follow-up:** • Clinical recurrence rate was lower in group I (EVLA) compared with group II (4% vs 20.4%; P < 0.001) • Clinical recurrence was associated with worse AVVQ scores (P < 0.001)
	Rass K, Frings N, Glowack P, et al. Comparable effectiveness of endovenous laser ablation and high ligation with stripping of the great saphenous vein. Arch Dermatol 2012;148:49.	Patients with GSV incompetence + incompetent saphenofemoral junction + saphenous reflux at least down to knee level Tumescent local anesthesia for both procedures Group I (n = 185): 810 nm diode laser, bare fiber, continuous laser withdrawal ,applied energy 20 J/cm2 vein surface versus Group II (n = 161): OS **Results at 2 years of follow-up:** • PREVAIT: Group I, 2%; group II, 23.1% (P = NS) • DUS recurrence: reflux at the SFJ: Group I, 17.8% (clinically silent in 81%); Group II, 1.3% (P < 0.001) • (HVSS): no difference between groups • HRQoL (CIVIQ): no difference between groups • Recovery time, ability to work: no difference between groups
	Samuel N, Carradice D, Wallace T, et al. Randomized clinical trial of endovenous laser ablation versus conventional surgery for small saphenous varicose veins. Ann Surg 2013;257:419.	Patients with incompetent SPJ + reflux in SSV Group I (n = 56): EVLA versus Group II (n = 56): OS **Results at 1 week to 1 year of follow-up:** • Better initial technical results in group I (EVLA) compared with group II (96.2% vs 71.7%; P < 0.001) • Lower postoperative pain in group I (EVLA) compared with group II (P < 0.05) • Earlier return to work and normal function in group I (EVLA) compared with group II (P < 0.001) • Minor sensory disturbance in group I (P = 0.009) **Results at 1 year of follow-up:** • No difference between groups regarding VCSS and HRQoL improvement

Continued on following page

Table 10.5 Open Surgery Versus Endovenous Laser Ablation (Continued)

Operative procedure	Reference*	Summary
	Rasmussen LA, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins with 3 years follow-up. J Vasc Surg Venous Lym Dis 2013;1:349.	Patients with GSV incompetence in CEAP $C_{2\text{-}4}E_pA_sP_r$ Group I (n = 69): Diode 980 nm diode laser, bare fiber, stepwise laser withdrawal versus Group II (n = 68): OS Local tumescent anesthesia for both procedures Results at 1, 2 and 6 months, and then 1 to 5 years of follow-up **Results at 5 years of follow-up:** • *GSV persistent reflux at DS examination*: no significant difference between groups (P = 0.2145) • *Clinical recurrence*: no significant difference between groups (P = 0.7209) • *Retreatment:* no significant difference between groups (P = 0.9876) • *VCSS improvement*: lasted from month 1 month to year 5 without difference between groups • *AVVSS improvement*: significant improvement in both groups from 3 month and onwards (P < 0.0001), with no difference between groups at any time point • *SF-36 scores:* improved in all domains and similarly in both groups

	Flessenkämpfer I, Hartmann M, Stenger D, Roll S. Endovenous laser ablation with and without high ligation compared with high ligation and stripping in the treatment of great saphenous varicose veins: initial results of a multicentre randomized controlled trial. Phlebology 2013;28:16.	Patients with GSV incompetence + incompetent SFJ in CEAP $C_{2\text{-}6}E_pA_sP_r$
		Group I (n = 159): HL + ST
		Group II (n = 142): EVLA
		Group III (n = 148): EVLA + HL
		Diode 980 nm diode laser, bare fiber, continuous mode in groups II and III
		Anesthesia: unknown in group I; local tumescent anesthesia in groups II and III
		Results at day 1 after operation:
		• *Postoperative pain* was higher in group III compared with groups I and II (P = 0.0069)
		Results at 2 months of follow-up:
		• *VCSS scores:* no difference between groups
		• *Presence of inguinal reflux in GSV:* Group I = 0; Group II = 26.7%; Group III = 6.7%
		  • Group I versus group II; P < 0.0001
		  • Group I versus group III; P < 0009
		  • Group II versus group III; P < 0.0001

	Roopram AD, Lind MY, Van Brussel JP, et al. Endovenous laser ablation versus conventional surgery in the treatment of small saphenous vein incompetence. J Vasc Surg Venous Lym Dis 2013;1:357.	Patients in CEAP $C_{2\text{-}6}$ SSV diameter <10 mm with incompetent SPJ Group I (n = 118): EVLA with 810 nm diode laser, bare fiber, continuous laser withdrawal under local anesthesia versus Group II (n = 57): SPJ ligation under general or spinal anesthesia **Postoperative results:** • *Easiness of procedure* in favor of group I (EVLA; P < 0.001) • Persistent reflux at SPJ in group I: 0.9 % vs group II: 21% • Decrease in pain intensity on VAS in favor of group II (P = 0.03) • AVQQ scores: no difference between groups • Return to work shortened in group I (P < 0.05) **Results at 6 weeks of follow-up:** • Fewer neurologic complications in group I (P < 0.001) • Fewer infections in group I (P < 0.05)

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.

APG, Air plethysmography; AVVQ, Aberdeen varicose vein questionnaire; AVVSS, Aberdeen varicose vein severity score; DUS, duplex ultrasound; EVLA, endovenous laser ablation; GSV, great saphenous vein; HL, high ligation; HRQoL, health-related quality of life; HVSS, Homburg varicose vein severity score; PREVAIT, presence of varices after operative treatment; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); QALY, quality adjusted life year; QoL, quality of life; ST, GSV stripping; SFJ, saphenofemoral junction; SFP, saphenopopliteal junction; SSV, short saphenous vein; VCSS, venous clinical severity scoring.

Table 10.6 Open Surgery Versus High Ligation + Tributary Phlebectomy

Operative procedure	Reference*	Summary
Operative surgery versus HL + tributary phlebectomy +/– perforator ligation	Campanello M, Hammarsten J, Forsberg S, et al. Standard stripping versus long saphenous vein saving surgery for primary varicose veins: a prospective, randomized study with the patients as their own controls. Phlebology 1996;11:45. Hammarsten J, Pederson P, Cederlund C G, Campanello M. Long saphenous vein saving surgery for varicose vein. A long-term follow-up. Eur J Vasc Surg 1990;4:361. Hammarsten J, Campanello M, Pedusen P. Long saphenous vein saving surgery for varicose vein. Eur J Vasc Surg 1993;7:763. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins. Five year results of a randomized trial. J Vasc Surg 1999;29:589. Winterborn R.J, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. J Vasc Surg 2004;40:634.	Group I (n = 18): OS of GSV versus Group II (n = 18): HL + tributary phlebectomy +/– perforator ligation of GSV **Postoperative results** Less subjective postoperative discomfort in group II **Results at 4 years of follow-up:** • No difference between groups in terms of clinical outcome and plethysmography as far as incompetent perforators had been treated • Ultrasound examination: patent and compressible GSV in group II Group I (n = 52): OS of GSV versus Group II (n = 58): HL + tributary phlebectomy +/– perforator ligation of GSV **Results at 5 and 11 years of follow-up:** No difference between groups in terms of VV recurrence rate but more redo surgery in group II

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
HL, high ligation; GSV, great saphenous vein; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); VV, varicose veins.

Table 10.7 Open Surgery Versus CHIVA

Operative procedure	Reference*	Summary
Open surgery versus CHIVA	Carandina S, Mari C, De Palma M, et al. Stripping vs haemodynamic correction (CHIVA): a long-term randomised trial. Eur J Vasc Endovasc Surg 2008;35:230.	Patients C_{2-6} Group I (n = 75): OS versus Group II (n = 75): cure CHIVA **Results at 10 years of follow-up:** Less VV recurrence in group II (CHIVA) compared with group I (OR 2.2, 95% CI –1 to 5, P = 0.04)
	Parés JO, Juan J, Tellez R, et al. Varicose vein surgery. Stripping versus the CHIVA method: a randomized controlled trial. Ann Surg 2010;251:624.	Patients C_{2-6} Group I (n = 167): OS with clinical marking versus Group II (n = 167): OS with duplex marking versus Group III (n = 167): CHIVA **Results at 5 years of follow-up:** • Better clinical outcome (symptoms and signs) in group III (CHIVA) compared with group I and II • Less recurrence in group III (CHIVA) compared with group I and II (OR 2.01,CI –1.4 to 3, P < 0.001)

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
CHIVA, Ambulatory conservative hemodynamic management of varicose vein; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); VV, varicose veins.

Table 10.8 Open Surgery Versus Foam Sclerotherapy

Operative procedure	Reference*	Summary
Liquid chemical ablation versus OS	Einarsson E, Eklöf B, Neglén P. Sclerotherapy or surgery as treatment for varicose veins: A prospective randomized study. Phlebology 1993;8:22.	164 patients with symptomatic primary VV located in GSV and/or SSV Group I (n = 80): OS Group II (n = 84): Liquid sclerotherapy **Postoperative results:** • *Loss of working days*: 1 day in group I vs 20 days in group II **Results at 5 years of follow-up:** • *Failure rate:* 10% in group I vs 74% in group II • *Foot volumetry measurement*: in favor of group I; $P < 0.01$
Liquid chemical ablation + HL versus OS	Rutgers PH, Kitslaar PJEHM. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. Am J Surg 1994;168:311.	156 patients and 181 lower limbs with primary GSV incompetence Group I (n = 78; 89 lower limbs): OS under general anesthesia Group II (n = 78; 92 lower limbs): HL + Liquid sclerotherapy **Results at 3 years of follow-up:** • *Clinical results:* in favor of group I ($P < 0.05$) • *Doppler results:* in favor of group I ($P < 0.001$)
Liquid chemical ablation versus OS + liquid chemical ablation versus OS	Belcaro G, Nicolaides AN, Ricci A, et al. Endovascular sclerotherapy, surgery and surgery plus sclerotherapy in superficial venous incompetence. A randomized, 10-year follow-up trial—final results. Angiology 2000;31:529.	150 patients with primary GSV incompetence Group I: liquid sclerotherapy (polidocanol 3%; 5–10 mL) + complementary session at 3 months if needed Group II: HL + phlebectomy (?) + liquid sclerotherapy under spinal or general anesthesia Group III: HL + phlebectomy (?) **Results at 1,5 and 10 years of follow-up:** • *Reflux at SFJ:* 18.8% in group I vs none in groups II and III • *Below the knee reflux:* 43.8% in group I vs 16.1% in group II and 36% in group III No conclusion can be drawn from this study.
Liquid and foam chemical ablation versus various open surgery procedures	Belcaro G, Cesarone NM, Di Renzo A, et al. Foam sclerotherapy, surgery, sclerotherapy and combined treatment for varicose veins. A 10-year, prospective, randomised, controlled trial (VEDICO trial). Angiology 2003;54:307.	749 patients with primary GSV incompetence Six groups: Group A (n = 123): liquid sclerotherapy Group B (n = 112): high dose of liquid sclerotherapy Group C (n = 132): multiple ligations Group D (n = 122): stab avulsion Group E (n = 129): foam + tensio-active substance Group F (n = 131): surgery (ligation) **Results at 1, 5 and 10 years of follow-up:** All treatments were similarly effective at 10 years. Low-dose sclerotherapy appeared to be less effective than high-dose sclerotherapy and foam sclerotherapy, which may obtain results comparable to surgery in selected subjects. It is difficult to draw conclusion from this study.
Phlebectomy versus liquid chemical ablation	De Roos KP, Nieman FHM, Neumann M. Ambulatory phlebectomy versus compression sclerotherapy: results of a randomized controlled trial. Dermatol Surg 2003;29:221.	92 patients and 98 lower limbs classified C2 Ep A5 Pr Group I (n = 49 lower limbs):liquid sclerotherapy + 10 day-compression therapy Group II (n = 49 lower limbs): ambulatory phlebectomy under local anesthesia + 10 day compression therapy **Results at 2 years of follow-up:** • *Complications:* more minor complications in group I compared with groups II • *Recurrence:* 18/48 in group I vs 1/48 in groups II; $P < 0.001$

Table 10.8 Open Surgery Versus Foam Sclerotherapy (Continued)

Operative procedure	Reference*	Summary
Chemical ablation (USGFS) + HL versus OS (HL + S)	Bountouroglou DG, Azzam M, Pathmarajh M, et al. Ultrasound guided foam sclerotherapy combined with saphenofemoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. Eur J Vasc Endovasc Surg 2006;31:93.	Patients with incompetent GSV Group I (n = 30): HL + USGFS versus Group II (n = 30): HL + S General anesthesia for all procedures **Results at 3 months of follow-up:** • No difference between groups in terms of complication and occlusion • Less expensive and less loss of working days in group I *vs* group II; P < 0.0001. • Early recanalization in 13% of patients in group I after complementary injection.
	Abela R, Liamis A, Prionidis I, et al. Reverse foam sclerotherapy of the great saphenous vein and saphenofemoral ligation compared to standard and invagination stripping: A prospective clinical series. Eur J Vasc Endovasc Surg 2008:36:485.	Patients with incompetent GSV Group I (n = 30): HL + reverse foam sclerotherapy versus Group II (n = 30): HL + invagination S versus Group III (n = 30): HL + standard S General anesthesia for all procedures **Results at 2 weeks of follow-up:** Fewer postoperative complications and better patients satisfaction in group I compared with groups II and III.
	Liu X, Jia X, Guo W, et al. Ultrasound-guided sclerotherapy of the great saphenous vein with saphenofemoral ligation compared to standard stripping. Int Angiol 2011;30:321.	Patients with incompetent GSV in C_2–C_6 Group S (n = 30): HL + S +/– TP versus Group F (n = 30): HL + USFGS of which 5 received complementary foam sclerotherapy General anesthesia for all procedures **Results at 6 months of follow-up:** • Shorter operation time, earlier return-to work and less analgesics intake in group F compared with group S (P < 0.01) • *Obliteration:* 80% in group F vs 89.5% in group S; P = NS
	Kalodiki E, Lattimer C R, Azzam M, et al. long-term results of a randomized controlled trial on ultrasound guided foam sclerotherapy combined with sapheno-femoral ligation vs standard surgery for varicose veins. J Vasc Surg 2012;55:451.	Patients with incompetent GSV in C_2–C_6 Group S (n = 39): HL + S +/– TP of which 25 received complementary foam sclerotherapy versus Group F (n = 41): HL + USFGS of which 33 received complementary foam sclerotherapy General anesthesia for all procedures **Results at 3 to 5 years of follow-up:** • *VCSS*: no difference between groups • *VSDS*: no difference between groups • *HRQoL* (with specific AVVQ) better in group S compared with group F; P < 0.0005 • *HRQoL* (with generic SF-36): no difference between groups for the physical component
Chemical ablation (USGFS) versus OS (HL + S)	Figueiredo M, Araujo Q, Barros Jr N, Miranda Jr F. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised trial. Eur J Vasc Endovasc Surg 2009;38:758.	Patients with incompetent GSV, C_5, Ep, As, Pr Group I (n = 27): Foam sclerotherapy, 1–3 sessions, 10 mL/session versus Group II (n = 29): HL + S Surgery under local anesthesia **Results at 6 months of follow-up:** • Significant clinical improvement in both groups. • *Vein ablation at DS*: 78% in group I vs 90% in group II; P = NS related to the small number of included patients.

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Table 10.8 Open Surgery Versus Foam Sclerotherapy (Continued)

Operative procedure	Reference*	Summary
	Shadid N, Ceulen R, Nelemans P, et al. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. Br J Surg 2012;99:1062.	Patients with incompetent GSV at least 20 cm at the thigh Group I (n = 23): USGFS polidocanol 3%;.1 mL versus Group II (n = 200): HL + S partial GSV stripping +/– tributary phlebectomy under general anesthesia **Results at 2 years of follow-up:** • *PREVAIT:* similar in both groups • *Symptoms persistence*: 11.3% in group I vs 9% in group II; P = 0.407 (NS) • *Reflux (* more than 2 cm in the length of the treated GSV): 35% in group I vs 21% in group II; P = 0.003 • *Cost:* €774 in group I vs €1824 in group II
Chemical ablation (liquid or USGFS) versus HL or HL + S or phlebectomy	Wright D, Gobin J P, Bradbury A W, et al. Varisolve® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. Phlebology 2006;21:180.	Patients with incompetent GSV and SSV in C_{2s}–C_6 Surgery: 710 patients randomized to Group I: foam sclerotherapy (Varisolve® polidocanol), Group II: surgery (HL 92%, stripping 88%, phlebectomies 53%); no information on the type of anesthesia Group III: conventional sclerotherapy (92% homemade foam) Endpoint ultrasound determined occlusion of truncal veins and elimination of reflux **Results at 1 year of follow-up:** • *Occlusion of truncal veins and elimination of reflux determined by US:* • 63% in group I vs 86% in group II; P = 0.06 • 90% in group I vs 76% in group III; P = 0.001 • Foam resulted in less pain and earlier return to work than surgery.

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
AVVQ, Aberdeen varicose vein questionnaire; CA, chemical ablation; DS, duplex scan; GSV, great saphenous vein; HL, high ligation; OS, open surgery (HL + S +/– perforator ablation +/– tributary phlebectomy); S, saphenous stripping; SSV, small saphenous vein; TP, tributary phlebectomy; USFGS, ultrasound foam guided sclerotherapy; VCSS, venous clinical severity score; VSDS, venous segmental disease score; VV, varicose vein.

SFJ AND/OR SPJ LIGATION PLUS INCOMPETENT TRIBUTARIES PHLEBECTOMY WITH OR WITHOUT INCOMPETENT PERFORATOR INTERRUPTION

In addition to observational studies, two RCTs are available that include patients presenting with SFC and saphenous trunk incompetence (see Table 10.6 and 10.7). It is not clear whether this procedure provides better results than the ASVAL method (see later).

With the exception of one study,[17] the quality of the preserved saphenous trunk to be used as an arterial substitute has never been assessed in depth.

SFJ WRAPPING OR VALVULOPLASTY PLUS INCOMPETENT TRIBUTARIES PHLEBECTOMY WITH OR WITHOUT INCOMPETENT PERFORATOR INTERRUPTION

Some observational studies have been reported claiming both good clinical and hemodynamic results for this procedure.[22,23] Again it is not known whether this procedure produces better results than ASVAL, or whether the quality of the preserved saphenous trunk is suitable for use as an arterial substitute.

AMBULATORY PHLEBECTOMY

The results from Muller's technique of ambulatory phlebectomy are difficult to assess as it is used either as an isolated procedure or in combination with any kind of trunk ablation, including the different stripping modalities.

HOOK PHLEBECTOMY OR POWERED PHLEBECTOMY

According to the RCTs there is no evident benefit in using powered phlebectomy (Tables 10.13).

VARICES PHLEBECTOMY WITH CONSERVATION OF THE REFLUXING SAPHENOUS TRUNK

A retrospective study was undertaken of 303 lower extremities (221 patients) all presenting with saphenous trunk (ST) reflux of more than 0.5 seconds (GSV, 85.8%; SSV, 11.9%; and GSV and SSV, 2.3%), which had been treated according to the ASVAL method. The ST reflux was shown to be reduced to less than 0.5 seconds in 69.6%, 69.2%, 68.7%, 68.0% and 66.3% of limbs, respectively, after 6 months and 1, 2, 3 and 4 years of follow-up. Symptoms improved or disappeared in 84.2%, 84.2%, 83.4%, 81.4% and 78.0% of limbs at each annual check-up until year 4. Nonrecurrence

Table 10.9 Open Surgery Versus Endovenous Laser Ablation Versus Ultrasound Guided Foam Sclerotherapy

Operative procedure	Reference*	Summary
OS versus EVLA versus UGFS	Biemans AAM, Kockaert M, Akkersdijk GP, et al. Comparing endovenous laser ablation, foam sclerotherapy and conventional surgery for great saphenous varicose veins. J Vasc Surg 2013;58:727.	240 consecutive patients in CEAP C_{2-6s} with incompetent GSV and SFJ reflux All treatments just below or above the knee Group I (n = 80): OS under general or spinal anesthesia versus Group II (n = 80): EVLA 940 nm, bare fiber, continuous laser withdrawal under local anesthesia versus Group III (n = 80): UGFS with complementary session after 3 months when needed **Results at 1 year of follow-up:** • Lower occlusion rate in group III (72.7%) compared with this in group I (88.22%) and group II (88.5%); $P < 0.02$ • Low complication rate, comparable between the groups • All groups showed significant improvement in HRQoL (EQ5D) with no difference between the groups
	Brittenden C, Cotton SC, Elders A, et al. A Randomized trial comparing treatments for varicose veins. N Engl J Med 2014.371:1218.	Multicenter study of 798 varicose veins patients Group I (n = 210): EVLA under local anesthesia. Saphenous truncal ablation completed after 6 weeks by USGFS if needed versus Group II (n = 286): UGFS using the Tessari method with STS 1–3%; ratio air/ sclerosing agent 3/1; 12 mL maximum/ session versus Group III (n = 289): OS consisting of HL+GSV stripping+ tributary phlebectomy under general anesthesia **Results at 6 weeks to 6 months of follow-up:** • Lower complication rate; lower in group II compared to groups I and III ($P < 0.001$) • *HRQoL scores*: (AVVQ, EQ-5D, SF–36): similar scores after treatment in all groups (nonsignificantly worse in group II using the disease-specific AVVQ) • *VCSS scores*: similar clinical results in the 3 groups • *Anatomical outcome* on DS assessment: lower ablation rate in group II compared with groups I and III ($P < 0.001$)
	Tassie E, Scotland G, Brittenden J, et al. Cost- effectiveness of ultrasound-guided foam sclerotherapy, endovenous laser ablation or surgery as treatment for primary varicose veins from the randomized CLASS trial. Br J Surg 2014;101:1532.	Multicenter study of 798 varicose veins patients Group I (n = 210): EVLA under local anesthesia. Saphenous truncal ablation completed after 6 weeks by USGFS if needed. Group II (n = 286): USGFS using the Tessari method with STS 1–3%; ratio air/ sclerosing agent 3/1; 12 mL maximum/ session Group III (n = 289): OS consisting of HL+GSV stripping+ tributary phlebectomy under general anesthesia **Results at 6 months of follow-up:** *Costs*: group III > group I > group II *QALY:* QALYs was derived from responses to the EQ-5D and is often used in cost–utility analysis. For patients considered eligible for all three treatment options, the results suggest that **EVLA has the highest probability of being cost-effective** at accepted thresholds of willingness to pay per QALY

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.

AVQQ, Aberdeen varicose vein questionnaire; AVVSS, Aberdeen varicose vein severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire; DS, duplex ultrasound; EQ5D, Euro QoL 5D; EVLA, endovenous laser ablation; GSV, great saphenous vein; HS, high ligation; OS, open surgery (saphenofemoral ligation + stripping, +/– perforator ligation+/– tributary phlebectomy); LA, local anesthesia; QALY, quality adjusted life year; QoL, quality of life; RFA, radiofrequency ablation; STS, sodium tetradecyl sulphate; USGFS, ultrasound guided foam sclerotherapy; VCSS, venous clinical severity score.

Table 10.10 Open Surgery Versus Radiofrequency Ablation Versus Ultrasound-Guided Sclerotherapy

Operative procedure	Reference*	Summary
OS versus EVLA versus RFA versus UGFS	Rasmussen LA, Lawaetz M, Bjoern L, et al. A randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079.	580 lower limbs in CEAP $C_{2-4}E_pA_sP_r$ with incompetent GSV and SFJ reflux Group I (n =142): OS versus Group II : EVLA 980 (n = 17) and 1470 nm (n = 127), bare fiber versus Group III (n = 148): RFA Closure Fast versus Group IV (n = 144): USGFS) 1 or 2 sessions when needed All procedures under local anesthesia and completed by phlebectomy **Results at 3 days and 1 month of follow-up:** • Better HRQoL (SF–36) in addition to a lower pain score ($P < 0.001$) and shorter time off work in group III and IV compared with groups I and II ($P < 0.001$) **Results at 1 year of follow-up:** • DS examination: GSV occlusion better in group I, II, III compared with group IV ($P < 0.001$) • Clinical recurrence: no significant difference between groups
	Rasmussen LA, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins with 3 years follow-up. J Vasc Surg Venous Lym Dis 2013;1:349.	580 lower limbs in CEAP $C_{2-4}E_pA_sP_r$ with incompetent GSV and SFJ reflux Group I (n = 142): OS versus Group II : EVLA 980 (n = 17) and 1470 nm (n = 127), bare fiber versus Group III (n = 148): RFA Closure Fast versus Group IV (n = 144): USGFS) 1 or 2 sessions when needed All procedures under local anesthesia, and completed by phlebectomy **Results at 3 years of follow-up:** • *DS examination*: GSV occlusion better in group I, II, III compared with group IV ($P < 0.001$) • *Clinical recurrence*: no significant difference between groups ($P = 0.6596$) *Reoperations* were more frequent in group IV ($P < 0.001$), but were mainly treated by UGFS in all groups • *VCSS* improved in all groups and with no significant difference between groups • *AVVSS* improved significantly in all groups from 3 days and onwards ($P < 0.0001$), with no significant difference between groups at any time point • *SF–36 scores* improved in all domains and in all groups

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
AVVSS, Aberdeen varicose vein severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire; DS, duplex ultrasound; EQ5D, Euro QoL 5D; EVLA, endovenous laser ablation; GSV, great saphenous vein; OS, open surgery (saphenofemoral ligation + stripping, +/– perforator ligation +/– tributary phlebectomy); QoL, quality of life; RFA, radiofrequency ablation; USGFS, ultrasound-guided sclerotherapy; VCSS, venous clinical severity score.

of varices was 95.5%, 94.6%, 91.5% and 88.5%, respectively, at 1, 2, 3 and 4 years.

When reflux in the saphenous trunk extended from its termination to the malleolus preoperatively, the elimination of the ST reflux was less frequent (47.6% vs 70.3%; $P < 0.05$).[32]

CHIVA METHOD

A great number of observational studies have been reported, mostly retrospective by Italian and Catalonian teams. Their analyses are sometimes difficult for other practitioners to understand as a result of the use of the specific CHIVA terminology and the modification of the technique itself. CHIVA protagonists are happy with this method if the preoperative hemodynamic shunt type (CHIVA language) is correctly identified. Two long-term RCTs are available that support its use (see Table 10.7).

INDICATIONS FOR SURGERY

In the absence of long-term follow-up RCTs evaluating the different treatment methods, which includes surgery, only weak recommendations, according to Guyatt,[121] can be

Table 10.11 Open Surgery Versus Endovenous Microwave Ablation

Operative procedure	Reference*	Summary
HL + S + tributary phlebectomy + Pe ligation versus HL + EMA GSV + EMA tributary phlebectomy + EMA Pe ablation	Yang L, Wang XP, Su WJ, et al. Randomized clinical trial of endovenous microwave ablation combined with high ligation versus conventional surgery for varicose veins. Eur J Vasc Endovasc Surg 2013;46:473.	100 patients (108 lower limbs) classified C_{3-6} with GSV reflux below knee and SFJ incompetence. Group I (n = 108 lower limbs): HL + EMA GSV + EMA Trib phleb. + EMA Pe ablation versus Group II (n = 98 lower limbs): HL + S + Trib phleb. + Pe ablation **Postoperative results:** • Skin burns in group I: 10.2% • Less ecchymosis in group I compared with group II (P = 0.004) • Less sensory impairment in group I compared with group II (P = 0.03) **Recurrence of VV at 6 months:** Recurrence in group II (10.2%) > group I (2.8%); P = 0.03 **Recurrence of VV at 2 years:** • Lost to follow-up at 2 years: 8 lower limbs in group I vs 9 lower limbs in group II (P = 0.02) • Recurrence in group II (28.2%) > group I (14.3%); P = 0.02 No difference between groups at any time regarding HRQoL (AVVQ) and severity scores (VCSS)

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
AVVQ, Aberdeen varicose vein questionnaire; EMA, endovenous microwave ablation; GSV, great saphenous vein; HL, high ligation; HRQoL, health-related quality of life; Pe., perforator; S, stripping; SFJ, saphenofemoral junction; Trib phleb., tributary phlebectomy; VCSS, venous clinical severity scoring.

Table 10.12 Open Surgery Versus Cryostripping Versus Radiofrequency Ablation

Operative procedure	Reference*	Summary
RFA versus invagination stripping versus cryostripping	Stötter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping and cryostripping in the treatment of great saphenous vein. Phlebology 2006;21:60.	60 patients and lower limbs with GSV primary VV and reflux at SFJ Group I (n = 20): RFA Group II (n = 20): HL + invagination stripping Group III (n = 20): HL + cryostripping **Postoperative results: Follow-up 1week to 1 year** Immediate success 2 GSV open segments in group III vs 1 in group I and 0 in group II **Results at 6 weeks of follow-up:** • *Pain score, time to return to full activity:* better in group I compared with groups II and III; P = 0.012 and P = 0.014 respectively **Results at 1 year of follow-up:** 1 patient lost to follow-up in each group • *Groin neovascularization:* groups I and II = 0, group III = 1 • *Segmental recanalization* <10 cm: group I = 2, group II and III = 0 • *Patient satisfaction:* group I > group III > group II; P = 0.001 for all groups

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
GSV, great saphenous vein; HL, high ligation; RFA, radiofrequency ablation; SFJ, saphenofemoral junction; VV, varicose veins.

given. Nevertheless, it appears that surgery is presently giving way to minimally invasive procedures such as chemical and thermal ablation. In Europe surgery with preservation of the saphenous trunk (including ASVAL and CHIVA) has some supporters.

INDICATIONS ACCORDING TO ETIOLOGY

Only primary varices will be considered; postthrombotic or congenital varices are a specific problem that will not be developed in this chapter. The systematic use of DUS, including routine investigation of the deep vein combined with other examinations, assists in selecting the correct treatment for VV in postthrombotic syndrome.

INDICATIONS ACCORDING TO THE CLINICAL PRESENTATION

Clinical presentation may sometimes influence the indication.

Table 10.13 Open Surgery With Various Types of Tributary Phlebectomy

Operative procedure	Reference*	Summary
Open surgery with various types of tributary phlebectomy	Aremu M, Mahendran B, Butcher W, et al. Prospective randomized controlled trial: conventional versus powered phlebectomy. J Vasc Surg 2004;39:88.	141 patients and 188 lower extremities VV in GSV territory General anesthesia Group I (n = 100): OS with tributary stab avulsion versus Group II (n = 88): OS with tributary avulsion with Trivex **Results at 2 to 52 weeks of follow-up:** • Fewer incisions in group II (Trivex) compared with group I ($P < 0.0001$) • No difference between groups in terms of operative time ($P = 0.16$) • No difference between groups in terms of patient satisfaction and cosmetic result
	Scavée V, Lesceu O, Theys S, et al. Hook phlebectomy versus transilluminated powered phlebectomy for varicose veins surgery. Early results. Eur J Vasc Endovasc Surg 2003;25:473.	80 patients VV in GSV territory General or spinal anesthesia Group I (n = 40): OS with tributary stab avulsion versus Group II (n = 40):OS with tributary avulsion with Trivex **Results at 6 weeks of follow-up:** Fewer incisions in group II (Trivex) compared with group I ($P < 0.0001$) • More bruising in group II (Trivex) compared with group I ($P = 0.06$) • No difference between groups in terms of postoperative pain, number of complications, residual varices, cosmetic result
	Ray-Chaudury SB, Huq Z, Souter RG, McWhinnie D. A randomized controlled trial comparing transilluminated powered phlebectomy with hook avulsions: an adjunct to day surgery. J One Day Surg 2003;13:24.	98 patients VV in GSV territory Group I: OS with tributary stab avulsion versus Group II: OS with tributary avulsion with Trivex **Postoperative results:** No difference in terms of postoperative pain
	Chetter I C, Mylankal, K J, Hughes H, Fitridge R. Randomized clinical trial comparing multiple stab incision phlebectomy and transilluminated powered phlebectomy for varicose veins. Br J Surg 2006;93:169.	62 patients symptomatic with complicated VV in GSV territory Group I (n = 33): OS with multiple stab incision phlebectomy versus Group II (n = 29): OS with transilluminated powered phlebectomy **Postoperative results:** • No difference in terms of surgery duration • Fewer incisions in group II compared with group I • More skin bruising and pain in group II compared with group I
	Krasznai AG, Sigterman TA, Willems CE, et al. Prospective study of a single treatment strategy for local tumescent anesthesia in Muller phlebectomy. Ann Vasc Surg 2015;29:586.	101 patients C_{3-4}, E_p, A_s, Pr_{2-4} scheduled for ambulatory Muller phlebectomy under LA Group I: anesthetic solution lidocaine 1% + epinephrine in sodium bicarbonate 1.4% versus Group II: anesthetic solution lidocaine 1% + epinephrine in saline 0.9% standard solution **Postoperative results:** • Significantly less pain during injection in group I compared with group II ($P < 0.01$) • No significant difference between groups in terms of preoperative and postoperative pain

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.

GSV, great saphenous vein; LA, local anesthesia; OS, open surgery (high ligation + saphenous stripping +/– perforator ligation +/– tributary phlebectomy); VV, varicose veins.

Table 10.14 Endovenous Laser Ablation Versus Cryostripping

Operative procedure	Reference*	Summary
EVLA versus cryostripping	Disselhoff BC, der Kinderen DJ, Moll FL. Is there a risk for lymphatic complications after endovenous laser treatment versus cryostripping of the great saphenous vein? A prospective study. Phlebology 2008;23:10.	33 patients with incompetent GSV Group I (n = 17): 810 nm diode laser, bare fiber, continuous laser withdrawal versus Group II (n = 16): HL + cryostripping Anesthesia: general (day case procedure) or local (outpatient procedure) **Results at 6 months of follow-up:** One complication in group II (= Lymphedema grade1)
	Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. Br J Surg 2008;95:1232.	120 patients with incompetent GSV Group I (n = 60): 810 nm diode laser, bare fiber, continuous laser withdrawal versus Group II (n = 60): HL+ cryostripping Anesthesia: general (day case procedure) or local (outpatient procedure) **Postoperative results:** • Cryostripping procedure (group II) quicker than EVLA ($P < 0.001$) • Less postoperative pain in group I (EVLA) compared with group II ($P = 0.003$) • Shorter time to return to normal activity in group I (EVLA) compared with group II ($P < 0.001$) **Results at 2 years of follow-up:** • No difference between groups in terms of VV recurrence, HRQoL improvement (AVVSS) or clinical amelioration (VCSS)
	Disselhoff BC, Buskens E, Kelder JC, et al. randomized comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2-year results. Eur J Vasc Endovasc Surg 2009;37:357.	120 patients with incompetent GSV Group I (n = 60): 810 nm diode laser, bare fiber, continuous laser withdrawal versus Group II (n = 60): HL + cryostripping Anesthesia: general (day case procedure) or local (outpatient procedure) **Results at 2 years of follow-up:** • Cryostripping procedure (group II) less expensive (P = 0.234), more cost-effective (P = 0.788) and with a better QALY (P = 0.824) than EVLA

*Abstracts corresponding to references can be found using the listing 'RCTs by alphabetical order' or 'RCTs by topic'.
AVVSS, Aberdeen varicose vein severity score; EVLA, endovenous laser ablation; HL, high ligation; HRQoL, health-related quality of life; QALY, quality adjusted life year; VCSS, venous clinical severity score.

PREGNANCY

In women, pregnancy may influence the treatment selection. It has been established that the REVAS risk after GSV conventional surgery in a woman who has already had a child is higher in subsequent pregnancies.[122] If an operative treatment is decided upon a less invasive procedure may be recommended, such as combining it with chemical or thermal ablation to avoid open surgery at the groin.

ASSOCIATION OF VV WITH ANOTHER DISEASE

Obesity

Given the understanding that postoperative complications are higher in obese people following SFJ surgery, open surgery at the groin is not recommended.

Coronary and Peripheral Arterial Occlusive Disease

The treatment of varicose veins in the presence of peripheral arterial occlusive disease (PAOD) or coronary disease (CD) tends to be conservative particularly because of the potential need for a vein graft. In this situation, if VVs need to be treated then surgery preserving the saphenous trunk is recommended providing the saphenous vein is suitable for use as a replacement conduit. Nevertheless, a vein that cannot be used as a graft should be treated and the practitioner must not forget that the association of severe VVs and PAOD increases the risk of ulcer.

Lymphedema

If operative treatment is needed, chemical and thermal ablation are less dangerous than surgical techniques with the aim being not to damage the lymphatics.

INDICATIONS ACCORDING TO THE CEAP CLASS

In the C_2 class (noncomplicated VVs) there is no argument that favors surgery to other operative treatments. In complicated VVs, particularly in C_6 patients, only RCTs comparing classical surgery to conservative treatment are available,[55,56,58] with the exception of one small series involving treatment with CHIVA.[60] This does not demonstrate that classical surgery provides a better outcome in patients presenting with venous ulcer, because observational studies with thermal and clinical ablation include C_6 patients.[123]

INDICATIONS ACCORDING TO ANATOMIC AND PHYSIOPATHOLOGIC ANOMALY

Reflux at the SFJ and/or at the SPJ

In theory with major reflux at the SFJ or SPJ (particularly when the terminal valve is incompetent and the terminal portion of the saphenous trunk very enlarged), classical surgery is the best option as HL + S are supposed to solve the problems. This recommendation was stated by Cappelli but no data support it.[12] However, patients with an incompetent terminal valve treated with preservation of the SFJ had a good outcome in Pittaluga's series.[14] Furthermore, outcome in patients treated using thermal ablation by RF with preservation of the SFJ was as good as after classical surgery at 5 years.[61,62,124] In any case, SFJ has been examined at a median follow-up of 25 months by DUS, and the most common finding in the groin was an open, competent SFJ with a greater than 5 cm patent terminal GSV segment conducting prograde tributary flow through the SFJ (82%) (Fig. 10.17).[125]

It is believed that neovascularization at the groin is frequent and the major cause of recurrence at the SFJ after HL[13,62,125,126] (Fig. 10.18), whatever the pathophysiology, but this finding is inconclusive; there is no RCT comparing saphenous trunk stripping with and without HL.

COMPETENT SAPHENOUS TRUNK

When the saphenous trunk is competent there is no RCT that indicates a preference for surgery with preservation of the saphenous trunk over surgical, thermal or chemical ablation, but the former seems to be logical.

COMBINATION OF PRIMARY DEEP REFLUX AND PRIMARY VARICES

When primary deep reflux (PDR) is sequential there is a large consensus that considers that it does not modify the indication for VV treatment. Conversely, when PDR is axial and in the presence of severe chronic venous insufficiency (C_{4b}, C_6), particularly with recurrent ulceration, valvuloplasty must be considered in the patient reluctant to wear stockings or noncompliant to compression.[127]

COMBINATION OF PRIMARY DEEP OBSTRUCTION AND PRIMARY VARICES

According to Raju and Neglen primary iliac obstruction is frequently associated with varices in patients with severe venous symptoms or chronic venous insufficiency. When patients show no improvement with complete VV treatment, investigation of the iliac vein is recommended to identify obstruction and possible stenting.[128,129]

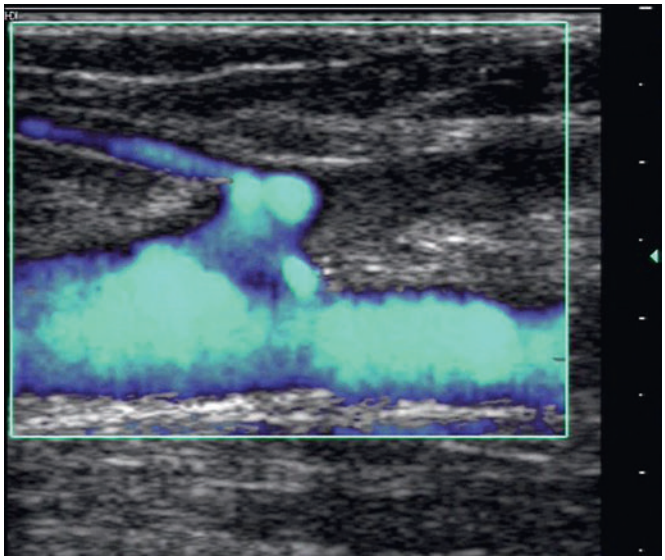

Figure 10.17 Duplex ultrasound. Physiological drainage of the superficial epigastric vein in the stump of the saphenofemoral junction after radiofrequency ablation. (From Perrin M. Traitement chirurgical endovasculaire des varices des membres inférieurs. Techniques et résultats. EMC [Elsevier Masson SAS, Paris], Techniques chirurgicales—Chirurgie vasculaire, 43-161-C, 2007).

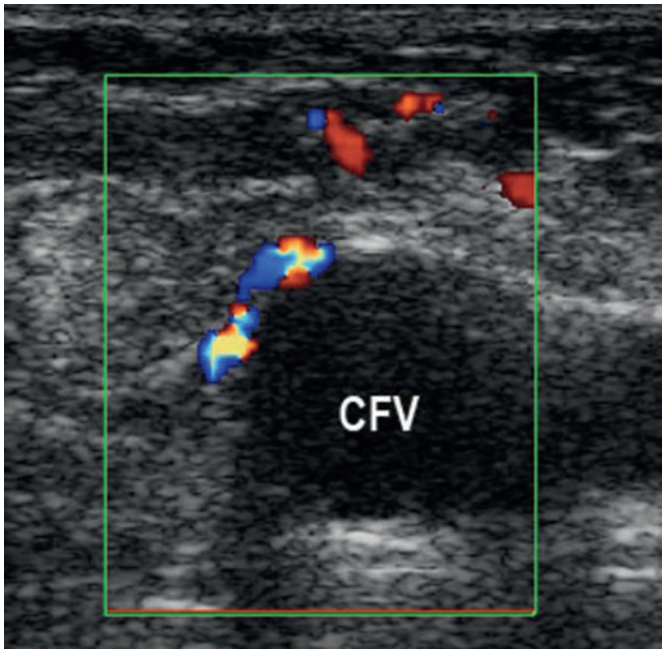

Figure 10.18 Duplex ultrasound. Neovascularization at the previous area of the saphenofemoral junction after high ligation. CFV, Common femoral vein. (Courtesy Dr Gillet.)

INCOMPETENT PERFORATOR AND VARICES

Although perforator incompetence can be treated by surgery this topic will only be mentioned briefly in this chapter. In presence of skin changes and when surgery has been chosen, subfascial endoscopic surgery is preferred to open surgery. Even though perforators can be treated either by chemical or thermal ablation, or by surgery, there is no RCT comparing the outcome of these different techniques.

Nevertheless, there is a consensus that recommends treating VVs first when incompetent perforators are associated with primary venous reflux.

CONCLUSIONS

Long-term follow-up should be able to reveal information on the precise indications for surgery in the era of endovenous ablation and should help determine what the appropriate procedure is for treating VV according to clinical and hemodynamic features. New procedures are introduced frequently, and when results on their usage are reported the techniques are quickly either modified, abandoned or supplanted.

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APPENDIX 10.1

INFORMATION FOR THE PATIENT

Surgery for varicose veins in the legs
Dear Madam, Dear Sir,

You have chronic superficial venous insufficiency (more commonly called varicose veins), which is caused by poor superficial vein function in the legs.

Varicose veins
Blood flows from the heart to the extremities through arteries and returns to the heart through superficial and deep veins. The deep veins provide most of this venous return and are the most important. The walls of superficial veins may become damaged and lose their elasticity. The sick veins become dilated and tortuous. Venous return to the heart is then slowed down, particularly in immobile or seated positions. The blood stagnates in the feet, ankles and legs, leading to edema, unsightly venous dilatations (varicose veins) that may be more or less visible, dilatation of the small vessels (telangectasias), etc.

The exact cause of primary superficial venous insufficiency is not known. In women, it is promoted by pregnancy. Other aggravating factors have been identified: heredity, obesity, sedentary, lifestyle static professional activities, plantar arch disorders (flat feet, arched feet, etc.).

More rarely, superficial venous insufficiency is caused by an abnormality in the deep veins including post-thrombotic syndrome or congenital malformations.

Symptoms and risks of progression
Varicose veins may be associated with symptoms: heaviness and pain in the legs, itching, restlessness, night cramps, feeling of burning and or swelling, etc.

In the absence of appropriate treatment for varicose veins, complications develop insidiously in many patients: pigmentation, eczema, hardening of the skin on the legs (lipodermatosclerosis) or even ulcers. Varicose veins may also cause acute complications:

- hemorrhage (either spontaneous or caused by direct injury);
- superficial venous thrombophlebitis (inflammation and thrombosis of the superficial veins) that may sometimes cause deep vein thrombosis (= clot in a deep vein), the major immediate risk of which is pulmonary embolism (= clot that moves to the lung) with a risk of death depending on the severity

Therapeutic possibilities
Surgery is one of the fundamental treatments for extensive varicose veins. The aim is to remove the "sick" superficial veins or to modify the abnormal flux that perturbs proper functioning of the venous circulation. An ultrasound examination (Doppler ultrasound) is used to determine whether a surgical procedure is necessary and to choose the most appropriate technique for your case.

Other non-surgical treatments exist:
- use of elastic compression which relieves and prevents complications but does not cure;
- drugs for relieving symptoms
- sclerotherapy which involves injecting a sclerosing product into the varix to destroy it.

This last treatment is often necessary in addition to other operative treatment including surgery

Operative procedures
Until the last years, the procedure usually performed was sapheno-femoral/popliteal ligation—in association with saphenous trunk stripping and incompetent tributary phlebectomy

In each limb, there are two veins that are usually responsible for superficial venous insufficiency:
- the great saphenous vein (which runs from the medial surface of the ankle to the fold of the groin. There, it connects with a deep vein the femoral vein. To remove I—the great saphenous vein, an incision must be made in the fold of the groin and another incision (smaller) must be made on the medial surface of the ankle and/or at the garter;
- the small saphenous vein which extends from the lateral surface of the ankle to the calf and hollow of the knee where it connects with a deep vein the the popliteal vein.

To remove it, an incision must be made in the hollow of the knee and in the calf.

The tributaries of these principal superficial veins may also be responsible for varicose veins, which are removed by phlebectomy (micro-incisions in the skin, through which they are removed with a hook).

Other operative techniques less invasive have been developed in the last decades.

These include:
- isolated phlebectomy
- various procedures which principle will be explained by your doctor
- the thermal techniques that ablate the vein by radiofrequency or laser beams using a probe (or catheter) that is inserted into the lower section of the sick vein and that is pushed up to the groin or hollow of the knee.
- sclerotherapy which involves injecting a sclerosing product into the varicose veins to obliterate them

Prevention and treatment
Regardless of the surgical technique used, it is performed in an environment that meets prevailing aseptic and safety norms for all surgical procedures. It requires local and sometimes general anesthesia that must be defined depending on the vein treated, the surgical treatment, the expected duration of the procedure, your age, health and medical history. The anesthesia procedures will be described during the preoperative consultation in the institution where the procedure will be performed. Remember to take with you a list of all medication you take regularly and report possible allergies. The procedure will require short hospitalization ranging from a few hours or ambulatory basis to a few days depending on the severity of the surgery, your age, health and medical history.

Postoperative period
After the procedure, diffuse ecchymosed ("bruises", without consequence) rapidly disappear, as do hematomas (effusion of blood) near the incisions or along the stripping pathway.

The postoperative period is generally without complications and activities can be progressively resumed a few days after the procedure. The duration of sick leave depends on the severity of the operation, on the technique used and the postoperative period. Your physician will specify how long your must wear bandages or compression stockings.

Possible complications
A certain number of complications related to the surgery may occur. You may discuss this with your physician prior to the procedure.

Benign complications
The benign complications are as follows:
- painful hardening (nodules sensitive to the touch) under the incisions or along the pathway of stripping:
- delayed healing of incisions or injections (rare, more common in obese people).
- unsightly or hypertrophic scars (cheloids);
- persistent pigmentation or redness of the skin, appearance of telangectasias (small blue or red dilated venules).

Minor complications
The minor complications are as follows:
- postoperative hemorrhage (very rare) requiring exceptionally repeat surgery. If bleeding occurs near an incision, firmly press the location for at least 5 minutes. If it continues, call your doctor;
- rare superficial venous thrombophlebitis in a triutary not severe, but that requires medical treatment;
- rare effusion of lymph from the scars (lymphorrhea) that disappears;
- transient postoperative edema (swelling) of the ankle and/or foot, that disappears without sequela and is often the result of poorly applied elastic bandages or stockings (wear the prescribed compression properly);
- persistent edema requiring prolonged elastic compression;
- onset or aggravation of lymphedema in predisposed people;
- localized sensory disorders (abnormal feeling on the skin) that may present as dysesthesia (localized reduction or disappearance of sensitivity to the touch, feeling of tingling, pins and needles, that usually disappears within a few weeks) or, in rare cases, hyperasthesia (feeling of burning, electric shock, pain sometimes requiring medication until it subsides).

More severe complications
Rare cases of deep vein thrombosis that may be:
- localised (in the veins in the calf), often without sequela following treatment;
- extensive at the root of the thigh or higher, with a risk of later post-thrombotic syndrome.

In rare cases, this may be complicated by pulmonary embolism (= migration of a clot to the lungs), which is serious and may cause immediate death or later respiratory problems. Deep vein thrombosis mainly occurs in obese people or those with reduced mobility, elderly people, patients with coagulation disorders or personal or family history of deep vein thrombosis, in patients with severe concomitant diseases. In these cases, postoperative prevention may be necessary (injections of heparin). Your physician will do everything in his/her power to avoid this very rare complication, which may also occur if one neglects to treat varicose veins.

Complications during repeat surgery
During operations for recurrent varicose veins, skin complications and healing disorders are most common. Lymphorrhea (effusion of a yellowish fluid, lymph) may appear in the fold of the groin when the great saphenous vein is operated again. The risks of sensory disorders are more common in association with redo procedures in the popliteal fossa (area behind the knee).

Long-term monitoring
Varicose veins are a progressing disease. Therefore, it is crucial that you receive long-term postoperative follow-up (for several years, even for the rest of your life) to prevent recurrences by treating them early.

The aim of this information is not to worry you but to inform you and make you aware that there is no such thing as minor surgery. Not treating varicose veins is not without risk either.

Furthermore, rest assured that the surgery proposed to you is the result of a well-thought-out and substantiated decision based the best benefit/risk ratio for you.

Declaration
Following an appointment with Dr _____, I acknowledge having received clear and detailed information on the planned surgery. I have been informed of the particular risks and possible complications of this procedure.

11

Intravascular Approaches to the Treatment of Varicose Veins: Radiofrequency, Lasers and More

Mitchel P. Goldman, Jean-Jérôme Guex, with contributions by Misha Heller

INTRODUCTION

For nearly a century, open surgical treatment has been considered the gold standard to treat uncomplicated varicose veins. Since the early 1990s, however, techniques have shifted toward minimally invasive approaches.[1] Foremost among these techniques are endovenous thermal ablation using radiofrequency and endovenous laser therapy. Multiple randomized clinical trials have now established the equivalent efficacy of both radiofrequency ablation (RFA) and endovenous laser therapy (EVLA) techniques as compared with conventional open surgery.[2,3] The cost effectiveness and economic impact of these minimally invasive procedures also appear to be comparable,[4] and their associated adverse effects profiles are superior.[5] As a result, many specialized surgical vein centers and dermatologic phlebologists have now adopted these minimally invasive approaches as first line treatment.

Other techniques reported in the literature include ultrasound-guided foam sclerotherapy (UGFS), in addition to less common approaches such as cyanoacrylate glue, mechanochemical ablation (MOCA) and steam ablation. The shift toward minimally invasive approaches is further highlighted by the United Kingdom's National Institute of Health and Care Excellence (NICE) guidelines, published in 2013, advising the use of endovenous treatments with RFA or EVLA, followed by UGFS, ahead of open surgery for the treatment of varicose veins.[6] In the following sections, each of these intravascular approaches to the treatment of varicose veins will be discussed in detail.

OPEN VENOUS SURGERY

Open venous surgery is a highly invasive procedure that involves ligation of the saphenofemoral junction (SFJ), with or without stripping/removal of the great saphenous vein (GSV). Unfortunately, ligation and stripping usually requires general or regional anesthesia, with the patient usually taking a week or more to return to normal activities.

The current debate surrounding the utility of open venous surgery, as compared with minimally invasive endovenous treatments, involves its high rates of postoperative morbidity, cost and vein recurrence. In general it is widely accepted that patients suffer less postoperative discomfort and resume daily activities sooner when undergoing endovenous treatments using RFA or EVLA. Furthermore, these treatments have the added benefit of being performed with tumescent anesthesia, without the need for general or regional anesthesia, which results in cost savings.[1]

The meta-analysis by Murad et al.[7] studied over 8000 patients undergoing all forms of treatment intervention for primary varicose veins including open surgery. The study showed that less invasive treatments were associated with less periprocedural disability and pain. As expected, open surgery was associated with an increase in complications including wound-related infection, hematoma formation and sensory nerve injury.

In addition, open surgery demonstrated a high degree of recurrence of varicose veins, upwards of 50% at 3 to 11 years.[8–14] Specifically, Winterborn et al[8] conducted a randomized trial of 100 patients (133 legs) who underwent SFJ ligation with or without GSV stripping. After an 11-year follow-up, a cumulative total of 83 legs (62%) had developed clinical recurrent varicose veins. There was no statistically significant difference between the ligation only and the ligation plus stripping groups. However, reoperation was required for 20 of the 60 legs that underwent ligation alone, as compared with 7 of the 64 legs that underwent SFJ ligation plus GSV stripping. Stripping of the GSV significantly reduced the risk of reoperation by 60% after 11 years, even though it did not reduce the rate of clinical recurrent varicose veins.[8] Therefore, SFJ ligation plus GSV stripping was recommended as part of routine open varicose vein surgery.

The necessity for SFJ ligation plus GSV stripping led to a demand to develop minimally invasive alternatives resulting in the advent of endovenous techniques using intravascular lasers or radiofrequency devices to thermocoagulate endothelial cells and vein walls, thereby allowing for specific destruction of the targeted vessel without the necessity for ligation or stripping.

RADIOFREQUENCY ABLATION

The first theories of endovenous ablation were based on the belief that specifically directing relatively omnidirectional radiofrequency energy into vein walls to cause their

destruction was potentially safer, easier to engineer and more controllable than other mechanisms for doing so. Initial designs involved a mechanism by which radiofrequency current heated tissue by resistive (or ohmic) heating of a narrow rim (less than 1 mm) of tissue in direct contact with an electrode. Deeper tissue planes could be slowly heated by conduction from the small-volume region of heating, although heat was typically dissipated by conduction into surrounding normothermic tissue.[15] By carefully regulating the degree of heating with microprocessor control, subtle gradations of either controlled collagen contraction or total thermocoagulation of the vein wall could be achieved.

The initial design was such that when the radiofrequency catheter was pulled back, a feedback-controlled loop regulated by readings from a thermocouple enabled the operator to heat a section of vein wall to a specified preset temperature. This produced relative safety because the temperature increase remained localized around the active electrode. This necessitated the maintenance of close, stable contact between the active electrode and the vessel wall without coagulum formation. It was believed by strictly limiting the temperature to 85°C, boiling, vaporization and carbonization of the tissues could be avoided.[16] It was also believed that heating the endothelial wall to 85°C resulted in heating the vein media to no more than 65°C, the minimal temperature at which collagen contracts.

Ex vivo studies by Reich-Schupke et al[17] investigated histological changes following RFA at various powers and application times. When low power (5 W) and an application time up to 400 ohms was applied histological changes were not uniform. Necrosis was limited to the endothelium in the majority of vein segments and rarely reached the media. This would not likely result in complete vein shrinkage and occlusion. At 20 W and an application time up to an impedance of 400 ohms, histological changes included widespread necrosis of the intima and media and collagen bundle coagulation. The authors concluded that with increased power and application time there was a more homogeneous and extensive heating of the vein wall, which was thought to lead to a more successful outcome.

Vessel wall ablation using electrode-mediated radiofrequency is a self-limiting process. As coagulation of tissue occurs there is a marked decrease in impedance that limits heat generation.[18] Alternatively, if a clot builds up on the electrodes, blood is heated instead of tissue and there is a marked rise in impedance (resistance to radiofrequency). The radiofrequency generator can be programmed to rapidly shut down when impedance rises, thus assuring minimal heating of blood, but efficient heating of the vein wall. The problem is that the electrodes must be manually debrided of coagulum, which requires the removal of the catheter, cleaning by the operator and then reinsertion, which is problematic during tumescent anesthesia.

The initial system developed in part by Mitchel Goldman and Robert Weiss, introduced along with electrode-mediated RFA was the Closure system (VNUS Medical Technologies, Sunnyvale, CA, now Covidien, North Haven, CT). With the Closure catheter system bipolar electrodes are deployed by spring action and placed in contact with the vein wall. As the vein wall contracts, the electrodes are able to retract within the vein allowing vein wall narrowing. Selective insulation of the electrodes results in a preferential delivery of the radiofrequency energy to the vein wall and minimal heating of the blood within the vessel.

The initial catheter designs included collapsible catheter electrodes and a central lumen to allow a guidewire and/or fluid delivery structured within the 5-French (1.7-mm) catheter. This permits treatment of veins as small as 2 mm and as large as 8 mm. A larger 8-French catheter allowed treatment of saphenous veins up to 12 mm in diameter. Both catheters had thermocouples on the electrodes embedded in the vein wall, which measured temperature and provided feedback to the radiofrequency generator for temperature stabilization. The control unit displayed power, impedance, temperature and elapsed time so that precise control could be obtained. The unit delivered the minimum power necessary to maintain the desired electrode temperature. For safety, if a coagulum formed on the electrodes, the impedance rises would cut off the radiofrequency generator.

The initial experience dating back to 1998, demonstrated an efficacy equal to or better than that of ligation and stripping with few, if any, adverse sequelae.[19–30] Early experience directly comparing with ligation and stripping procedures, even with RFA performed under general anesthesia, noted equal efficacy with less pain, shorter sick leave and faster return to normal activities.[20]

When performed by us (MPG, RAW), the procedure was entirely under local tumescent anesthesia with over 90% of patients resuming normal activities 1 to 2 days postoperatively. Its main drawbacks were the high cost of single-use catheters, the necessity to withdraw the catheter manually at a speed of 2 to 3 cm per minute and frequent cleaning of coagulum on the electrodes, which made the procedure tedious at times. To speed up the procedure, Goldman[19] recommended that only the most proximal 20 cm of the GSV be treated with RFA and the remaining varicose GSV be treated with ambulatory phlebectomy. Goldman[19] believes that the addition of ambulatory phlebectomy minimizes the possibility of recurrence from distal perforators. Proebstle et al[31] confirmed that up to 30% of tributary veins do not resolve with laser ablation of the GSV alone, thereby necessitating removal with ambulatory phlebectomy.

In addition, treatment of the GSV below the knee may not be entirely necessary, as others have shown that ligation and stripping procedures from the groin to the knee add little to the procedure's efficacy.[22,32] Others have also demonstrated equal effectiveness with less than 2 years follow-up when only the proximal 30 to 40 cm of the GSV was treated without treating distal varicose tributaries.[21–23,30,33,34]

Weiss and Weiss[23] evaluated patients treated with a percutaneous approach allowing access of the Closure catheter to treat the proximal GSV. Patients (mean age, 47.2 ± 12.6 years; 76% female) had symptomatic saphenous reflux with a saphenous vein diameter of 2 to 12 mm (mean, 7.4 mm). Most of the veins treated were above-knee great saphenous (73%), some entire great saphenous (21%), and the remaining included below-knee great saphenous, small saphenous and accessory saphenous. Adjunctive procedures performed at the time of treatment were phlebectomy on more distal branches in 61% and high ligation in 21%, but the adjunctive procedures did not affect outcome.

Vein occlusion at 1 week was documented by duplex ultrasound in 300 out of 308 legs, or a success rate of 97%.

Occlusion persisted at 6 weeks in 95% and at 6 months in 92%. In this report if the saphenous vein was closed at 6 months, it was noted by duplex ultrasound to remain closed to 12 months and beyond. Subsequent follow-up for up to a decade by duplex ultrasound indicates that any vein noted to have been eliminated at 12 months by RFA will not recur. Typically when the GSV is treated, there is closure or elimination of major tributaries at the SFJ except for the superior epigastric vein, which is intentionally not treated and continues to empty superiorly into the common femoral vein. We believe that there is a high margin of safety by maintaining flow through this tributary. The high flow rate appears to diminish the possibility of extension of any thrombus (in the unlikely event that this would occur) from the GSV and has the additional benefit of allowing normal venous flow from the lower abdominal wall into its proper drainage into the common femoral vein. By leaving the superior epigastric vein intact, thrombus in the GSV following this procedure has not been observed.[30]

Long-term efficacy with the RFA has been documented by Merchant et al[35] investigating 1222 limbs (great saphenous, small saphenous and accessory saphenous veins). Occlusion rates (evaluated via duplex ultrasound) of 96.8%, 89.2%, 87.1%, 88.2%, 83.5%, 84.9% and 87.2% were found at 1 week, 6 months, 1 year, 2 years, 3 years, 4 years and 5 years, respectively. Body mass index greater than 25 was associated with an increased incidence of nonocclusion, groin reflux and recanalization. A pullback speed above 3 cm/minute at 85°C was more likely to result in nonocclusion and recanalization. In the study by Vasquez et al,[36] factors associated with improved occlusion rates included increasing age, female sex and volumes greater than 250 mL of tumescent anesthesia. The authors theorized that increased failure rates associated with male sex and younger age are secondary to variations in collagen and inflammation in these populations.

Regarding clinical symptoms, a successful radiofrequency (or laser) endovenous occlusion procedure rapidly reduces patient pain, fatigue and aching, correlating with a reduction in the CEAP (clinical, etiologic, anatomic, pathophysiologic) clinical class for symptoms and clinical severity of venous disease. When patients have had simultaneous surgical stripping on the opposite leg, the degree of pain, tenderness and bruising have been far greater on the leg treated by stripping. Side effects of this technique have included thrombus extension from the proximal GSV in 0.8% (with one case of pulmonary embolus), skin burn (before the tumescent anesthesia technique) in 2.5%, clinical phlebitis at 6 weeks in 5.7% and temporary 1–2 cm sized areas of paresthesia in 18%, with most of these occurring immediately above the knee and resolving within 6 months to a year. Compared with most techniques—but in particular, traditional ligation and stripping of similar size saphenous veins—the effectiveness of endovenous radiofrequency occlusion is quite high.

In a study by Goldman and Amiry,[24] closure of the GSV with endoluminal radiofrequency thermal heating in combination with ambulatory phlebectomy was easily accomplished and efficacious. The first 47 sequential, nonrandomized patients having an incompetent GSV from an incompetent SFJ and painful varicosities in 50 legs were treated with the VNUS Closure procedure. The varicose

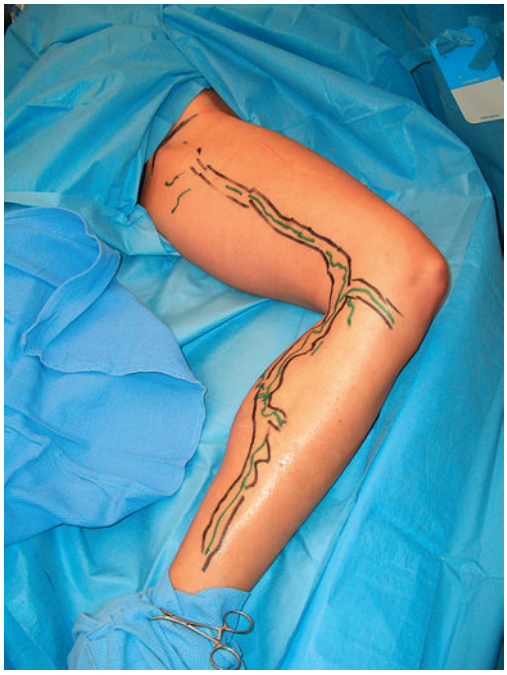


Figure 11.1 Premarkings. Varicose veins were marked with the patient standing and again with the patient lying down in the operative position with a Venoscope (LLC, Lafayette, LA).

veins were marked with the patient standing and again with the patient lying down in the operative position with a Venoscope transilluminator (LLC, Lafayette, LA) (Fig. 11.1).[19,37,38] After appropriate marking, the area surrounding the GSV and distal tributaries to be treated was infiltrated with 0.1% lidocaine tumescent anesthesia. The amount of tumescent fluid averaged 800 mL with a lidocaine dose of 8 mg/kg. The GSV was then accessed through a 2- to 3-mm incision in the medial mid thigh, usually 20 cm inferior to the SFJ. The proximal portion of the GSV was then treated with VNUS Closure and the distal portion, including all varicose tributaries, was removed with a standard ambulatory phlebectomy technique.

Thirty-nine patients with 41 treated legs were available for evaluation at the longest follow-up period. Six patients (9 treated legs) could not be located for re-evaluation after 6 months because of change in location (often out of the state).

The average time to access the GSV in the medial thigh with a phlebectomy hook was 7 minutes (range, 1–30 minutes). Twenty-seven patients had the GSV accessed in less than 1 minute. The average catheter pullback rate was 2.76 cm/minute over an average length of treated GSV of 19 cm (range, 6–42 cm). Complete surgical time, including the phlebectomy portion of the procedure, was approximately 20 minutes (range, 13–35 minutes).

Ninety-five percent of all patients could resume all preoperative activities within 24 hours. The other two patients could resume all activities within 48 hours. Every patient had complete elimination of leg pain and fatigue. Twenty-one of 22 patients who presented with ankle edema had resolution of ankle edema. All patients said that they would recommend this procedure to a friend.

Adverse sequelae were minimal, with four patients complaining of heat distal to the SFJ during the procedure

which resolved with additional tumescent anesthesia. Twenty-eight of 50 treated legs had some degree of purpura lasting 1 to 2 weeks. Five patient legs developed mild erythema over the GSV closure site that lasted 2 to 3 days. Eight legs had an indurated fibrous cord over sites of ambulatory phlebectomy that lasted up to 6 months.

Clinical and duplex evaluation performed by an independent laboratory and/or physician at 6, 9, 12, 18 and 24 months disclosed 90% abolition of reflux. No new varicose veins were noted to appear in three patients with recurrent reflux in the GSV. One patient who developed reflux had the development of new veins at 1 year posttreatment.

Other surgeons have had a different experience with the use of VNUS Closure in the treatment of incompetent GSV. The reason for the difference in results is likely to be secondary to the anesthesia and technique used as described hereafter.

Three separate papers detail a similar cohort of patients treated in multicenter studies encompassing 16 to 31 clinics, 210 to 324 patients and 6 to 12 month follow-up.[21,30,39] The vein occlusion rate at 1 year examination was 91.6% from nine centers and 81.9% from fourteen centers. Forty-nine patients were followed at 2 years with duplex scans and showed an 89.8% closure rate. There was a 3% incidence of paresthesia, which was decreased to 1.6% when treatment was confined to the thigh. Two limbs (0.8%) developed scarring from skin burns and three patients developed a deep vein thrombosis (DVT) with one embolism. The reason for the increase in adverse effects appears to be the use of general anesthesia instead of tumescent anesthesia by a majority of the surgeons.

Sybrandy and Wittens[40] from Rotterdam reported 1-year follow-up of 26 patients treated with VNUS Closure. They reported five patients with postoperative paresthesia of the saphenous nerve and one with a cutaneous burn, for an overall complication rate of 23%. One patient (3.8%) had total recurrence of the GSV. One patient (3.8%) could not be treated because of a technical failure. Eight patients (30.8%) had closure of the GSV, but with persistent reflux of the SFJ. Thirteen patients (50%) had closure of both the GSV and SFJ. Overall 88% of patients had a totally occluded GSV.

One probable reason for the increase in adverse effects was the use of spinal anesthesia instead of the recommended tumescent anesthesia. In addition, they treated all patients from the ankle proximally, which exposed the GSV within the calf to heat from the radiofrequency catheter. The mean operating time was 67 minutes (range, 25–120 minutes).

Another report describes two episodes of DVTs in 29 patients treated with the RFA.[41] Here the surgeons treated the patient with a groin incision and passage of the catheter from the groin downward. The authors do not report the type of anesthesia used or the length of vein treated. It is presumed that patients were not ambulatory and were treated under general anesthesia.

The important information to come out of a review of various treatments of the GSV is that the use of tumescent anesthesia in awake patients who can ambulate immediately after the procedure is important in preventing skin burns and DVTs. Treatment when limited to the GSV segment above the knee is also important in preventing paresthesia to the saphenous nerve.

In our experience using tumescent anesthesia in awake patients, two patients developed focal numbness 4 cm in diameter on the lower medial leg. These resolved within 6 months. Since adopting the principles outlined earlier with tumescent anesthesia and moving the catheter rapidly from any points of sharp pain, no paresthesia has been noted. No skin injury or thrombus has been observed in any of our patients. Unfortunately, with both endoluminal radiofrequency and laser procedures, complications in the form of DVTs, pulmonary embolism or angiogenesis have been reported if patients are not ambulatory after the procedure and/or if tumescent anesthesia is not given.[42–44] Tumescent anesthesia or the placement of large volumes of dilute anesthesia in a perivascular position serves several purposes:

- To protect perivascular tissues from the thermal effects of intravascular energy such as radiofrequency
- To decrease the diameter of the treated vein that allows for better contact of the radiofrequency electrodes or laser fiber tip with the vein wall, and thus secondarily reduce intravascular blood for nonspecific coagulation
- To provide local anesthesia for patients so that they may be awake during the procedure with the ability to report any pain or discomfort and walk off the operating table and around the recovery room

Contrary to the report by Hingorani et al,[42] we have never seen DVTs in any of our patients treated with intravascular laser or radiofrequency. We believe that the reason for our lack of adverse sequelae is the use of tumescent anesthesia in awake patients with immediate ambulation and avoidance of occlusion of the superior epigastric vein. Although we realize treating patients without general anesthesia is not standard practice for general or vascular surgeons,[45] some vascular surgeons who perform tumescent anesthesia on awake patients with immediate ambulation have reported similar results with virtually no DVTs. A DVT was noted in a female patient treated using tumescent anesthesia while awake, but she weighed more than 350 pounds and did not ambulate after the endoluminal radiofrequency procedure.[46,47]

Salles-Cunha et al[43] reported on the development of angiogenesis and fibrotic tissue along the course of the GSV treated with RFA under general anesthesia. Contrary to this report, our experience with tumescent anesthesia is a complete lack of detection of small vessel networks (angiogenesis) by duplex ultrasound. We believe that the reason for our lack in detecting small vessel networks is not from a lack of trying to see them, but from the minimization of inflammation that occurs with tumescent anesthesia placed in the perivascular space during either RFA or EVLA.[48]

We have not performed ligation of the SFJ in any of our over 2000 patients (to date, January 2016) and question the accuracy of the findings of Salles-Cunha et al,[43] who found a decreased incidence of small vessel networks in patients undergoing RFA with SFJ ligation. We suspect that the small number of patients who were treated without ligation (6 out the 13 patients or 46%) as compared with the those who were treated with ligation (13 out of the 93 patients or 14%), produced falsely positive statistical significance. We question if inflammation is the most likely cause for small

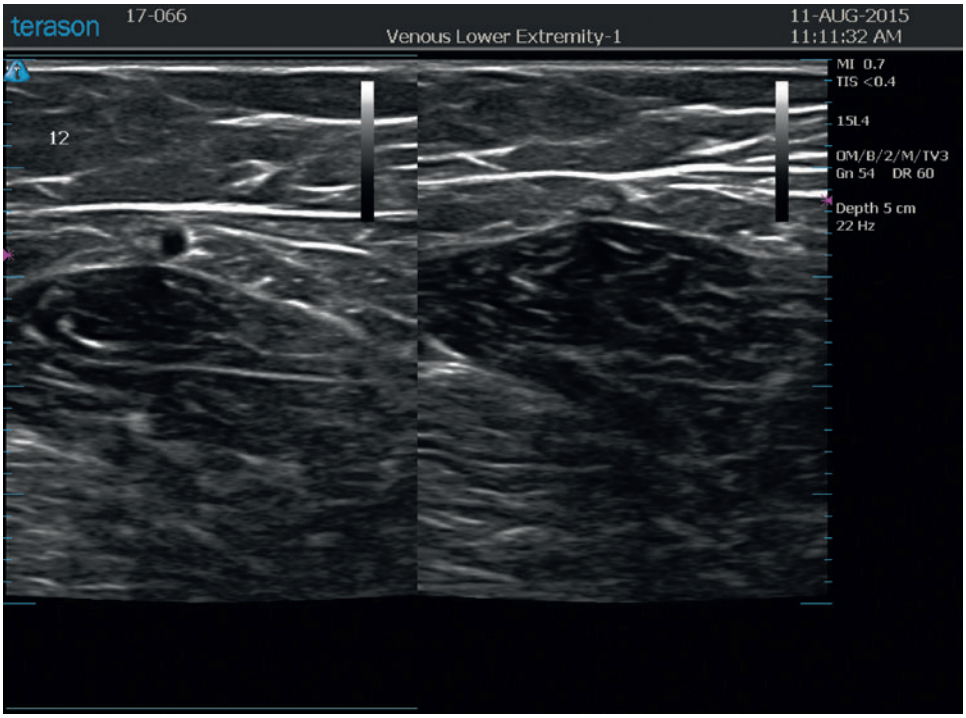


Figure 11.2 Heating element of an endovenous radiofrequency catheter (VNUS ClosureFAST catheter). After heating to 120°C, 7-cm segments of the varicose vein are treated.

vessel networks because ligation should not increase or decrease the extent or time of inflammation.

CLOSUREFAST CATHETER

In 2006 VNUS introduced the ClosureFAST catheter. This new device promised increased efficiency with ablation of incompetent veins of any size. The 7F ClosureFAST catheter allows 7 cm segments of vein to be uniformly heated for 20 seconds at 120°C (Fig. 11.2). The temperature is maintained by a radiofrequency generator through a feedback loop, and vein segments are treated serially[49] with continuous pullback not needed.[50] Although treatment with the Closure system was limited to veins of less than 12 mm, no diameter restrictions are indicated with the ClosureFAST catheter.[49,50] The manufacturer recommends the initial and most proximal 7 cm of GSV to be treated with two consecutive cycles, whereas the remaining vein segments may be treated with a single cycle.

Proebstle et al[49] treated 252 GSVs with ClosureFAST and either adjuvant ambulatory phlebectomy (in 71.6%) or foam sclerotherapy (in 13.9%). Mean treatment time (spanning the time between catheter insertion and removal) was 16.4 ± 8.2 minutes and 6.7 ± 1.7 treatment cycles. The linear endovenous energy density was 116.2 ± 11.6 J/cm for the initial 7 cm of GSV, and 68.2 ± 17.5 J/cm for the subsequent 7 cm. Patients were followed at 3 days, 3 weeks, 3 months and 6 months postprocedure. All patients had successful occlusion of their GSV. Life-table analysis indicated that occlusion rates were 99.6%. Seventy percent of patients experienced no post procedural pain. No DVTs or skin burns were seen. Side effects were infrequent with 3.2% paresthesia, 0.8% phlebitis, 1.6% hematomas, 2% hyperpigmentation and ecchymosis in 6.4%. Mean patient down time was 1.0 ± 1.9 days. Finally 99% of treated patients would recommend the ClosureFAST system to their friends.

Calcagno et al[51] investigated the relationship of size to efficacy in 338 great and small saphenous veins following ClosureFAST treatment. Initial occlusion rates evaluated between 2 to 5 postoperative days were not significant (94% in veins ≤12 mm and 96% in those >12 mm). At 6 months, complete occlusion rates in veins less than or equal to 12 mm or greater than 12 mm were similar (98% and 100%, respectively). Interestingly, veins partially occluded in the immediate postoperative period developed complete occlusion at 6 months follow-up. Diameter did not affect the outcome for successful treatment of incompetent saphenous veins with ClosureFAST.

The Recovery Study by Almeida et al[52] compared 87 GSVs treated with either ClosureFAST or 980-nm diode endovenous laser. This small, short term follow-up study of only 1 month, demonstrated increased incidence of ecchymosis, pain, phlebitis and tenderness in the 980-nm laser group during the initial postoperative 2 weeks. These increased side effects were attributed to microperforations caused by the 98-nm diode. Although quality of life and venous severity scores were more favorable in the initial 2 weeks in the ClosureFAST group, no difference was seen at 1 month follow-up. No comparisons of efficacy were provided in this short-term study.

Long-term studies are necessary to assess prolonged efficacy of the ClosureFAST system. Radiofrequency and 1320-nm Nd:YAG laser both stimulate collagen contraction, have negligible development of thrombi and show decreased incidence of side effects because of a lack of perforations in the vein wall.[53] We feel a randomized blinded trial comparing the efficacy and safety of these two technologies is justified.

COMBINATION WITH AMBULATORY PHLEBECTOMY

Based upon our experience in over 2000 patients, the combination of endovenous ablation techniques with ambulatory phlebectomy can be very effective in eliminating saphenous reflux along with varicose tributaries. The two procedures may even have a synergistic effect as single phlebectomies alone have shown benefit in reducing GSV incompetence.[54] This procedure is not recommend for the small saphenous vein (SSV).

When an incompetent GSV is diagnosed, the patient stands and the locations of all varicose veins are highlighted with a marking pen. The patient then lies down and the exact location and depth of the GSV is confirmed using a duplex scan with the patient lying on the examining table in the operative position. All varicose veins are transilluminated and marked with different colored marking pens.

The leg is then prepped with Techni-Care solution, and sterile drapes are placed allowing exposure of the varicose veins including the SFJ and medial thigh. The table is placed in a 30-degree Trendelenburg position. Tumescent anesthesia is then given through a 21-gauge spinal needle. Intravenous midazolam (2–3 mg) is sometimes given through a heplock to alleviate patient apprehension. Tumescent anesthesia is given along the entire course of the varicose veins, and around the GSV both above the facial sheath and circumferentially around the GSV within its facial sheath. Typically 750 to 1000 mL of tumescent anesthesia is used, and is comprised of 0.1% lidocaine with 1:1,000,000 epinephrine, with an average dose of lidocaine between 5 and 10 mg/kg.

A 2 to 3 mm incision is then made with a number 11 blade scalpel medial to the GSV in the mid-to-distal thigh, typically 20 to 40 cm distal to the SFJ. A No. 3 Muller hook is used to grasp the GSV and bring it through the incision. This 'blind' retrieval of the GSV is usually accomplished in less than 1 minute. Hemostats are placed across the exposed GSV and it is ligated. The proximal portion is then opened with two toothed hemostats. The catheter is then placed into the vein and its tip positioned within 1 to 2 cm of the SFJ. Correct tip placement is confirmed by measuring the length of the catheter with duplex ultrasound. A slow heparin or saline drip is then started and the catheter withdrawn slowly maintaining venous wall temperature at 90°C.

After the entire proximal GSV is treated with endovenous thermal ablation (using RFA or EVLA), the distal stump is ligated with a Vicryl 3-0 suture (Ethicon Inc, Somerville, NJ). The distal GSV and varicose veins are then removed through a series of 2-mm incisions with a standard ambulatory phlebectomy technique.

At the conclusion of the surgery the entire leg is wrapped in a short stretch compression bandage with copious gauze padding over the incision sites from the varicose veins removed through phlebectomy. None of the incisions are closed. The open 2-mm incisions allow for drainage of the anesthetic solution over 24 hours. This helps to minimize swelling and bruising. The patient is seen the next day, the compression bandage is removed and the leg is examined for hematoma formation or other adverse sequela. All incisions are covered with an ointment and a sticking plaster. A class II (30 to 40 mmHg) graduated stocking is applied. The stocking is left on 24 hours a day for 1 week.

Patients may note some bruising over the veins removed with phlebectomy. Anesthesia of the treated portion of the leg may persist for 8 to 24 hours. It is advisable to limit endovenous treatment to the GSV segment above the knee to minimize the risk of paresthesias resulting from injury to the saphenous nerve. The patient is followed up with a duplex ultrasound study at 6 weeks. At that time any open segments can be treated with sclerotherapy. In our experience, when occlusion is seen at 6 weeks, the GSV will remain closed, fibrosed and almost indistinguishable from surrounding tissue at 6 months in all cases. Symptom reduction is rapid, with many patients experiencing relief at 3 days but some not until 6 weeks. Clinical improvement in appearance of varicosities is typically seen within 6 weeks.

The associated complications of endovenous treatment using RFA or EVLA plus ambulatory phlebectomy include bruising and erythema, thermal skin injury with blistering, pigmentation over the treated vein, temporary sensory nerve damage, hematoma formation, localized superficial thrombophlebitis and temporary lymphocele. All other adverse effects are extremely rare.[55]

ENDOVENOUS LASER ABLATION

Use of lasers with this application began with only a slight delay following the development of RFA. Various lasers have proven to effectively close axial veins through thermal damage to endothelium with subsequent thrombosis and resorption of the damaged vein. Endoluminal laser closure is less costly because fiber optics are less expensive than more complex and more engineered radiofrequency fibers. Before the development of ClosureFAST, lasers performed more quickly with the speed of pullback typically 10 to 20 cm/minute for 810- to 980-nm lasers and 6 cm/minute for the 1320-nm laser. By increasing the energy of the 1320-nm laser from 6 W to 10 to 12 W, the pullback rate can be increased to 2 mm/second, which doubles the speed of this endoluminal laser.

EVLA allows delivery of laser energy directly into the blood vessel lumen to produce endothelial and vein wall damage with subsequent fibrosis (Fig. 11.3). It is presumed that destruction of the GSV with laser is a function of thermal damage to the endothelium and/or vessel wall. The presumed target for lasers with wavelengths of 810, 940, 980 and 1064 nm is intravascular red blood cell absorption of laser energy. However, thermal damage with resorption of the GSV has also been seen in veins believed to be "emptied" of blood, although it is virtually impossible to completely eliminate hemoglobin as a chromophore by maneuvers such as leg elevation. Although direct thermal effects on the vein wall probably occur, absorption by blood usually plays a significant role.

Some authors advocate emptying the vein of blood via manual compression, leg elevation and tumescent anesthesia immediately before the procedure.[56,57] The presence of blood has several drawbacks including decreased transmission of laser energy to the vein wall, potential of complete laser energy absorption by blood resulting in thrombosis and recanalization, melting of the laser tip via carbonization and when the laser energy is given continuously and not pulsed, carbonization of the laser fiber tip with excessive

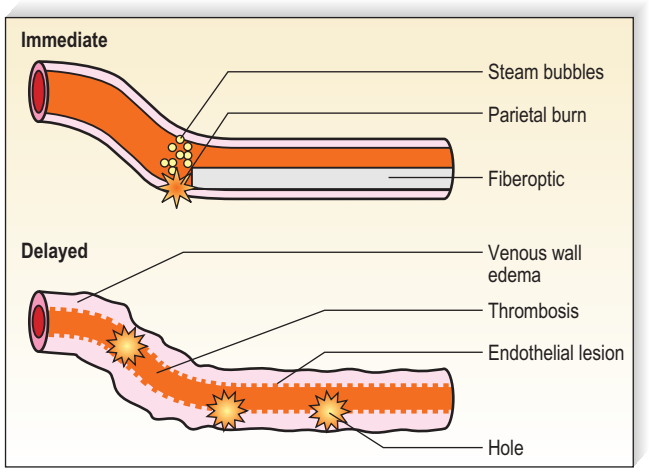


Figure 11.3 Effects of endovenous laser treatment on the venous wall. Application of laser energy in the varicose vein is responsible for various types of venous wall lesions: because of direct absorption (according to wavelength); because of fiber tip heating caused by carbonization; and because of production of steam bubbles (there is always enough H_2O to evaporate even if exsanguination has been realized). They result in a nonspecific inflammatory process (partial internal layers destruction, venous wall edema, followed by late sclerosis) accompanied by specific lesions: holes (maybe related to pulsed mode) and thrombosis.

thermal effects. However, the presence of blood leads to steam bubble production, which may contribute as a secondary mechanism to EVLA efficacy.[56,58]

The extent of thermal injury to tissue is strongly dependent on the amount and duration of heat to which the tissue is exposed. Linear endovenous energy density (LEED) is defined as the total joules delivered divided by total centimeters of treated vein. On the one hand some authors recommend a LEED above 70 J/cm to reduce the incidence of recanalization and recurrence,[59] whereas on the other hand, others have shown no statistical difference in failure rates based on LEED.[60] In addition, because each laser wavelength has a unique effect on the endothelial cells, water content of the blood and/or red blood cells, the total energy of one laser wavelength may not have the same efficacy as another wavelength and cannot be casually compared. Moritz and Henriques[61] investigated the time–temperature response for tissue exposed to up to 70°C. They found that skin can withstand temperature rises for very short exposure times and that the response appears to be logarithmic as the exposure times become shorter. For example, an increase in body temperature to 58°C will produce cell destruction if the exposure is longer than 10 seconds. Tissues, however, can withstand temperatures up to 70°C if the duration of exposure is less than 1 second. Any tissue injury from brief exposure to temperatures less than 50°C would likely be reversible.

One in vitro study model has predicted that thermal gas production by laser heating of blood in a 6-mm tube results in 6 mm of thermal damage.[33,62] These authors used 810-, 940- and 980-nm diode lasers with multiple 15 J, 1-second pulses to treat the GSV. A median of 80 pulses (range, 22–116) were applied along the treated vein every 5 to 7 mm. Histologic examination of excised veins demonstrated thermal damage along the entire treated vein with evidence of perforations at the point of laser application described as 'explosive-like' photodisruption of the vein wall. This produced the homogeneous thrombotic occlusion of the vessel. This effect occurred only with blood-filled veins, not with saline-filled veins, attesting to the absorption of laser energy by hemoglobin (Hb) and HbO_2 at these wavelengths. Because a 940-nm laser beam can only penetrate 0.3 mm in blood,[63] the formation of steam bubbles may contribute to the mechanism of action. Multiple in vitro and animal models were performed to delineate the mechanism of action for vein closure. A consecutive series of events occur in endovenous ablation:

1. Laser energy absorption by blood
2. Coagulum formation at the fiber tip
3. Steam bubble formation and integration into the coagulum
4. Carbonization of the laser tip

Carbonization seen histologically on the vein wall indicates a direct contact with the laser fiber. This interaction leads to fibrosis and is believed by some to be the primary mechanism of vein wall closure. Thrombus formation results from steam bubble production at the laser tip[58,64] and is thought to contribute to vein closure. However, the volume of steam produced in EVLA is not enough to result in significant collagen damage. Of note in the experiments of Disselhoff et al,[58] continuous mode resulted in more carbonization, steam bubble formation and higher and more persistent endovenous temperatures than was found with an intermittent (pulsed) mode. It is interesting to note that Der Kinderen[65] found no histological differences were seen between veins treated with continuous or intermittent modes.

Another possibility for the mechanism of action of EVLA is similar to that of RFA closure–collagen contraction. Collagen has been noted to contract at about 50°C, whereas necrosis occurs at between 70°C and 100°C.[66] Whether collagen contraction, thermal damage or a combination of the two effects is responsible for destruction and resorption of the GSV is unknown and remains controversial.

A meta-analysis by van den Bos and colleagues[67] compared occlusion rates following EVLA (all wavelengths included), RFA, UGFS and high ligation with stripping from 64 studies and 12,320 limbs. At 3 years, success rates were 94.5% for laser ablation, 84.2% for RFA, 77.4% for UGFS and 77.8% for high ligation with stripping. After 5 years treatment success was seen in 95.4%, 79.9%, 73.5% and 75.7% for laser ablation, RFA, UGFS and high ligation and stripping, respectively. The authors found efficacy for high ligation and stripping, RFA and UGFS were equal, but EVLA was more effective than the other three regimens. The incidence of DVTs were less than 1% in both the radiofrequency and laser ablation, and less than 2% in conventional surgery. Risk factors for the development of DVTs following EVLA include general or epidural anesthesia, presence of a coagulation disorder or incorrect placement of the laser fiber tip.[68]

Ultimately the mechanism of action in EVLA is dependent on the wavelength of laser used (Table 11.1). The wavelengths that primarily target tissue water (such as, the 1320-nm Nd:YAG laser) have proven to be superior to those

Table 11.1 Endovenous Laser Ablation (EVLA) Mechanism of Action The mechanism of action of EVLA is dependent on the wavelength of laser and the subsequent selective target.

Wavelength (nm)	Target	Mechanism of Action
810–1064	Hemoglobin	Heating of blood causes thermal destruction and contraction of the vein wall.
1320, 1440, 1550	Water	Direct targeting of tissue water results in a more controlled uniform heating of the vein wall. The presence of red blood cells within the vessel not required.

that primarily target Hb (810–1064 nm),[69,70] as described subsequently.

810-nm DIODE LASER

Initial reports have shown that the technique with an 810-nm diode laser has excellent short-term efficacy in the treatment of the incompetent GSV, with 96% or higher occlusion at 9 months and less than a 2% incidence of transient paresthesia.[71–77] Two year success rates ranged from 93% to 100%.[59,74,76] Although most patients experience some degree of postoperative ecchymosis and discomfort, major side effects are rare. The lack of significant heating of perivenous tissues probably explains the low complication rate found and argues well for the continued lack of significant complications.

Our patients treated with EVLA with an 810-nm diode laser have shown an increase in posttreatment purpura and tenderness when compared with those treated with RFA. Most of our patients do not return to complete functional normality for 2 to 3 days, as opposed to the 1 day 'downtime' with RFA of the GSV. Because the anesthetic and access techniques for the two procedures are identical, we believe that nonspecific perivascular thermal damage is the probable cause for this increased tenderness. In addition, recent studies suggest that pulsed 810-nm diode laser treatment with its increased risk for perforation of the vein, as opposed to continuous treatment, which does not have intermittent vein perforations, may be responsible for the increase in symptoms with EVLA versus RFA (Fig. 11.4).

As mentioned earlier, DVTs occur in less than 1% of patients following EVLA.[67] Kabnick[78] classified the development of 'endovenous heat-induced thrombosis (EHIT) at the superficial-deep-venous junction' as follows:

Class 1: thrombus in close proximity to the junction
Class 2: thrombus extending past the junction occluding less than 50% of the vein
Class 3: thrombus extending past the junction occluding more than 50% of the vein
Class 4: completely occluded deep venous thrombosis

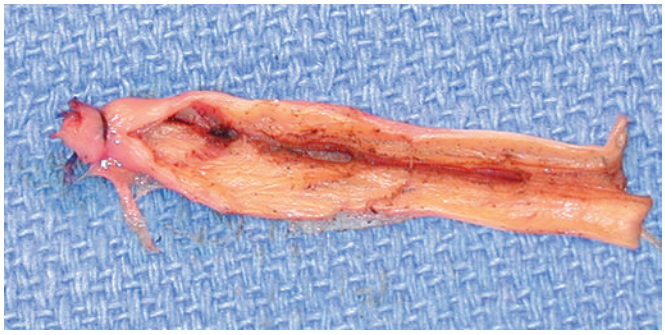


Figure 11.4 Vein perforation with an 810-nm diode intravascular laser.

Isolated cases of pulmonary emboli have been reported in 810-nm, 940-nm, 980-nm and 1320-nm endovenous lasers.[6,68,74,78–81] Seromas and hematomas occur infrequently.[80,82,83] Other rare events include the development of arteriovenous fistulas,[84] which can form from thromboses via inflammation and neovascularization.[85] The area most at risk for arteriovenous fistula development is the popliteal fossa, as the SSV lies in close proximity to the superficial sural artery.[68] Tumescent anesthesia was not used in this patient. The authors proposed the use of tumescent anesthesia to aid in the separation of the veins from nearby arteries with a resultant decreased incidence of arteriovenous fistulas.[84] Septic thrombophlebitis from *Staphylococcus aureus* has been described after EVLA; in that case, the patient made a full recovery following extensive debridement and intravenous antibiotics.[86] Infection is not specific for EVLA, but can occur from any venous surgical procedure. Retained guidewires have been described following EVLA, resulting in dyspnea and chest pain. Guidewires more than twice the length of the sheath are recommended to decrease the chance of this complication when percutaneous access is used. Finally, secondary to improper surgical technique, an endovenous catheter sheath fragment was found in a patient's heart septum resulting in arrhythmias.[68] If the laser fiber tip fails to project outside of the protective sheath that is used to guide the optical fiber, the fiber can melt the plastic sheath and release a fragment into the systemic circulation with devastating consequences.[68,87]

Continuous pullback speed of a fiberoptic is faster than electrode-based radiofrequency ClosureFAST pullback, and may be simplified by the technique described by Guex[88] using a cutaneous centimetric scale and an external electronic metronome when it is not included in the laser generator software. Power and speed are easily calculated from Table 11.2.[33,89,90] Corcos[90] developed a manual technique of pulling the fiber back and forth within the vein in an attempt to limit vein wall perforation. Even with his expert technique in judging by feel when the vein has been sufficiently damaged to stop the back and forth movement, Corcos[90] still found perforation in 2 of 24 treated veins and full-thickness injury in 22 of 24 veins. In our experience, trying to vary the fluence and treating with a continuous laser pullback versus pulsed pullback has not resulted in an elimination of vein perforation.[66]

Although most studies report 1 to 2 years of follow-up, we have been seeing patients back in follow-up now 15 years

Table 11.2 Examples of Pullback Speeds According to Mode, Applied Power and Desired Energy

	Generator Setting			
Desired Energy	**Pulsed Mode 12 W, 1 s, Pause 1 s**	**Pulsed Mode 15 W, 1 s, Pause 1 s**	**Continuous Mode 12 W**	**Continuous Mode 15 W**
48–50 J/cm	4 impacts/cm or 8 s/cm or 7.5 cm/min	3 impacts/cm or 6 s/cm or 10 cm/min	4 s/cm or 15 cm/min	3 s/cm or 20 cm/min
60 J/cm	5 impacts/cm or 10 s/cm or 6 cm/min	4 impacts/cm or 8 s/cm or 7.5 cm/min	5 s/cm or 12 cm/min	4 s/cm or 15 cm/min

Adapted from Guex JJ. Phlebologie 2004;57:209.

after the procedure with recurrent or new GSV. Sadick et al[91] reported a 4 year follow-up evaluation of 94 limbs treated with the 810-nm diode laser (continuous mode, 14 W, 1–2 mm/second pullback) combined with ambulatory phlebectomy. The overall recurrence rate was 4.3%, with the majority of recurrences within the first 6 months. Our impression is that patients undergoing 810-nm diode laser treatment with continuous pullback at 12 W, including ambulatory phlebectomy of distal veins, have a far higher recurrence rate than those treated with RFA at similar follow-up times. Our estimate is a 20% recurrence rate with 810-nm diode laser versus a 10% recurrence rate with RFA.

940-nm DIODE LASER

A longer wavelength such as 940 nm has been hypothesized to penetrate deeper into the vein wall with resulting increased efficacy. This is a false assumption because penetration is not the result of the length of the wave in nanometers, but is a result of the intensity of absorption by water and can be predicted based on water absorption data.

A report of 280 patients with 350 treated limbs with 18 month follow-up demonstrated complete closure in 96%.[92] Twenty vein segments were examined histologically. When veins were treated with 1 second duration pulses at 12 J, perforations were not present. When the fluence was increased to 15 J with 1.2- and 1.3-second pulses, microperforations did occur but were said to be self-sealing. The author suggests that his use of tumescent anesthesia and the laser parameters mentioned earlier are responsible for the lack of significant perforations and enhanced efficacy.

An additional study of 109 treated GSVs followed for 12 months with duplex scanning demonstrated a 10% recurrence rate.[31] Another 5% exhibited incomplete proximal recanalization over 12 months. A 3 to 12 month evaluation of 33 patients who had an incompetent small saphenous vein showed no recanalization.[93] An analysis of the 10% of nonoccluded/closed veins suggested that low laser fluences were the primary reason for recanalization.[94] Proebstle et al[95] investigated the 940-nm diode laser (continuous mode) at two settings—15 W (5 mm/second pullback) and 30 W (3–4 mm/second)—in 263 GSVs. At 12 months, occlusion rates were 82.7% and 97% in the 15 W and 30 W groups, respectively. No difference in side effects was found between the two cohorts.

980-nm DIODE LASER

A 980-nm laser has also been used to treat the GSV.[80,96–98] Complete closure without adverse effects was seen in the 20 and 15 patients with 1 and 3 month follow-up, respectively. The authors' experience with the 980-nm laser is similar to their experience with the 810- and 940-nm lasers. They speculate that the 980-nm wavelength would allow increased penetration into the vein wall with better results. However, no major differences between 810-, 940- and 980-nm lasers were found in an in vitro study.[62]

A comparison study in 60 limbs randomized to receive either 810-nm or 980-nm endoluminal laser treatment of the GSV revealed minimal differences between the two lasers immediately after the procedure and at 12-month follow-up.[97] A short-term success rate of 97% was shown in a multicenter study of 1703 limbs treated with the 980-nm diode laser.[80] A 97.1% occlusion rate at 4 year follow-up was reported in 511 GSVs (continuous mode, pullback 3 mm/second, 10 W).[98]

1064-nm ND:YAG LASER

Three published studies have evaluated a 1064-nm Nd:YAG endoluminal laser.[99–101] In one study,[100] the lateral saphenous goat vein was used. Occlusion was more likely when fluence exceeded 84 J/cm^2. More importantly, treated vessels were not perforated even with a fluence of 224 J/cm^2. A diffusing fiber was also used to obtain circumferential damage.

The article by Chang and Chua[99] reported a clinical study using an endoluminal 1064-nm Nd:YAG laser in the treatment of incompetent GSVs in 151 men and women with 252 treated limbs. Unfortunately, the surgeons also ligated the SFJ, which did not allow for a determination of the efficacy of SFJ ablation. Spinal anesthesia was used. Laser power was set at 10 or 15 W, delivered with a pulse duration of 10 seconds, with manual retraction of the laser fiber at a rate of 10 seconds/cm. Skin overlying the treated vein was cooled with cold water. Unfortunately, this treatment resulted in superficial burns in 4.8% of patients, paresthesia in 36.5%, superficial phlebitis in 1.6% and localized hematomas in 0.8%. This wavelength has not gained wide acceptance because of the high complication rate. This can be predicted by relatively poor absorption of water, leading to greater penetration and nonspecific heating.[99]

1320-nm ND:YAG LASER

In an attempt to heat vein walls more directly by heating water in the vein walls (and to reduce the risks of superheating of Hb and subsequent thrombus formation), Goldman and Weiss helped develop and patented a 1320-nm endoluminal laser. At this wavelength, tissue water is the target and the presence or absence of red blood cells within the vessels has relatively little effect. An important element was the inclusion of a mechanical catheter drawback system and a radial delivery of energy to provide more uniform and predictable heating of the vessel. Studies in porcine GSV demonstrated full-thickness thermal damage at 5 W with the 1320-nm laser and at 20 W with the 1064-nm laser.[101] In a mathematical model comparing the 1320-nm and 980-nm lasers, the 1320-nm laser had increased venous wall absorption and produced vein wall damage at a lower energy.[102]

Clinical studies have demonstrated close to 100% efficacy without evidence of vessel perforation with use of the 1320-nm Nd:YAG intravascular laser in 24 patients with 6- to 12-month follow-up (Fig. 11.5).[69] We investigated the 1320-nm laser in 64 patients at 5 to 6 W with pullback of 1 mm/second. Follow-up extended up to 5 years, with a mean follow-up of 25.3 months. A 7.8% failure rate was found.[103] Clinical results in addition to postoperative adverse sequelae were identical to those seen with VNUS Closure treatment (Fig. 11.6).

Weiss et al[104] have compared 36 GSVs treated with the 810-nm diode laser to 42 GSVs treated with the 1320-nm Nd:YAG laser and 174 GSVs treated with radiofrequency closure. They found a 95% success rate with both radiofrequency and 1320-nm endoluminal treatment without adverse effects. In contrast, the 810-nm diode laser achieved an 86% success rate, with 52% of patients experiencing significant pain interfering with walking for 2 to 3 days, and 99% with significant bruising covering 75% or greater of the treated area.[104]

Proebstle et al[105] evaluated 282 limbs treated with 1320-nm Nd:YAG (continuous mode, pullback 1 mm/second, 8 W), 940-nm diode (continuous mode, pullback 4–5 mm/second, 15 W) and 940-nm diode (continuous mode, pullback 3 mm/second, 30 W). Success rates at 3 months were 97%, 90.3% and 100%, respectively. No statistical differences in phlebitis or paresthesia were noted between the three groups, but the 1320-nm group had significantly less pain. The 1320-nm laser resulted in lower incidences of ecchymosis than the 940-nm diode at 30 W.[105]

1470-nm DIODE LASER

With the concept of targeting water without targeting Hb, additional wavelengths targeting tissue water are in the

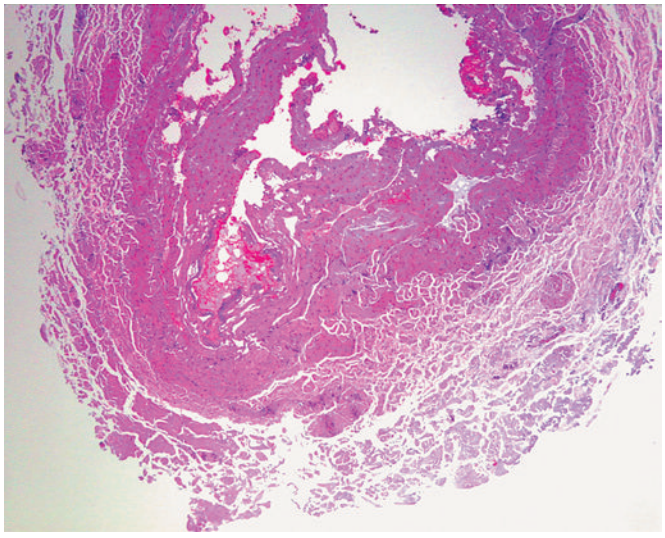


Figure 11.5 Full-thickness thermal damage affecting endothelium, smooth muscle and adventitia 1.3 to 1.5 mm after endoluminal laser treatment with a 1320-nm laser at 5 W, with continuous pullback at a rate of 1 mm/s.

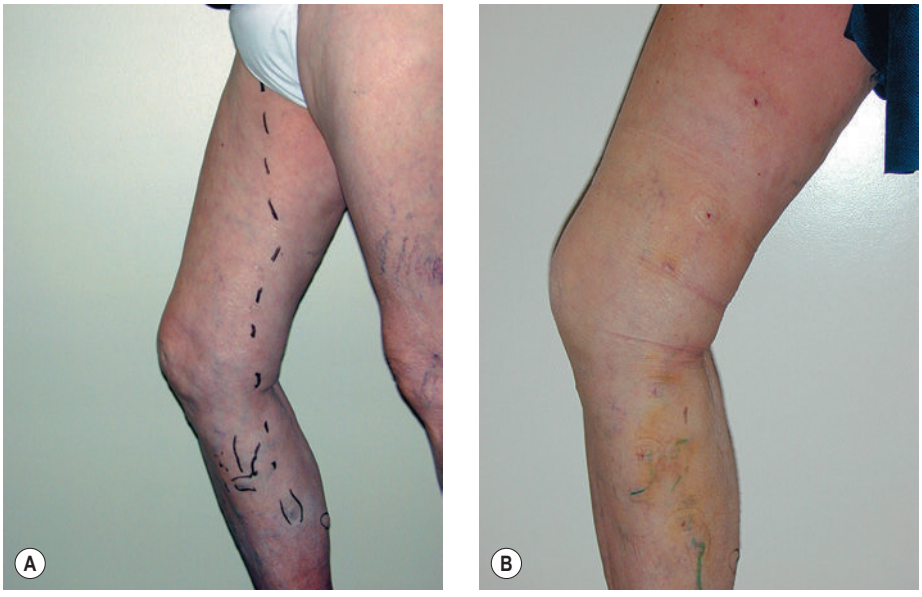


Figure 11.6 **A,** Before; **B,** 1 week after 1320-nm Nd:YAG laser treatment with ambulatory phlebectomy. Note there is no bruising over the proximal great saphenous vein, only over the veins treated with ambulatory phlebectomy.

process of being introduced for endovenous ablation. Successful implementation of the 1320-nm laser by us resulted in fewer adverse events and high efficacy rates, and so it was predictable that other available wavelengths that avoid Hb but heat water would be tried. Most recently, in 2009 a 1470-nm diode laser was tested as this wavelength has a high affinity for water. Because this wavelength is rapidly absorbed by the water content of blood and uses a fiber tip with a spacer instead of the traditional bare tip fiber, a significant compression of the vein is required along with copious tumescent anesthesia for fiber and vein wall contact.[106]

In a study by Pannier,[107] 117 limbs were treated with the 1470-nm diode (continuous mode, 15 W) and a LEED of either greater than or less than 100 J/cm. Both groups maintained 100% occlusion at 1 year follow-up. All patients were prophylactically treated with 7 days of low molecular weight heparin. No DVTs or pulmonary emboli occurred. Paresthesia occurred in 9.3%, with an increased incidence noted in the patients treated with a LEED of over 100 J/cm. As the two groups displayed similar efficacy, the authors recommend that a LEED of less than 100 J/cm be used to decrease the risk of side effects. One hundred and six GSVs were randomized to receive either 1470-nm or 980-nm, both at 15 W with adjuvant ambulatory phlebectomy. Significantly less pain, ecchymosis, induration, transient paresthesia and time to return to daily activities were seen in the 1470-nm laser cohort.[108]

1500-nm DIODE LASER

The 1500-nm diode laser is another recent advancement in endovenous laser ablation technology. Similar to the 1470-nm diode laser, the 1500-nm diode targets water in the vein wall. Compared with the 980-nm laser, the 1500-nm diode laser showed more uniform destruction of the vein wall in an animal model.[109]

Vuylsteke et al[110] treated 158 GSVs with a 1500-nm diode laser (6 W above the knee and 5 W below the knee using continuous mode and a pullback rate of 1 mm/second). The average LEED was 53.4%. An occlusion rate of 93.3% was found at 6 months follow-up. Ecchymosis was mild in 31.6% of patients, moderate to severe in 19% and undetectable in 49.4% of patients. Moderate pain was detected in 1% of patients and no paresthesia was encountered. The authors suspect the decreased incidence of the adverse events was the result of the absence of perforation in the vein wall. A further comparison was made with their previous study investigating the 980-nm diode (10 W) laser occlusion and adverse event rates. Though the efficacy rates were equivalent, side effects such as ecchymosis, induration, discomfort and paresthesia were statistically less with the 1500-nm diode.[110]

ENDOVENOUS LASER TREATMENT OF THE SMALL SAPHENOUS VEIN

Varicose veins are associated with an incompetent SSV in one-fifth of patients. The SSV course lies in close proximity to the sural nerve. As a result, increased incidences of paresthesia have been noted following EVLA of the SSV. Endovenous laser ablation using the 980-nm diode (accessed by micropuncture technique, continuous mode, 10–14 W, pullback 3–5 mm/second) for SSV was investigated by Gibson et al.[111] Ninety-four percent of patients had at least one adjuvant treatment at the time of EVLA (e.g., foam sclerotherapy, microphlebectomy, ligation of perforators or EVLA of the GSV). Of the 210 small saphenous veins treated via tumescent anesthesia, 100% were occluded at 1 week. Three months posttreatment, 96% of SSV remained occluded. Nonocclusive DVTs extending into the popliteal vein were found in 5.7% of patients at 1 week postoperative. Numbness developed in 1.6%.[111]

A study by Park et al[112] explored the 980-nm diode laser (assessed percutaneously, pulsed mode, 12–15 W, 2 mm/second pullback) in treating 390 incompetent SSVs. All patients were treated using 70 to 220 mL of tumescent anesthesia. One-third of patients had concomitant EVLA of their GSV. High closure rates of the SSV were reported, with 99.7% at 1 week postoperative and 99.4% at 1 year. The majority of patients experienced ecchymosis and skin tightness, which resolved in 2 weeks. Other side effects were infrequent, with 2.3% phlebitis and 2% paresthesia. No skin burns or DVTs developed.[112]

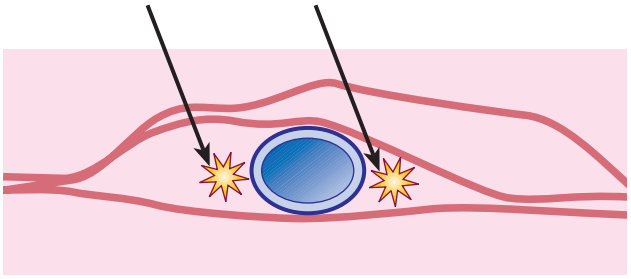
Jung et al[113] used the 810-nm diode laser to treat 41 SSVs (continuous mode, 8–10 W, pullback 2–3 mm/second) and 135 GSVs (continuous mode, 12–14 W, pullback 1.5–2 mm/second) under tumescent anesthesia. Spinal anesthesia was added if phlebectomy was simultaneously performed. Recanalization was found in 7.3% of the 41 SSVs at the 3 month postoperative follow-up. One case of foot drop was reported following endovenous laser ablation of the SSV and ambulatory phlebectomy. Following surgery, intramuscular hemorrhage resulted in muscular edema and pressure on compression of the peroneal nerve. The patient recovered following 2 months of physical therapy.[113]

TECHNIQUE FOR ENDOLUMINAL LASER ABLATION USING A STANDARD SHARP FIBEROPTIC

Varicose veins are marked with the patient standing and again with the patient lying down in the operative position with a Venoscope transilluminator.[37,38] After appropriate marking, the area surrounding the GSV and distal tributaries to be treated are infiltrated with lidocaine 0.1% tumescent anesthesia. The amount of tumescent fluid averages 800 mL with a lidocaine dose of approximately 8 mg/kg. An alternative is semitumescent anesthesia with a cocktail of 20 mL lidocaine with epinephrine plus 20 mL normal saline plus 10 mL sodium bicarbonate injected in the saphenous fascia under ultrasound guidance (Fig. 11.7). The GSV is then accessed either under duplex guidance according to Seldinger technique at any level or through a 2- to 3-mm incision (Fig. 11.8).

A 500- to 600-μm laser fiber is inserted into the vein within a protective sheath so that only the distal 2 to 3 mm of laser fiber exits from the sheath (Fig. 11.9). A helium–neon (HeNe) aiming beam that is continuously illuminated when the laser is on ensures that the laser fiber is outside of the sheath. If the laser fiber retracts within the sheath, thermal destruction of the sheath occurs.

Correct placement of the laser fiber tip 2 cm distal to the SFJ (Fig. 11.10) is confirmed through catheter length measurement, duplex examination and viewing the HeNe



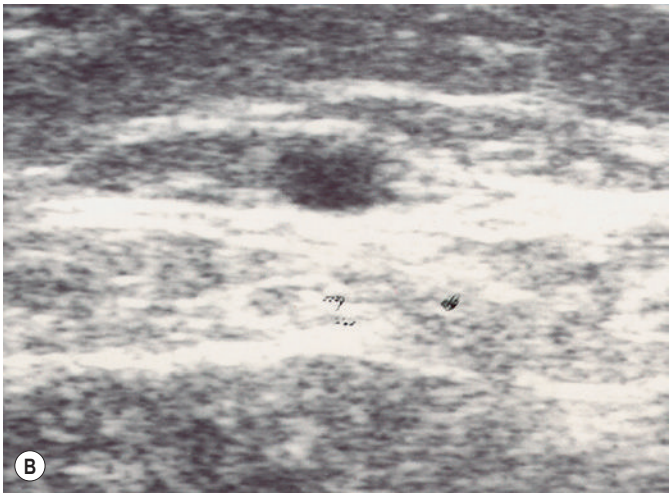


Figure 11.7 Points of injection for ultrasound-guided semitumescent local anesthesia.

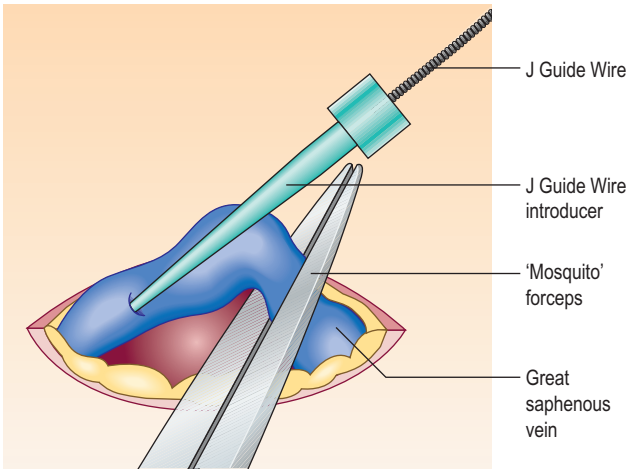


Figure 11.8 Introduction of J Guide Wire through phlebotomy when echo-guided access is not possible.

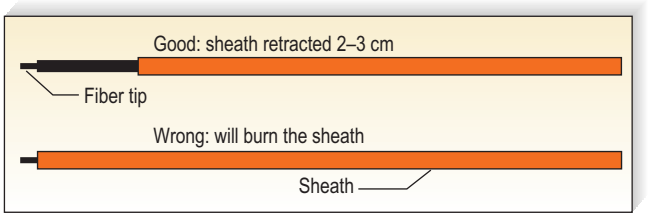


Figure 11.9 Fiberoptic/sheath relative positions to avoid burning of sheath.

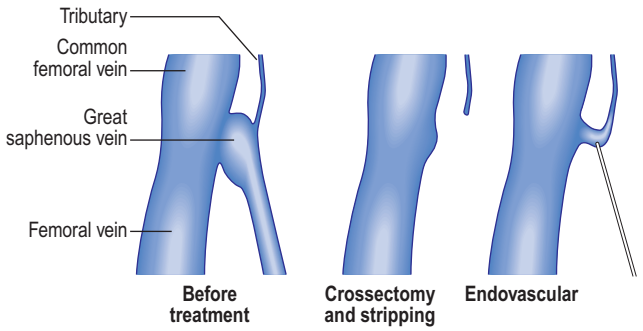


Figure 11.10 New therapeutic goals of endovenous treatments. Current endovenous treatments do not require junctional suppression; conversely, conservation of the junction provides drainage for tributaries (descending tributaries from abdominal and groin skin) limiting the trend for recurrence.

aiming beam through the skin (Fig. 11.11). The laser is in a continuous firing mode at a manufacturer recommended energy setting, which is wavelength dependent, with either slow mechanical withdrawal at a rate to approximate 1 mm/second or, in the case of the 1320-nm system, a continuous pullback mechanism set for 1 mm/second (Fig. 11.12).

Endovenous laser therapy is stopped when the distal tip of the fiber reaches a point 1 to 3 cm from the vein entry site. This can also be confirmed with direct visualization of the aiming beam through the skin or more typically by duplex ultrasonography. Total laser application time is then recorded. Repeat duplex ultrasonography of the saphenous vein is performed to confirm successful treatment. After the terminal portion of the vein (immediately adjacent to the point of entry) has been thermocoagulated, if the vein is accessed through phlebectomy, it is tied with a Vicryl 3-0 suture. If clinically indicated, ambulatory phlebectomy and/or sclerotherapy of tributaries are then performed.

The treated leg is then wrapped in gauze to absorb the tumescent fluid with an overlying compression bandage. When the patient returns the next day the bandage is changed to a class II (30 to 40 mmHg) graduated compression stocking. The compression stocking is then worn for 7 days continuously and while the patient is ambulatory for another 7 days.

Patients are evaluated 1 day, 7 days and 3 weeks postoperatively to determine treatment efficacy. Some authors propose retreating the patient if there is recurrent reflux in the GSV. We have not found this to be necessary in our patients as most recanalization can be treated by foam sclerotherapy.

ULTRASOUND GUIDED FOAM SCLEROTHERAPY

Endovenous thermal ablation techniques, namely RFA and EVLA, have revolutionized the way varicose veins are treated. These minimally invasive approaches are associated with earlier return to daily activity and less pain. However, they are known to cause adverse effects and involve infiltration of tumescent anesthesia, which can cause discomfort. Nonthermal, nontumescent techniques are thought to be

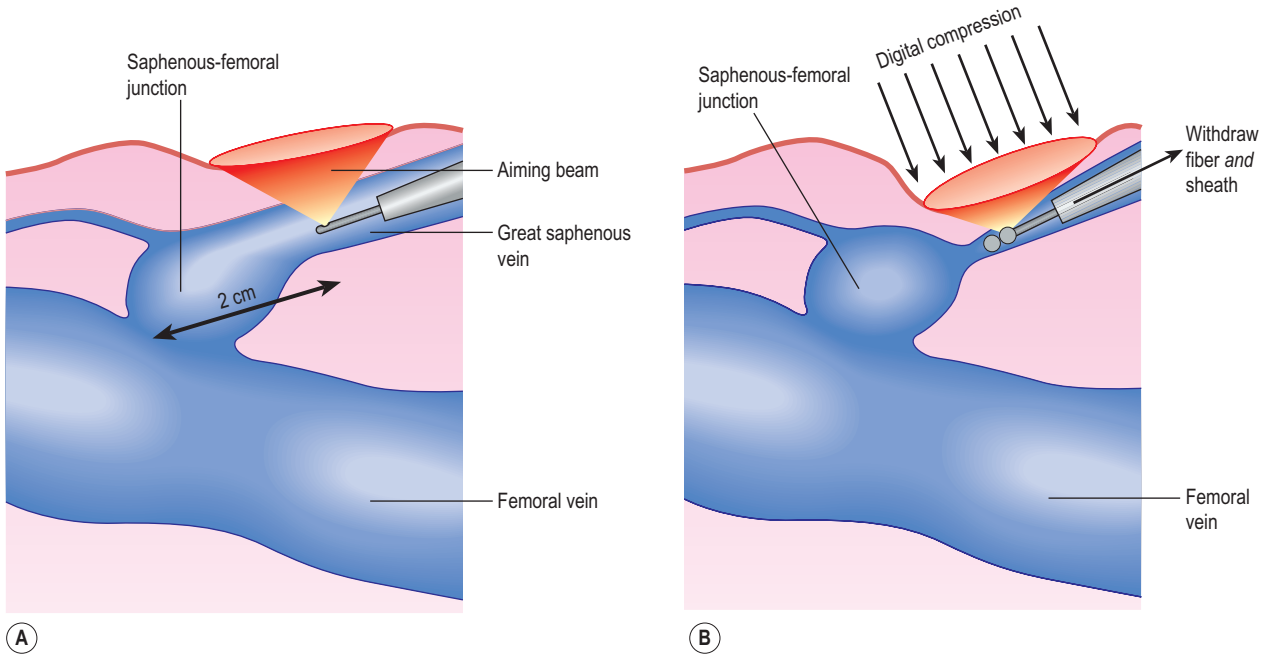


Figure 11.11 **A,** Fiberoptic starting position before applying laser energy and withdrawing in the great saphenous vein. **B,** Catheter and fiber withdrawal in pulsed mode.

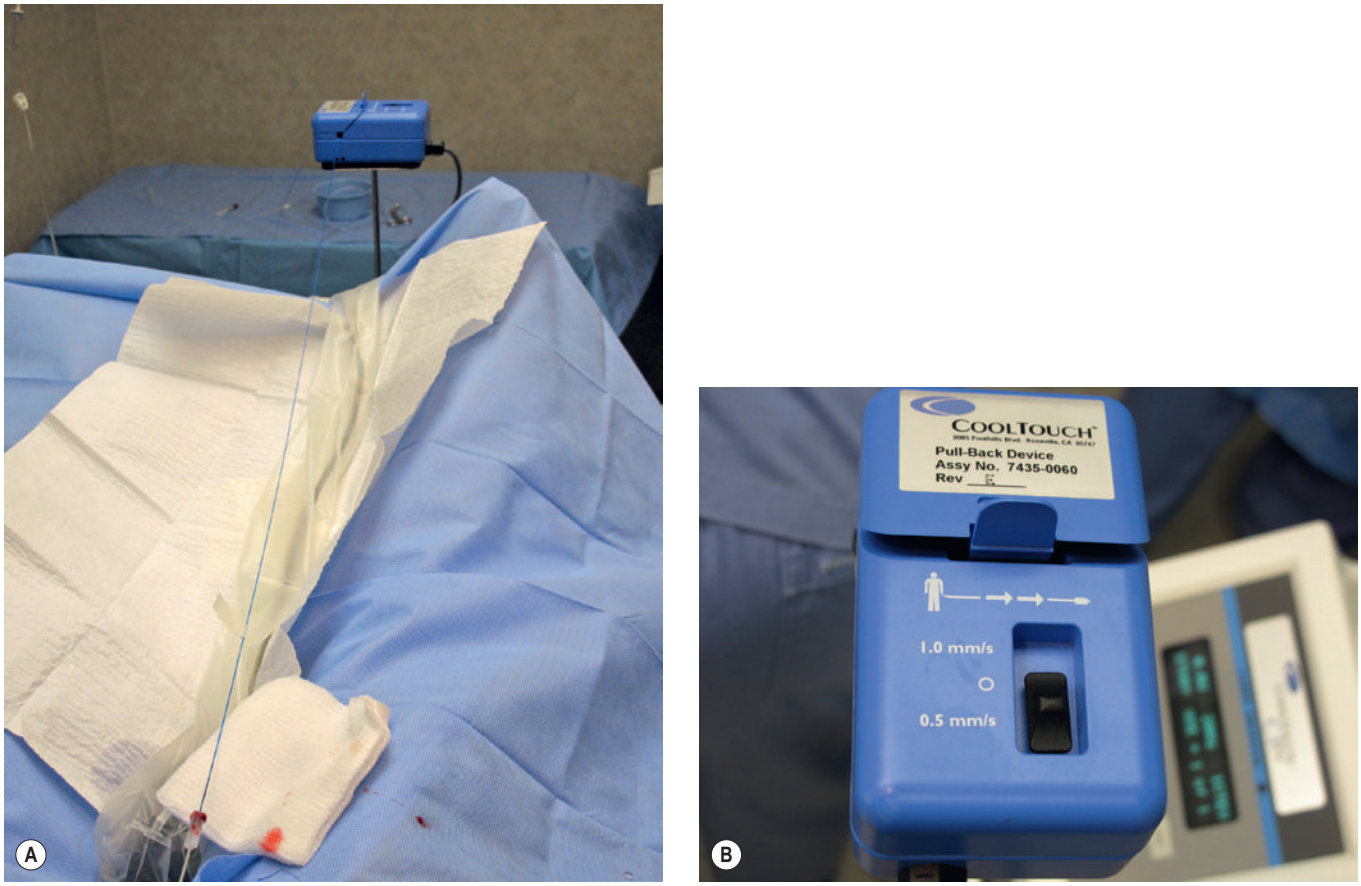


Figure 11.12 Fixed rate pullback with the 1320-nm system of endovenous ablation.

the answer to these unwanted effects. UGFS is one such nonthermal, nontumescent method that allows for effective closure of the GSV. Unfortunately, early studies suggest that its efficacy is not comparable to endovenous ablation techniques.[114]

UGFS is a technique whereby a foamed sclerosant agent such as sodium tetradecyl sulfate or polidocanol is injected into the GSV under ultrasound guidance. The foam displaces the blood, and the irritant nature of the sclerosant causes inflammation of the endothelium and subendothelium layers of the vessel wall resulting in fibrosis and occlusion of the vein. This procedure has been shown to improve quality of life of patients, despite the possibility of lower rates of venous occlusion.[115,116]

Reported side effects associated with UGFS include thrombophlebitis, skin pigmentation, thromboembolism and neurological symptoms such as migraines and visual disturbances. The occurrence of neurological symptoms has been attributed to the presence of a patent foramen ovale, a common finding in an estimated 20% to 30% of the general population.[114]

Polidocanol endovenous microfoam sclerosing agent (Varithena; 1% polidocanol injectable foam) was FDA approved in 2013 for the treatment of varicose veins and has shown some promise. In a randomized control study by Todd et al[117], polidocanol endogenous microfoam demonstrated improvement in clinical symptoms and esthetic appearance in 232 treated patients with SJF incompetence. Treatment with polidocanol endovenous microfoam was associated with mild-to-moderate, though tolerable side effects. The most common side effects in treated patients were retained coagulum, leg pain and superficial thrombophlebitis.[117]

Davies et al[118] performed a review of randomized controlled trials comparing UGFS with endothermal ablation with RFA and EVLA for the treatment of great saphenous varicose veins.[118] Although anatomical success (as determined by duplex ultrasound) appeared higher with endothermal ablation than UGFS, clinical success and patient-reported outcome measures were similar. There were also no significant differences between endothermal ablation and UGFS regarding morbidity and complication rates, which were both exceedingly low. In addition, UGFS was consistently less expensive than endothermal ablation.

In a randomized control trial, van der Velden et al[119] evaluated the long-term outcomes of patients undergoing conventional surgery, EVLA and UGFS for treatment of great saphenous varicose veins. Among the total of 224 legs initially treated (69 conventional surgery, 78 EVLA, 77 UGFS), 193 (86%) were evaluated at the final 5 year follow-up. Obliteration or absence of the treated GSV segment were 85% (95% CI 75–92%), 77% (95% CI 66–86%) and 23% (95% CI 14–33%) in the conventional surgery, EVLA and UGFS groups, respectively. Absence of GSV reflux above the knee was found in 85% (95% confidence interval [CI] 73–92%), 82% (95% CI 72–90%) and 41% (30–53%) in the conventional surgery, EVLA and UGFS groups, respectively. The Chronic Venous Insufficiency Questionnaire (CIVIQ) scores deteriorated over time in patients in the UGFS group and were significantly worse than those in the EVLA group. CIVIQ scores for the conventional surgery group did not differ from those in the EVLA and UGFS groups.[119]

CYANOACRYLATE ADHESIVE

Cyanoacrylate adhesive is a new, nonablative procedure using a proprietary formulation of cyanoacrylate adhesive (Sapheon Inc.). It has been developed for permanent closure of incompetent superficial truncal leg veins.[120]

Cyanoacrylate adhesive is widely approved as an implantable medical device for various therapeutic indications such as arteriovenous malformation and intracranial arterial aneurysms. Upon intravascular injection, cyanoacrylate adhesive rapidly solidifies and produces an inflammatory reaction in the vein wall. Granulomatous foreign body reaction is observed at 30 days after treatment and fibroblasts can be seen invading the contents of the tunica intima and tunica media at 60 days.[120]

In the treatment of varicose veins cyanoacrylate adhesive is delivered via a hydrophobic catheter advanced to a position 5 cm short of the SFJ. Aliquots of adhesive are methodically placed until the total length of the target vein is treated. Tumescent anesthesia is not indicated. Initial studies using cyanoacrylate adhesive have been promising. Common complications are minimal and include thrombophlebitis, which is likely a result of inflammation around the GSV and its untreated tributaries.[120,121] One concern is the possibility of recanalization of the treated vein with embolization of the adhesive. We have recently seen evidence of recanalization with the adhesive only partially adherent to the vein wall.

MECHANOCHEMICAL ABLATION

MOCA (ClariVein) is a technique that combines mechanical injury using a rotating wire with simultaneous infusion of a liquid sclerosant. This induces irreversible endothelial damage resulting in fibrosis of the vein. To begin this treatment the wire tip is passed out of the end of the catheter and positioned 2 cm distal to the SFJ under ultrasound guidance. Slow infusion of the sclerosant is started and the catheter is withdrawn, with the wire still rotating and the sclerosant still being infused at approximately 1–2 mm/s.[121]

MOCA has a low complication rate, successful venous occlusion and improved quality of life scores. Early studies suggest occlusion rates to be comparable to endothermal techniques with less postoperative pain and earlier return to normal activities. It also has the added benefit of not requiring tumescent anesthesia.[122–124]

Reported complications include thrombophlebitis, induration along the treated vein, hematoma formation and hyperpigmentation. One potential serious adverse event following MOCA is that the rotating wire tip can get caught. This may cause ecchymosis, patient discomfort and resistance to pullback. In fact, there has been a report of the wire tip becoming stuck and consequently caused the small saphenous vein to be stripped inversely. Fortunately, no reports of skin necrosis, DVTs or nerve injury have been published.[114]

ENDOVENOUS STEAM ABLATION

Whereas UGFS, cyanoacrylate adhesive, nonthermal techniques and MOCA are all nontumescent, endovenous steam ablation is obviously a thermal approach requiring tumescent anesthesia.[121] This novel technique has been used to achieve both radiological and clinical improvement of SFJ incompetence.[125]

Just as catheter-based thermal ablation using laser therapy and radiofrequency energy has been shown to be highly effective in ablating incompetent truncal veins, it should come as no surprise that catheter-based thermal ablation using steam is likewise effective at ablating veins. The major difference between thermal ablation using steam, as compared with laser therapy or radiofrequency, is how the thermal energy is delivered to the vein wall. This affects the temperature at the point of treatment.[121]

Endovenous steam ablation is similar to all catheter-based endovenous techniques with venous access being obtained under ultrasound guidance. Specifically, the catheter tip is placed 2 to 3 cm distal to the saphenofemoral junction and tumescent anesthesia is injected around the target vein. Initial pulses are given to clear the catheter followed by treatment pulses. The catheter is then withdrawn and with each centimeter, 1 to 4 pulses are given depending on vein diameter.[121]

In the randomized clinical trial of endovenous laser ablation versus steam ablation (LAST trial) for the treatment of great saphenous varicose vein, steam closure of the veins was shown to be not inferior to EVLA.[126] At 1 year follow-up, occlusion rates of the GSV were reported to be 92% for steam ablation and 96% for EVLA. The most common adverse effects with steam ablation was superficial thrombophlebitis seen in 8.5% at 2 weeks and 2.8% at 12 weeks. Two patients were reported to have nerve injury that was still present at 12 weeks. Steam ablation appeared to have several advantages including less postoperative pain, fewer days of analgesia use, satisfaction of the patients and quick return to normal activity.[126]

CONCLUSION

Minimally invasive approaches in which energy applied within the endoluminal space using RFA or EVLA have now surpassed open venous surgery as the gold standard for the treatment of saphenous vein reflux. Over the past two decades endovenous thermal ablation has proven itself to be as efficacious as ligation and stripping, with minimal adverse effects. In addition, endovenous thermal ablation is faster and less expensive. In our clinical experience the best results have been seen with intravascular therapies using RFA and EVLA with a 1320-nm laser. In comparison to RFA, 1320-nm endovenous treatment has the advantage of being able to treat more tortuous veins with a more flexible fiber optic and at a lower cost to the patient. Furthermore, performing ambulatory phlebectomy at the same time as endovenous ablation may help to improve long-term results. The efficacy of other intravascular approaches for SFJ incompetence including UGSF, cyanoacrylate adhesive, MOCA and steam ablation remains to be determined; further randomized control studies are needed. Thus endovenous thermal ablation appears to be an excellent therapeutic approach for both cosmetic and symptomatic improvement of varicose veins.[127]

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12 Clinical Methods for Sclerotherapy of Telangiectasias

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HISTORICAL REVIEW OF TECHNIQUES

Sclerosing treatment for telangiectasias was ignored until the 1930s, when Biegeleisen[1] injected sclerosing agents intradermally or subcutaneously into the general area of capillary enlargement. However, this procedure caused severe necrosis and lacked effect on the telangiectasias. Biegeleisen then developed and popularized a method of 'microinjection' of telangiectasias with sclerosing agents through the use of an extremely fine metal needle (later described as a handmade 32- or 33-gauge needle).[2] Unfortunately, he used sodium morrhuate in the treatment of these fragile small vessels, which produced multiple complications, including pigmentation, cutaneous necrosis and allergic reactions. Thereafter, sclerotherapy for leg telangiectasias was thought of disparagingly by most practitioners[3] until the 1970s, when Alderman,[4] Foley,[5] Tretbar,[6] and Shields and Jansen[7] published reports of procedures that had produced excellent results with few adverse sequelae. In these procedures, solutions less caustic to the telangiectasia were used—hypertonic saline (HS) with or without heparin and lidocaine (15% to 30%), and sodium tetradecyl sulfate (STS) 1%—as were techniques that ensured accurate placement of the solution into the blood vessels (use of 30-gauge needles).

INDICATION

Microsclerotherapy is theoretically indicated for any small telangiectatic vessel or venule on the cutaneous surface. Best results are obtained on superficial linear or radiating vessels on the lower extremities. Telangiectasias on the face are less reliably responsive to microsclerotherapy because they probably have more of an arteriolar component and result from active vasodilation, but they can be treated successfully (see Chapter 4).[8,9] In addition, bright red telangiectasias on the leg that have a rapid refilling time after diascopy (applying pressure with a glass slide) with the patient recumbent (Fig. 12.1) are probably also supplied through arteriolar flow (see Chapter 4).[10] These vessels are relatively recalcitrant to usual therapy and tend to recur after treatment. More importantly, these arteriolar leg veins are more likely to develop overlying cutaneous necrosis if sclerosing solutions reach the arteriolar feeding loop (see Chapter 8). They may be treated more effectively with the pulsed dye laser or intense pulsed light (IPL) sources (see Chapter 13).

The description in Chapter 9 of the injection of varicose veins by first closing off the high-pressure reflux points with sclerosing solution, followed by sclerotherapy of remaining abnormal vessels, forms the basis for the rationale of compression sclerotherapy of varicose veins. The treatment of 'spider' leg veins should be just as rational.

In the vast majority of cases, spider veins connect to underlying varicose veins either directly or through tributaries (Fig. 12.2) (see Chapter 3).[11–13] This is typical on the lateral aspect of the thigh when the lateral network described by Albanese is visible (Fig. 12.3). Doppler examination shows that almost all visible blue reticular veins are connected to telangiectasia.[14,15] Transillumination shows exactly the same pattern (Fig. 12.4). Therefore, as with varicose veins, treatment should be directed first at 'plugging' the leaking high-pressure outflow at its point of origin (Fig. 12.5). An appropriate analogy is to think of spider veins as the 'fingers' and the feeding varicose or reticular vein as the 'arm'. Treatment should first be directed to the feeding arm and then, only if necessary, to the spider fingers. Mariani et al[16] found, in a 3-year follow-up study, that telangiectasias treated in this manner showed enduring resolution in 95% of 109 patients.

There are a number of advantages to this systematic approach to sclerotherapy. When sclerotherapy is performed in this manner, the spider veins often disappear without direct treatment or decrease markedly in size, thus limiting the number of injections into the patient. The larger feeding vein is both easier to cannulate and less likely to rupture when injected with the sclerosing solution, thus minimizing the extent of extravasated red blood cells (RBCs) and solution. Theoretically, this method also should minimize the postsclerotherapy development of hyperpigmentation, cutaneous necrosis, telangiectatic matting (TM) and recurrence (see Chapter 8).

INJECTION TECHNIQUE

PREINJECTION PROCEDURE

After a physical examination, including the use of noninvasive diagnostic techniques when appropriate (see Chapter 5), the patient is scheduled for a sclerotherapy session and given a questionnaire, consent form and instructional material to read and complete at home. Questions about the procedure are answered, and all reasonable and appropriate complications and adverse sequelae are addressed. An estimate of the approximate number of treatment sessions

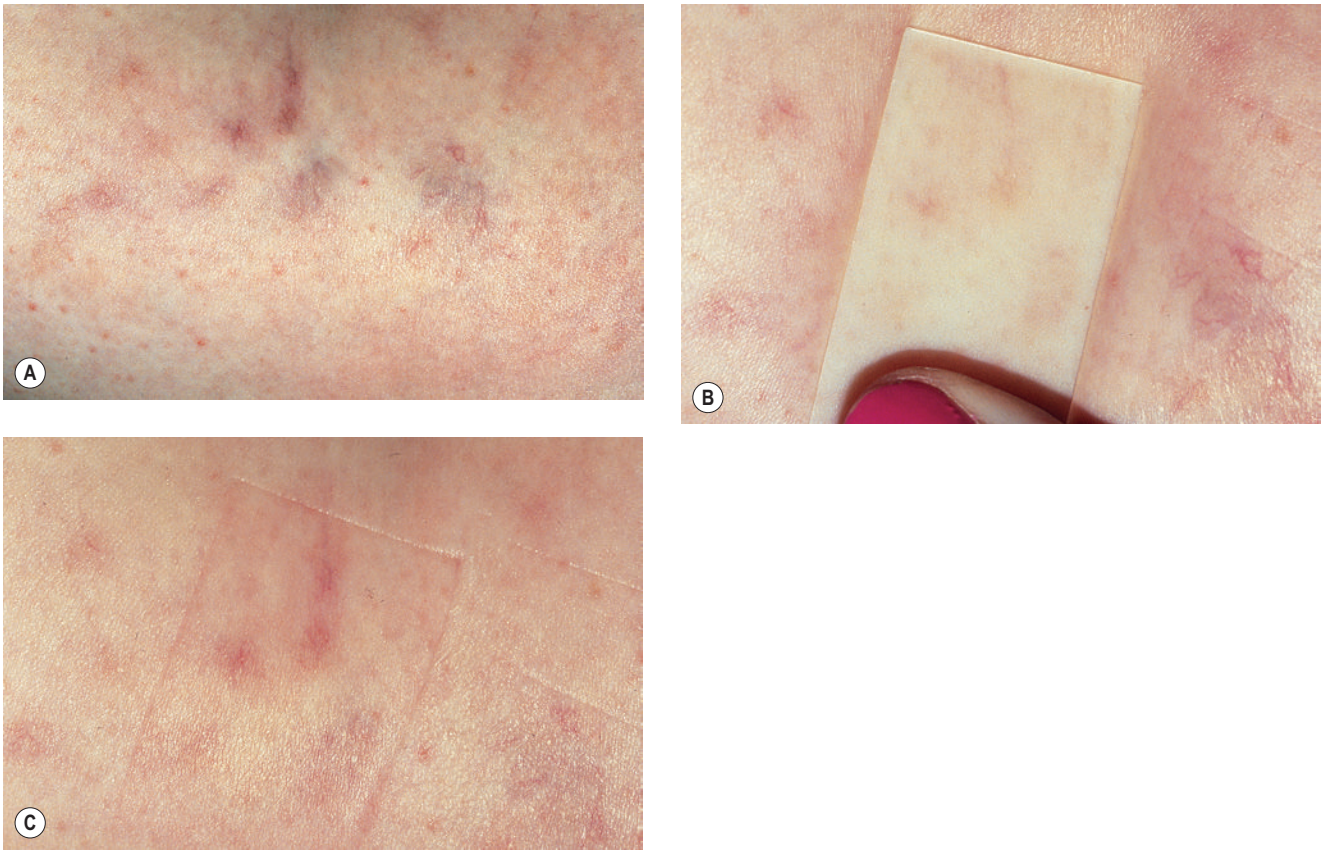

Figure 12.1 Bright-red telangiectasias may have an arteriolar origin. In this series, the telangiectasias were located on the medial thigh. **A,** Appearance while the leg is raised 45 degrees. **B,** Blanching with pressure under a glass slide. **C,** Immediate reappearance on removal of the glass slide while the leg is still elevated.

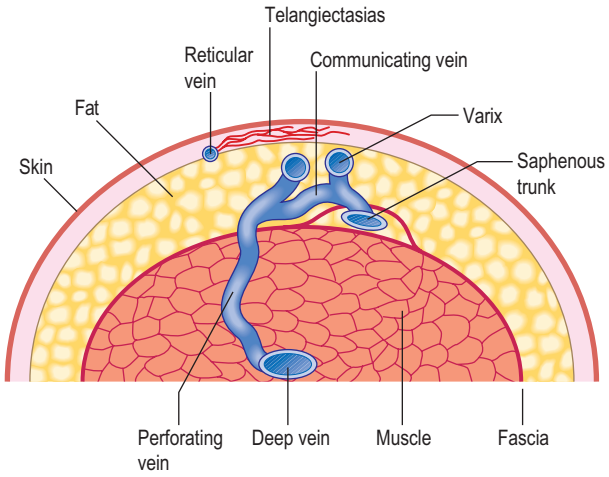

Figure 12.2 Simplified anatomy.

and the cost of treatment are given in writing to prevent any future misunderstandings. Insurance reimbursement policies are discussed and documented. Documentation of the relief of symptoms with compression stockings is helpful in gaining preauthorization of treatment from insurance companies, but in most cases insurance companies decide on the medical necessity for treatment based on the size (diameter) and type of vessel, not symptoms. If graduated compression stockings are planned to be applied after treatment, they are fitted at this time and given to the patient to wear

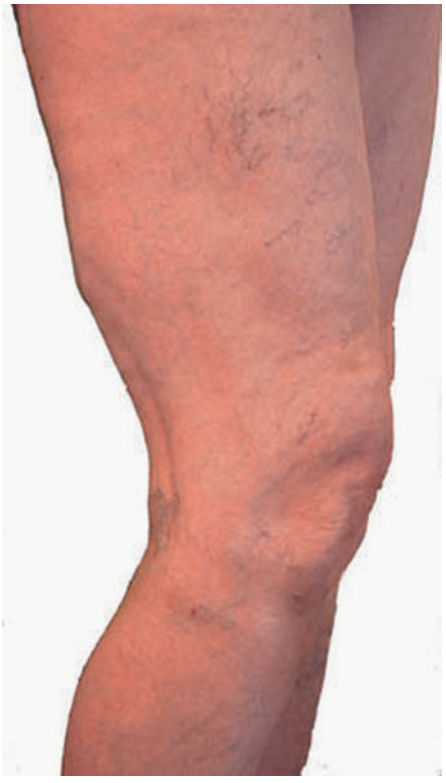

Figure 12.3 Albanese's lateral network.

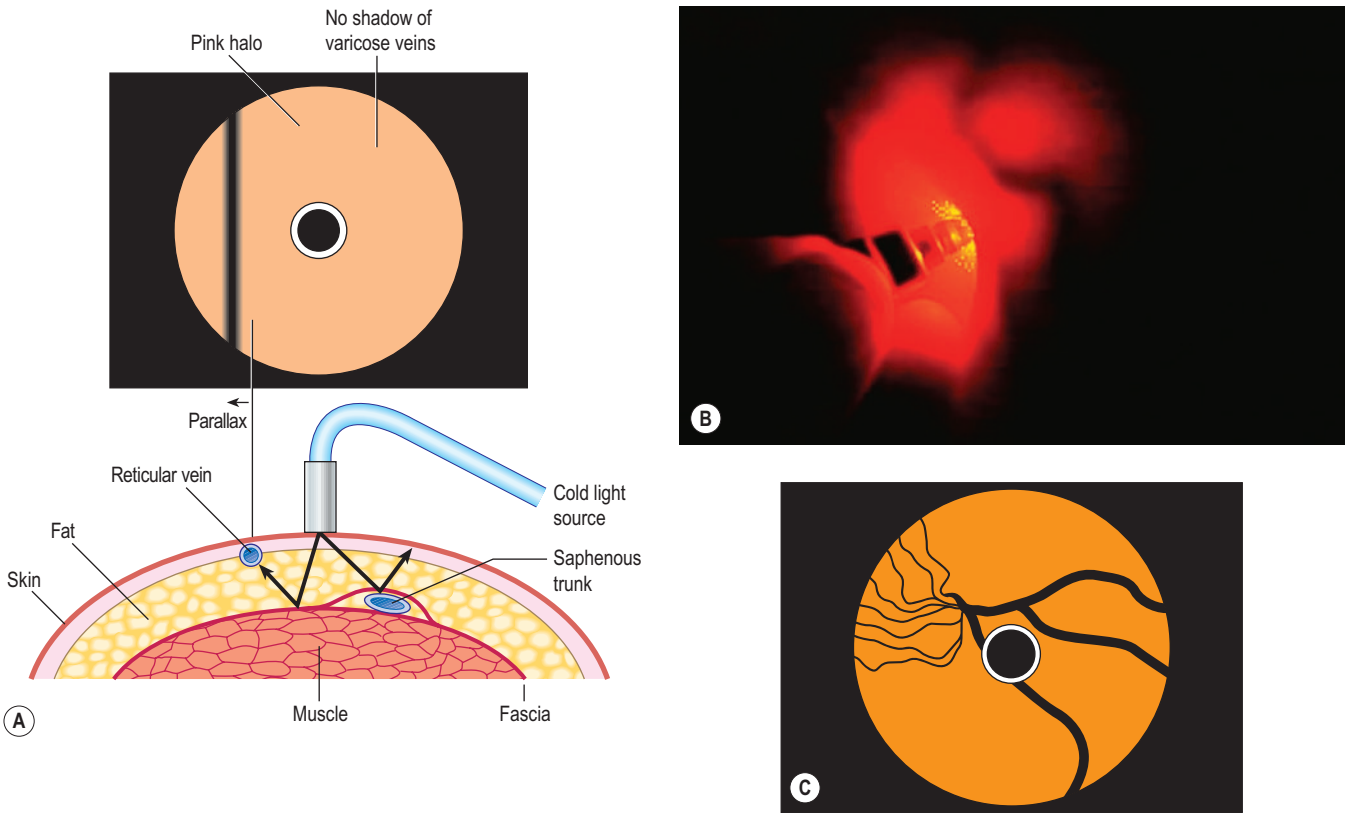

Figure 12.4 Transillumination. **A,** Principles. **B,** Reticular veins with a single cold light source. **C,** Connections between reticular and spider veins.

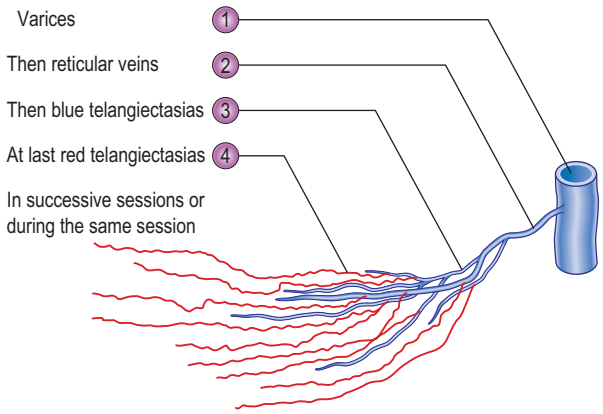

Figure 12.5 Strategy.

before treatment. If the stockings produce a resolution of symptoms, the physician can assume that successful sclerotherapy will give the same result. In addition, wearing the stockings before treatment helps answer any questions about their fit to ensure they will be worn for the prescribed length of time after treatment.

On the day of treatment, the patient's legs should not be shaved, because a burning sensation may result when alcohol is applied to the areas that will be treated. Moisturizers should not be applied on the day of treatment, because they cause unnecessary slipperiness of the skin. Patients are instructed to eat a light meal or drink juice 1 hour or so before the procedure in an effort to prevent a vasovagal reaction. Shorts, a bathing suit or a leotard should be worn during the procedure to minimize both patient and physician embarrassment, because some vessels may be near the groin. Providing disposable paper shorts to patients who do not bring them into the office is an appreciated feature.

With the patient standing on an elevated platform or stool, a complete set of photographs of the legs is taken from four different views, and the individual areas that will be treated are photographed up close (Fig. 12.6). Reticular veins and telangiectasias are photographed with the patient recumbent. Photographic documentation is important because patients frequently cannot remember exactly how their legs appeared before treatment. Any pretreatment pigmentation irregularities and scars may be blamed later on the sclerotherapy because patients usually look more closely at their legs once treatment has begun. In addition, when patients return in a few years with additional veins and telangiectasia, viewing pretreatment photographs will allay concerns regarding the possibility of unsuccessful previous treatment.

An easy method for measuring the diameter of the telangiectasia was devised by Jerry Garden, MD (Chicago, IL). He uses needles of various sizes placed next to targeted telangiectasias to compare vessel diameters (Table 12.1).

At the end of the treatment session, the treated areas are recorded on a diagrammatic chart to help check progress at follow-up examinations. Patients are given written postoperative instructions about activity and the disposition of their graduated compression stockings and/or bandages.

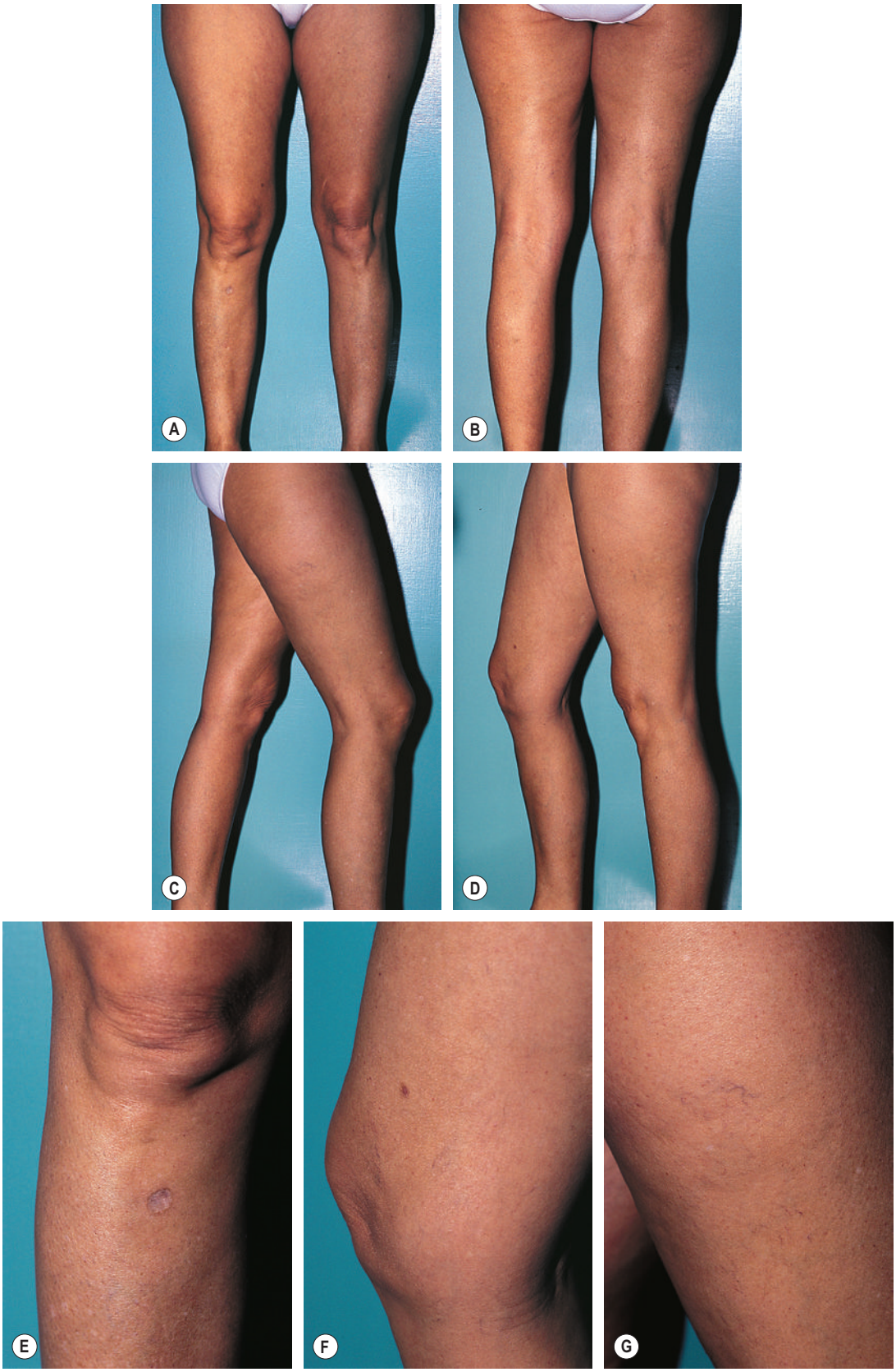

Figure 12.6 Standard photographs taken before treatment begins to allow accurate determinations of treatment outcome. Four standard views are shown at an F-stop of F8; close-up views were taken at an F-stop of F11, with macro close-ups taken at an F-stop of F16. All photographs were taken with Kodachrome ASA 64 film (Kodak, Rochester, NY) as described in Chapter 15. **A,** Frontal view. **B,** Rear view. **C,** Right side (the right foot is always in front of the left foot). The right knee is slightly bent so that the left inner thigh is better visualized. **D,** Left side (again with the right foot in front of the left). **E,** Documentation of scar from previous treatment for a verruca on the right anterior tibial area, which could later be thought of as a treatment scar. **F,** Documentation of dermatofibroma on the right medial knee area, which later could be thought of as punctate pigmentation from treatment. **G,** Close-up view of telangiectasia and venules (0.2–0.6 mm in diameter) on the right lateral thigh, along with pretreatment nonspecific light brown pigmentation, which could later be thought of as postsclerotherapy hemosiderin pigmentation.

Table 12.1 Needle Gauge Sizes and Vessel External Diameters Used by Garden

Gauge	External Diameter (mm)
30	0.30
27	0.41
26	0.46
25	0.51
22	0.71
20	0.89
18	1.27

PREPARATION AND VISUALIZATION OF THE VESSELS

Microsclerotherapy for spider veins is performed with the patient in the supine position. Gravitational dilation of telangiectasias is not necessary to minimize intravascular thrombosis. The skin is wiped with alcohol, making the telangiectasias more visible because of a change in the index of refraction of the skin. The glistening effect of alcohol renders the skin more transparent and helps clean the injection site. In addition, alcohol may cause some vasodilation of the telangiectasias. Alternatively, Sadick[17] recommended that the skin be wiped with a solution of isopropyl alcohol 70% with acetic acid 0.5%. He found that this solution improves the angle of refraction better than alcohol alone.

Scarborough and Bisaccia[18] recommended rubbing a few drops of the sclerosing solution on the skin overlying the venules with a gloved finger. They used polidocanol (POL), which also contains alcohol in water as the diluent. We agree that visualization is enhanced with this technique once the initial effects of the isopropyl alcohol have worn off through evaporation. To further enhance visualization of the vessels, we recommend the use of magnifiers from ×2.25 to ×5 (see Chapter 15). Other alternatives to improve visualization of blood vessels include dermoscopy and near-infrared imaging.[19–21]

If the vessels are too small to inject, having the patient stand for approximately 5 minutes and then placing him or her in a reverse Trendelenburg position may cause some vessel dilation. Alternatively, inflating a blood pressure cuff to approximately 40 mmHg proximal to the injection site may also result in some distention of the vessels. However, this will also increase the extent of vessel thrombosis and should be avoided whenever possible.

EQUIPMENT

NEEDLE AND SYRINGE

Although visualization of the vessel is important to ensuring proper needle placement, the examiner actually enters the needle into the vessel 'by feel'. This is particularly true in the injection of reticular varices. In this situation, it is best to pierce the skin rapidly and advance the needle superficially over the vessel at a slight angle in a 'double-piercing' technique. Penetration of the vessel is 'felt', even when the examiner uses a 30-gauge needle. Some authors state that the 'feel' is enhanced with the use of a 26- or 27-gauge needle, but we find this unnecessary.[22] In this regard, the use of a glass syringe would best reflect an impedance to flow if a vessel were not properly cannulated. However, glass syringes are more cumbersome to use and regulations regarding sterile technique and other hazards have relegated glass to being an undesirable choice. With the availability of high-quality plastic syringes, a good feel can be obtained and the risk of transmitting blood-borne diseases can be obviated (see Chapter 15).

Ideally, the goal of microsclerotherapy is to cannulate the vessel, injecting sclerosing solution within and not outside the vessel wall. Usually, a 30-gauge needle suffices for most vessels, although some physicians recommend the use of a 32- to 33-gauge needle to decrease the likelihood of inadvertent perivenular injection in the treatment of the smallest diameter vessels.[23–26] The disadvantages of using a 32-gauge needle are that it dulls rather quickly and easily bends away from the targeted vein (see Chapter 15). Boxes of needles sometimes contain individually defectively sharpened and dull needles, which give a 'scratchy' sensation to the tip. The physician should never hesitate to change needles if a vein cannot be cannulated easily. It is usually not the 'tough skin' of the patient but a dull needle that makes injection difficult.

Half-inch (1.27-cm), 30-gauge needles, although 0.3 mm in diameter, are honed to an oblique bevel that permits cannulation of vessels 0.1 mm in diameter or smaller. Needles longer than half an inch are too flexible for reliable and accurate cannulation.

We find the use of a 3-mL syringe filled with 2 mL of sclerosing solution ideal. This syringe fits well in the palm of the hand and can be manipulated easily. In addition, the quantity of solution is usually satisfactory for injecting either larger venules with 0.5 mL each or multiple smaller vessels. Alternatively, for those with small hands, a 1-mL syringe filled with 0.5 mL may be easier to handle, although a large number of syringes will be needed per treatment session and a smaller-barrel syringe will lead to higher injection pressures.

Injection with a syringe of smaller diameter will increase the pressure of the liquid at the tip of the needle. This may cause more extravasation and more transparietal burn and also may increase the risk for 'reverse flow' injection and subsequent necrosis. It has been measured and calculated that for the same force applied to the piston, the pressure can almost double with a small syringe (Fig. 12.7).

One theoretical disadvantage to multiple injections with the same needle is that the needle will become dull.[24] However, this was found not to occur upon microscopic examination of the needle tips after eight injections into the skin (see Chapter 15).

A small vein infusion set designed for sclerotherapy is available in various gauge and tubing lengths with 3/8-inch-long needles (Kawasumi Laboratories, Tampa, FL) (Fig. 12.8). These sets may provide enhanced control for cannulating small veins. In addition, the kink-resistant tubing allows for flow to ensure that the needle is in a vein and not an artery.

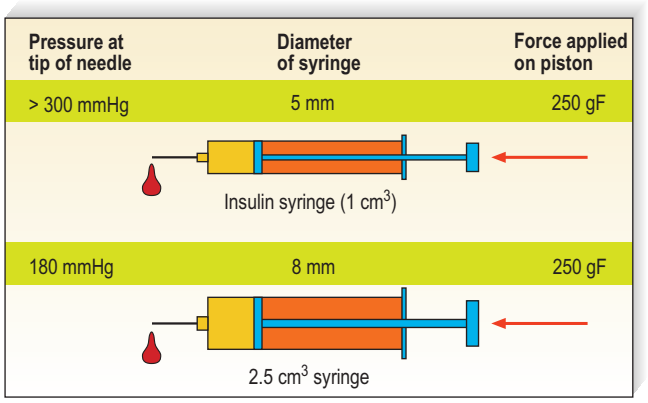

Figure 12.7 Pressure for the same injection force applied on piston. Small syringes increase the risk of extravasation and necrosis (micro arteriovenous fistulas, countercurrent injections).

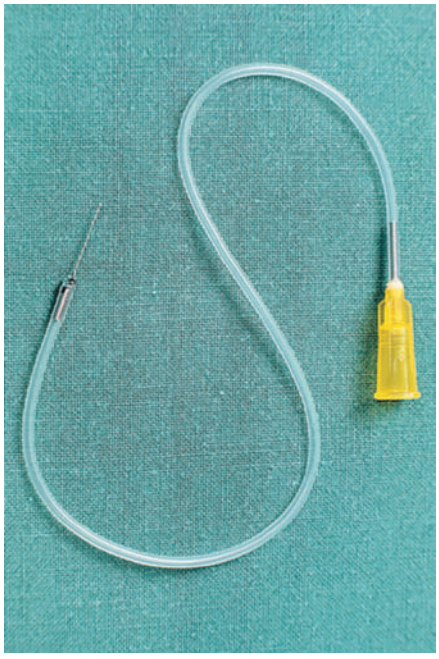

Figure 12.8 Sclerotherapy infusion set with a 30-gauge needle developed to aid in cannulating the smallest blood vessels. (From STD Pharmaceutical Products, Ltd, Hereford, UK.)

TABLE AND LIGHTING

Direct lighting should be avoided during treatment because it may produce a glare from the alcohol-soaked skin. Indirect lighting allows the best visualization. Sunlight or fluorescent lighting allows the best visualization of both blue reticular veins and red telangiectasia. A remote control or dimmer switch for room light is convenient because it allows dimming when using transillumination for marking or injections.

The ideal treatment table is one that can be raised or lowered easily to provide a comfortable position for the physician to ensure injection accuracy. It is helpful if the physician can easily maneuver around the table on a stool so that the best approach to a given vessel is attainable. Tables that can be positioned in Trendelenburg or reverse Trendelenburg positions can help in the treatment of an early vasovagal reaction and in effecting vessel dilation or contraction.

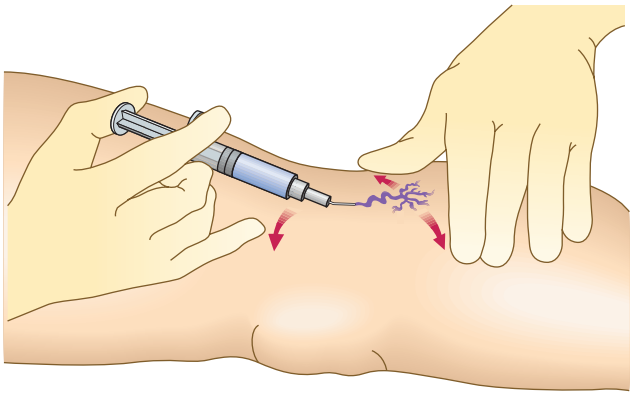

Figure 12.9 Proper hand placement to exert three-point traction to aid in needle insertion. Injection is made into the feeding 'arm' of the 'fingers' of the spider vein.

SKIN TENSION

The skin must be taut to facilitate cannulation of the vessel. This can be accomplished with the help of an assistant who stretches the patient's skin in at least two directions. Alternatively, with proper hand placement, the physician alone can produce three-point tension. Figure 12.9 illustrates the recommended technique for injection. The nondominant hand is used to stretch the skin adjacent to the treated vessel in two directions. Then the fifth finger of the dominant hand exerts countertraction in a third direction. With a little practice, even the most lax skin, such as that on the thighs, can be brought under tension with this technique. Skin laxity varies with patient age, adiposity and location on the leg.

DEPTH OF INJECTION

The location of most leg telangiectasias is in the upper dermis (see Chapter 1). The most common error in technique is to place the needle tip deep to the vessel. To enter the vessel at a less acute angle almost parallel to the skin surface, the physician should bend the needle to 145 degrees with the bevel up (Fig. 12.10).[27] If the needle is not within the vessel, the solution will either leak out onto the skin or produce an immediate superficial wheal. At times, gentle upward traction can be applied as the needle is advanced to ensure superficial placement.

Injection with the bevel of the needle up has the advantage of minimizing the chance of transecting the vessel. Inserting the needle bevel down may be easier, probably as a result of the vacuum produced by the bevel on the skin surface. An alternative technique is to puncture the skin very superficially, hook it, lift it a little to bring the vessel into the same axis as the needle and then cannulate it (Fig. 12.11).

When using a sclerosing solution that does not cause cutaneous necrosis on extravasation (e.g., STS 0.1–0.25%, POL 0.25–0.75% and chromated glycerin [CG]), the physician can inject it as the needle is being inserted into the vessel. As soon as the bevel is within the vessel, the telangiectasia

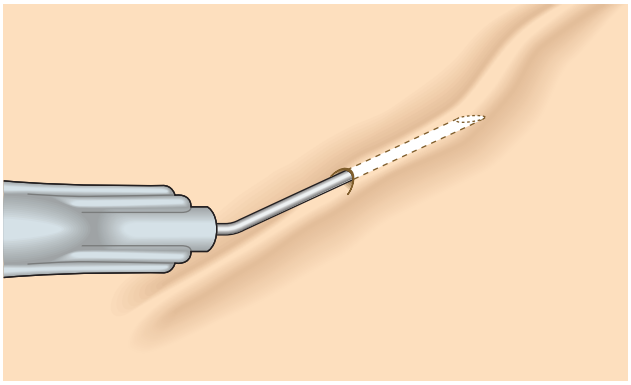

Figure 12.10 Needle is bent to 145 degrees with the bevel up to facilitate accurate insertion into the superficial telangiectasia. (Reprinted from Goldman MP, Bennett RG. J Am Acad Dermatol 1987;17:167, with permission from American Academy of Dermatology.)

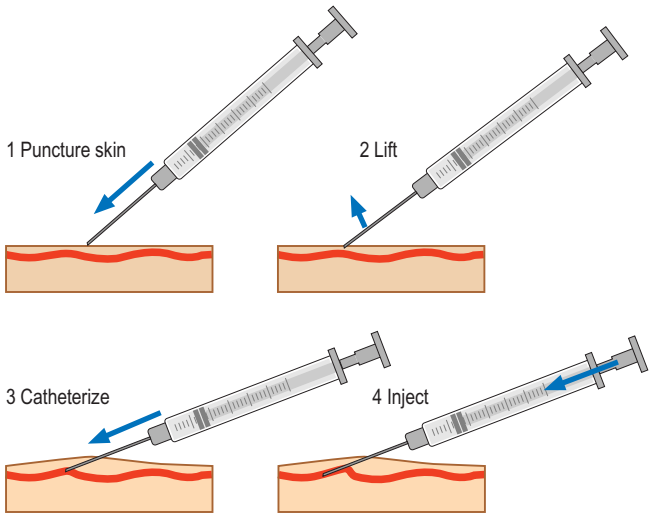

Figure 12.11 How to puncture a telangiectasia.

blanches. This technique permits the injection of vessels with diameters smaller than the diameter of the needle, because the tip of the bevel is thinner than the needle shaft; with injection, the telangiectasia dilates, allowing complete insertion to occur.

AIR-BOLUS (BLOCK) OR FOAM TECHNIQUE

The air-bolus technique—injecting a small amount of air to clear the vessel before instilling the sclerosing solution—is recommended by multiple physicians.[4,5,22] It is thought to minimize the risk of inadvertent intradermal injection. This may not occur, however, because once the vessel is cleared of blood, it is more difficult to see the progress of the sclerosing solution within its lumen. Therefore, others, including ourselves, have abandoned this technique.[24,26] Another theoretical advantage of the air-bolus technique is the decreased risk of intravascular thrombosis. It is thought that if the vessel is cleared of blood by first injecting air, the risk of extravasation of RBCs may also be minimized. However, antegrade and retrograde filling of the treated vessel occurs after the injection. Thus, the air-bolus technique may not prevent or lessen the incidence of posttreatment pigmentation. It is necessary to stress the risk of visual disturbances when using the air-block technique.[28,29]

FOAM INJECTION

Another variant of the air-bolus technique that helps visualize clearing of the vessels is that of creating a foamy solution before injection. This can be achieved with the use of any 'detergent' class of sclerosing solution such as STS or POL (see Chapter 7). Green and Morgan[30] added Haemaccel (Piramal, Bethlehem, PA) to STS to accentuate bubble formation. It is also thought that the foam causes the sclerosing agent to interact more efficiently with the endothelium (see Chapters 7 and 9). We have found that foaming a detergent solution increases its potency at least twofold while decreasing its caustic toxicity fourfold when a solution-to-air ratio of 1 : 4 is used. Therefore, the use of foam in treating telangiectasia less than 1 mm in diameter is tricky. Until a method is devised to standardize the size and stability of foam, the physician cannot accurately predict the foam's sclerosing strength. We reserve the use of foam for treating reticular and varicose veins.

To create foam, a small amount of a detergent solution can be drawn into a glass syringe. While the open end of the syringe is almost totally closed, the plunger is pulled back, allowing the introduction of air through the sides of the plunger and syringe. This technique produces foam of fair quality that degrades 50% over 1–2 minutes.[31] Silicone is present in syringes to lubricate the barrel, making for easier compression on the plunger. We have found that the foam half-life varies over 50% for different syringes.[32] Some phlebologists recommend using glass syringes to avoid this variability in foam half-life. The glass syringe method necessitates appropriate sterilization of the syringe between patients.

Other methods for producing long-lasting reproducible bubble diameter foam are under development and evaluation. Sclerosing foams can be made by adding air to the liquid solution or with a tensioactive agent and CO_2, according to Cabrera et al.[33,34]

The main difference between sclerotherapy with a solution and with foam is the longer duration of foam within the vein and the concentration of the damaging nonpolar end of the detergent molecule on the endothelial surface. This promotes sclerosis of the treated vessel with a lower concentration of sclerosing solution. Several methods for preparation of simple sclerotherapy foam have been proposed by Monfreux,[35] Benigni et al,[36] Mingo-Garcia,[37] Tessari,[38] and Frullini.[39] Tessari's method makes foam with a three-way tap and two syringes.

Hennet[40] used 3-mL glass syringes into which 0.3–0.4 mL of POL is made up as a 0.5% solution and then diluted with 0.1–0.2 mL of physiologic serum. The foam is stated to last for approximately 1 minute with this technique. The syringe is withdrawn until 0.6–1.3 mL of foam fills the syringe. The foam, as it is injected, prevents secondary back-bleeding and is therefore in contact with the vessel wall. Hennet reported treating 10,262 patients with over 70,000 injections between November 1995 and September 1998. Less than 0.5 mL of foam was given in each injection, and compression was not used. He reported excellent results without significant adverse sequelae.

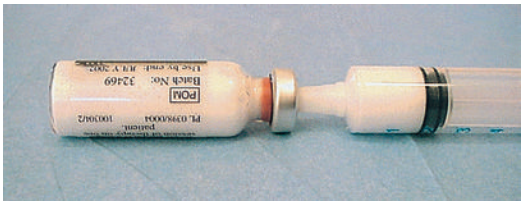

Figure 12.12 Syringe inserted into a vial containing approximately 0.2 mL of sodium tetradecyl sulfate 3%. (From Frullini A. Dermatol Surg 2000;26:705.)

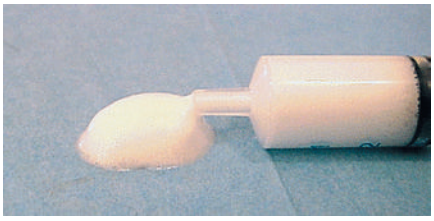

Figure 12.13 Foam produced by rapid movement of the plunger in and out of the vial is stable for 5–10 minutes. (From Frullini A. Dermatol Surg 2000;26:705.)

With Frullini's method, the foam is simply produced in a disposable vial with the air contained in the vial or, preferably, with prior withdrawal of most of the sclerosing solution. A small connector is inserted into the vial, and simply pulling and pushing the liquid produces the foam (Figs 12.12 and 12.13). The key point is to generate a turbulence that produces the foam. Foam can be produced even without the connector by directly fitting the cone of the syringe into the rubber of the cap of the vial. However, the connector makes the maneuver easier and permits reuse of the system on the same patient to reproduce the foam for a second injection.

Benigni and Sadoun[41] compared the efficacy and adverse effect profile of 0.25% POL foam with 0.25% POL liquid in treating telangiectasia. They reported a 20% improvement in efficacy with foam versus liquid, without an increase in adverse effects. This is contrary to Weiss,[42] who found an increased incidence of pigmentation and TM when 0.1% or 0.2% STS foam was used as compared with liquid STS. Forty percent of patients treated with STS 0.1% or 0.2% foam into telangiectasia of less than 1 mm had 76–100% improvement, and 82% had greater than 50% improvement. The incidence of pigmentation and TM increased to 20% each if a second treatment was required. Kern[43] has shown that more pigmentation occurs with foam, and we have demonstrated[29] that more side effects occurred with foam. Finally, and following the conclusion of the European consensus,[44] we do not recommend the use of foam as primary treatment of telangiectatic veins.

QUANTITY OF SCLEROSING SOLUTION PER INJECTION SITE

The maximum quantity of sclerosing solution that can be injected safely into a single site during treatment of varicose veins is detailed in Chapter 9. In short, the physician should not inject a volume that would travel undiluted easily into the deep venous system. This is especially important because contrast material has been noted to flow from

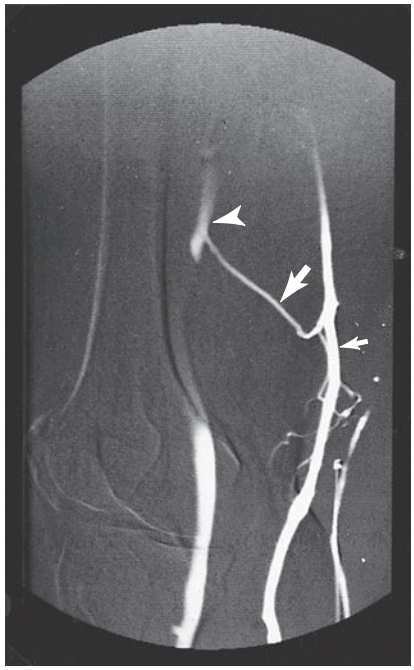

Figure 12.14 Main collector of telangiectatic vessels *(small arrow)* drains into the femoral vein *(arrowhead)* through a perforator vein. (*Large arrow*, great saphenous vein.) (From Böhler-Sommeregger K, Karnel F, Schuller-Petrovic S, Santler R. J Dermatol Surg Oncol 1992;18:403.)

telangiectasias directly into the deep venous system in 2 (13.3%) of 13 patients with digital subtraction phlebography (Fig. 12.14).[45] It appears reasonable to inject solution only until the physician cannot see further progression of blood displacement. When this point is reached, the solution is most likely traveling deeper and possibly into perforating or deep veins.

The maximum amount of sclerosing solution that can be injected into leg telangiectasias is unclear. Although Duffy[24] placed little emphasis on limiting the amount of solution injected at a single site, and Lary[46] recommended the injection of up to 3 mL at a single site when injecting a reticular 3-mm diameter vein, multiple complications can and do occur with use of this technique. Excessive inflammation and inadvertent flow of the solution into a feeding varicose vein or arteriole can produce ulceration with injection and damage to the deep venous system. Thrombosis and emboli can occur when amounts greater than 1 mL are injected into a single site. For example, injection of 0.5 mL of solution into a 2-mm diameter vessel fills a length of 16 cm (see Chapter 8).

Ouvry and Davy[47] recommend that the amount injected should be sufficient to produce blanching of vessels 1–2 cm around the point of injection. No more than 0.5 mL should be used to avoid the risk of initiating the formation of new telangiectasias around the edge of the treated area because of excessive inflammation. In this regard, the same area should not be retreated more often than every 4–6 weeks. In our practice, it appears that TM occurs more frequently if reinjections are given to a previously treated area that is still undergoing resolution. This unresolved state can be appreciated clinically by slight inflammation and evidence of microthrombosis of vessels.

In addition to limiting the inflammatory reaction of sclerotherapy, limiting the amount of solution may prevent pain and cramping when hypertonic solutions are used. Sadick[17] has found that volumes greater than 0.3 mL of HS 23.4% caused the most pain and cramping. One way to minimize the pain from injection of HS is to dilute the HS with lidocaine to the appropriate concentration. One study noted a decrease in pain of 30% with use of this dilution technique.[48]

Some areas, especially the ankles, should not be injected with more than 1 mL of any sclerosing solution. In this area, the skin is thinnest, the distance between the deep and superficial venous system is the least, and swelling after treatment is common (see Chapter 8). From a purely legal point of view, French regulations[49] recommend not exceeding 10 mL of STS 3%, two ampules of 2 mL of POL (any dosage) and 10 mL of CG.

CONCENTRATION AND STRENGTH OF SCLEROSING SOLUTIONS

Sclerosing solution concentration and strength are discussed in detail in Chapter 7, but a few points are mentioned here. The most important concept in sclerotherapy is that of achieving optimal destruction of the blood vessel wall with the minimum concentration of sclerosing solution necessary; too much will lead to excessive complications and adverse sequelae, and too little will lead to ineffective sclerosis or recurrence from recanalization (see Chapter 8). The physician should always estimate conservatively when choosing the concentration and type of sclerosing solution.

Researchers in three randomized, double-blind, paired comparative human studies evaluated the results of different sclerosing solutions and concentrations in the treatment of leg telangiectasia. Carlin and Ratz[50] tested POL 0.25%, STS 0.5% and HS 20% with heparin, 100 U/mL, in the treatment of leg telangiectasia. They found that whereas HS and STS gave quicker clearing of telangiectasia with fewer injections, the overall level of improvement was identical for all agents. POL was the best-tolerated sclerosing solution, with the smallest number of adverse sequelae. In a follow-up study comparing POL in four concentrations—0.25%, 0.5%, 0.75% and 1.0%—Norris et al[51] found that all concentrations were equally effective in treating leg telangiectasia. The POL 0.5% concentration was ideal, with the least number of adverse effects and the most rapid clearing in their patients with leg telangiectasias 0.2–1.0 mm in diameter. Sadick[52] compared HS in three concentrations—23.4%, 11.7% and 5.8%—and found that HS 11.7% was the minimal concentration of saline that produced the most effective vein sclerosis of vessels 1.0 mm in diameter while producing the least discomfort and morbidity.

A comparison of STS 0.25% and POL 0.5% in treating 61 patients with telangiectasias less than 1 mm in diameter demonstrated a similar degree of vessel disappearance of about 90% with one treatment.[53] This study demonstrated that sclerosing solutions of equal potency act in a similar manner in treating telangiectasia.

However, some sclerosing agents have a better adverse sequelae pattern. Although the incidence of TM was similar, patients treated with STS had an incidence of pigmentation of 63% versus 32% with POL. Thibault[54] found that STS is a stronger sclerosing agent than has been surmised and used a 0.12% concentration for treating telangiectasias greater than 1 mm in diameter, with a decreased incidence of pigmentation and TM.

Table 12.2 Summary of Adverse Events and Efficacy by Treatment Group

Adverse Event/Efficacy	Glycerin (*n* = 13)	STS (*n* =13)
Pain	3 (23%)	2 (15%)
Bruising	1 (8%)	7 (54%)
Swelling	0 (0%)	3 (23%)
Hyperpigmentation	1 (8%)	12 (92%)
Vessel clearance	7 (54%)	1 (8%)

Reproduced from Leach B, Goldman MP. Dermatol Surg 2003;29:612.
STS, Sodium tetradecyl sulfate.

Kern et al[43] compared the efficacy of CG 100%, POL 0.25% solution and POL 0.25% foam in the treatment of leg telangiectasias. A total of 150 patients were randomized to receive treatment. Foam was created by the Monfreux technique in a 1:4 solution-to-air ratio using glass syringes. The CG cleared vessels better than POL solution or foam, and, although it was more painful (35 of 100 vs 20 of 100), CG did not cause any episodes of pigmentation or TM. More TM and pigmentation was produced with POL foam than with POL solution.

In a study by Leach and Goldman,[55] glycerin 72% mixed 2:1 with lidocaine 1% with epinephrine was compared with STS 0.25% in 13 patients with leg telangiectasia of 0.2–0.4 mm in diameter. Patients were evaluated from 2 to 6 months postsclerotherapy for overall clinical improvement and incidence of adverse sequelae. Glycerin was comparable to STS in discomfort of injection but demonstrated a significant decrease in bruising, swelling and postprocedural hyperpigmentation. Glycerin also demonstrated better, more rapid clearance of treated telangiectasias (Table 12.2). The addition of lidocaine 1% with epinephrine to CG sclerotherapy is safe and effective with decreased pain severity as compared with pure CG.[56]

Munavalli et al[57] confirmed the lack of adverse effects and efficacy of glycerin compared with STS 0.1% foam. Patients were treated with either glycerin 72% or STS 0.1% foam and analyzed at 6 weeks. Discomfort was the same with each agent. Pigmentation occurred in 18 of 20 patients treated with STS 0.1% foam and in only 1 of 20 patients treated with glycerin. TM occurred in 4 of 20 STS patients versus 1 of 20 glycerin patients. Improvement was 90% for STS and 60% for glycerin. We recommend that leg telangiectasias less than 1 mm in diameter be treated with POL 0.25–0.5%, STS 0.1–0.25%, CG or HS 11.7%. Best efficacy and least adverse effects appear to occur when using glycerin 72% mixed 2:1 with lidocaine 1% with epinephrine.

PRESSURE OF INJECTION

Another variable of technique is the pressure and rapidity of injection. If leg telangiectasias are injected under

excessive force, they may rupture and result in extravasation of solution (see Chapter 8). Therefore, injections should be done with minimum pressure. This may be difficult upon injection of sclerosing solutions of high viscosity, such as CG, because more pressure is required to push them through a 30-gauge needle. Duffy[24] likens the proper injection pressure to that needed to fix a postage stamp to an envelope. In addition, the slower the injection, the longer the solution will be in contact with the vessel wall. Finally, injection pressure (with equal force applied to the piston) is inversely proportional to the square of the piston radius: $P = F/S = F/\pi r^2$; $P1/P2 = (r2/r1)^2$, where P = Pressure, F = force, S = cross section of the vein, r = radius. If the approximate piston radius of a 2-mL syringe is 8 mm and that of a 1-mL syringe is 5 mm, the applied force is 180 mmHg for a 2-mL syringe and more than 300 mmHg for a 1-mL syringe.

In treatment of varicose veins, patient position and movement determine the length of time the solution will be in contact with the endothelium (see Chapter 9). With the injection of telangiectasias, however, the blood flow is determined not by muscle movement or body position but by many other factors, including environmental temperature, nervous stress and the telangiectasias' association with arterioles and underlying veins. Therefore, injections should be done slowly enough that it takes approximately 5–10 seconds to fill the vessel. Many times the vessel will remain filled with sclerosing solution if the plunger of the syringe is held with almost zero force while the needle remains motionless.

POST-TREATMENT TECHNIQUES

Immediately after injection of the sclerosing solution, the perivascular tissues may swell, producing a clinically visible occlusion of the vessel, or the vessels may go into spasm. This usually occurs if the injection is given slowly and if the sclerosing solution is of adequate strength. Indeed, several authors recommend that a given vessel be treated until such an effect occurs.[22] This may require a second injection of a more concentrated solution (125%) into the same vessel during the same sclerotherapy session.

After hypertonic solutions are injected, the injected area should be massaged to minimize the stinging and help alleviate the associated muscle cramping by rapidly diluting the hyperosmotic solution outside the treated vessel.[24–26,58] The slower the injection, the less cramping will occur. When the needle is withdrawn, a small amount of sclerosing solution may be deposited under the skin, causing a burning sensation. This usually occurs only with hypertonic solutions and CG. Massaging for 30–60 seconds alleviates the pain and prevents necrosis from the HS solution.[25]

All sclerosing solutions, even unadulterated HS (see Chapter 8), produce some degree of erythema or urtication or both with injection. Pruritus may be associated with this effect, especially when associated with urticarial lesions. This probably occurs as a result of histamine release caused by perivascular release of mast-cell mediators because of perivascular irritation or as a result of intravascular degranulation of basophils and other white blood cells destroyed by the direct toxic effects of the sclerosing solution. This reaction and its associated pruritus can be minimized by the application of a potent topical corticosteroid cream, thereby providing relief to the patient, especially if injected areas will be occluded with compression pads or stockings.

For telangiectasias that do not respond to standard compression sclerotherapy, added vasoconstriction induced by cold temperature may be helpful. Orbach[59] found that vessels respond better to the injection of refrigerated sclerosing solution. Marteau and Marteau,[60] using similar logic, advised applying cold compression pads after injection. Although these two techniques seem logical, we have not found them helpful, as detergent sclerosants are theoretically more 'active' at higher temperatures.

Posttreatment bruising is common and bothersome to patients, even if its disappearance occurs over a few weeks without residual discoloration. It may be useful to recommend application of topical creams such as Hirucrème (contains *Hirudo medicinalis* extract) or Hirudex (Pharmafar, Torino, Italy), which has demonstrated efficacy on mild bruising.[61] In case of local discomfort, anti-inflammatory nonsteroidal creams can be applied as well.

POST-TREATMENT COMPRESSION

For many phlebologists, compression of the sclerosed vessel with a 30- to 40-mmHg graduated compression stocking should be maintained for a minimum of 24–72 hours after treatment of leg telangiectasias.[62] Postsclerosis compression serves a number of purposes. First, the pressure helps seal the irritated vascular lumen. Second, the pressure helps decrease the likelihood of recanalization of the sclerosed vessel, especially if compression is maintained for 1–2 weeks. Third, the possibility of clinical and symptomatic thrombosis is minimized, thus minimizing hyperpigmentation, TM and recanalization after sclerosis. Although some physicians do not advocate postsclerosis compression,[7,17, 25,28,60,63] and consider that its only use is to protect against side effects of an inappropriate technique,[64] the procedure is simple and safe and its benefits likely, so its routine use may be recommended. In addition, most patients actually like the feel of the compression stocking while they are ambulatory. (A complete discussion on the use of compression in the treatment of varicose and telangiectatic leg veins is presented in Chapter 6.)

A second aspect of compression is represented by the local dressing applied on the injected vein. It usually consists of a cotton ball or pad and adhesive tape. It exerts double compression: perpendicular (by application of Laplace's law) and tangential (by direct traction on the skin on both sides) (Fig. 12.15). This type of compression may be stronger than compression exerted by stockings. How long to keep it in place is unknown: advice ranges from 1 hour to more than 24 hours. This type of compression has at least one obvious advantage: it stops bleeding. Although bleeding is not usually a problem, especially if feeding reticular veins are treated first, some patients who have decreased coagulability may benefit from local compression.

MICROTHROMBECTOMY

Spider veins (especially those bigger than 0.6 mm in diameter) and reticular veins are likely to form microthrombi after being injected. This phenomenon is less frequent with glycerin than with detergent solutions, especially foam. As

discussed in Chapter 8, to prevent pigmentation, microthrombectomy is carried out as early as 1–2 weeks after injection. Microthrombectomy is easily executed with any needle, the important point being to puncture every millimeter of the 'blue line' of the microthrombi (Fig. 12.16A–C). In very small venules, manual pressure is unnecessary; a cotton ball is applied and kept in place for several hours with an adhesive tape.

REPEAT TREATMENT SESSIONS

All patients are informed that successful treatment of a given telangiectasia may require more than one treatment (in general, and also on each treatment site). Patients easily understand that, as for wall painting, two or three thin layers give a better result than a thick one. As previously mentioned, the same vessel or the immediate area is not retreated for 4–6 weeks to allow resolution of the endosclerosis or controlled phlebitis to occur. Waiting also allows appreciation of the effectiveness of treatment with a given solution and concentration. If little change is apparent 6 weeks after injection, the second treatment can be performed with a stronger sclerosing agent or more concentrated solution. Ramelet[65] described an interesting technique for treatment of refractory vessels. In this setting, tumescent infiltration is applied after treatment to increase perivascular compression and thus improve the efficacy of the sclerosant. However, a higher incidence of adverse events with use of this technique was reported, so it may be best reserved for experienced phlebologists and highly refractory vessels.[65] Different areas can be treated as often as every day, but the venous system of the leg is a complex interwoven network, so treatment of only one part may not prevent reflux pressure from another part promoting continued blood flow through the treated area (see Chapter 1). This leads to an increased incidence of complications from blood flow through a damaged endothelial system (see Chapter 8). Thus, in the treatment of superficial reticular and telangiectatic leg veins, the only real limiting factor is patient and physician motivation for treatment and adherence to using the maximum daily recommended amounts of sclerosing solution that can be injected (see Chapter 7). In addition, if compression is used, it may be best to wait until the pressure stocking has been removed for a few days before treatment is continued on the same leg.

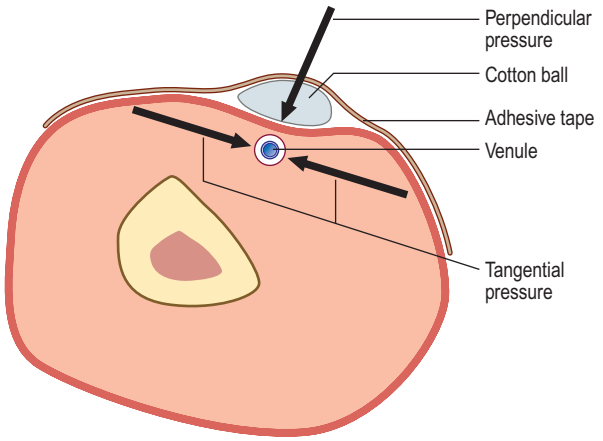

Figure 12.15 Lateral (tangential) and Laplace's (perpendicular) pressures exerted by local compression.

POOR RESULTS OF MICROSCLEROTHERAPY: HOW TO ANALYZE THE REASONS

Objective poor results present in many forms (Fig. 12.17). They differ from subjective poor results, where patients are not satisfied despite a satisfactory outcome. Most poor results are related to an inappropriate treatment. Two types of error are possible:

- Strategic, where superficial venous pressure and/or varicose reservoir have not been taken care of satisfactorily
- Tactical, where application of microsclerotherapy is not mastered by the sclerotherapist

The bad strategic approach is usually owing to an inadequate physical examination and/or duplex ultrasound assessment. If varicose veins are left untreated, although known and identified, microsclerotherapy alone is unlikely to produce a satisfactory result and may even lead to the production of new lesions.

When the technique is deficient, it can have three consequences. First, insufficient delivery of active drug in the spider network is responsible for a lack of efficacy. Second, excessive power of the sclerosing agent (too high

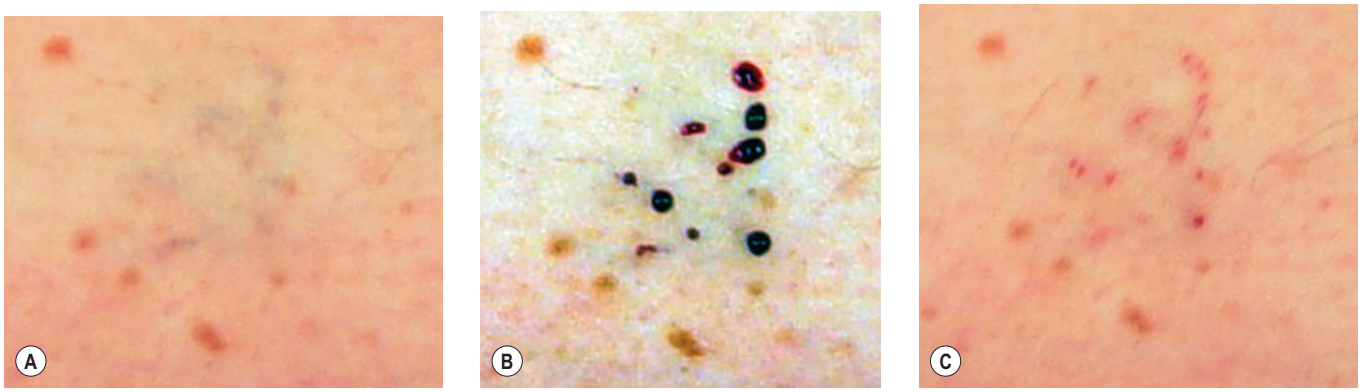

Figure 12.16 Microthrombectomy.

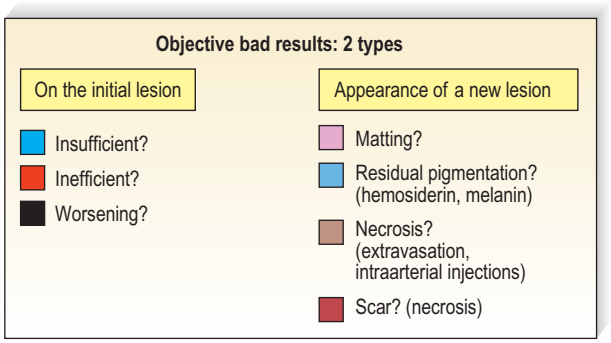

Figure 12.17 Objective bad results: two types.

a concentration and/or injection pressure and/or volume) results in a transparietal burn and subsequent inflammation (matting) and blood deposit with pigmentation. The third possibility is an imprecise injection, outside the vein lumen. This can result in inflammation or necrosis.

SCLEROTHERAPY FOR FACIAL TELANGIECTASIA

Sclerotherapy for facial telangiectasia has proved to be effective and safe (see Case Study 12).[8] However, there is a potential for sight-threatening complications from periocular vascular manipulation. This topic was reviewed elsewhere and is abstracted here.[66]

Inadvertent intra-arterial injection of corticosteroid suspensions in the periocular region has been reported to lead to embolic occlusion in the ophthalmic artery distribution, causing blindness.[67] Inadvertent intra-arterial injection is the likely factor permitting steroid particulate emboli to reach the retinal circulation. Severe visual loss has also been reported following intralesional steroid injection into a chalazion, again apparently causing retinal and choroidal embolic occlusion, presumably as a consequence of inadvertent intra-arterial injection.[68] Because it is not a suspension, distal embolic phenomena would not be expected to result from an injection of STS. However, as an intravascular sclerosant agent, it clearly presents a danger if it gains inadvertent access to normal vessels supplying the eye in therapeutic concentrations through the production of an embolus composed of denatured endothelial cells and blood cell elements (see Chapter 8). Presently accepted standards of injection technique, including careful placement of the needle, repeated aspiration and careful stabilization of the syringe, do not guarantee that the physician can detect if the bevel is against or within the vessel wall if the vessel is constricted, or if there has been any intra-arterial placement of the needle.[69]

Green[70] reported that, despite the numerous and variable anastomoses between the superficial facial and deep orbital venous systems, injection into superficial eyelid veins is 'highly unlikely' to reach the orbit; however, his technique uses comparatively large volumes (1–3 mL) of STS. Because venous pressure is quite low, it is not inconceivable that intravenous eyelid injection could reach the orbit (where there are no venous valves) and hence the ocular adnexae, the central retinal vein, the choroidal vortex veins or even the cavernous sinus through these anastomoses. Monocular blindness has been reported following STS injection into a venous malformation partially located in the orbit.[71] Green's technique uses compression only after delivery of the sclerosing solution. At that point, compression could conceivably force the solution into the orbital vessels through the variable anastomotic channels. Because the purpose of his compression is to delay the return of blood into the treated vein, the sclerosing solution forced upstream or downstream would not necessarily be significantly diluted and could potentially be dangerous.

Current treatments for cosmetically objectionable lower eyelid veins include direct cautery application through small cutaneous incisions and direct cautery plus surgical vein transection.[72] These procedures pose no known risks to the remainder of the vascular system but could be complicated by cutaneous scars. Surgical removal of the vein through a 2-mm incision with a phlebectomy hook has also been shown to be effective.[73] The vein can be tied off with an absorbable 6-0 suture with minimal bruising. However, this technique requires practice to avoid damage to perivascular tissue.

Our technique of sclerotherapy of lower eyelid veins has been reported previously as part of a larger series.[8] We recommend using very small quantities of dextrose, sodium chloride and phenethyl alcohol (Sclerodex; Omega Laboratories, Montreal, PQ, Canada) for treating facial telangiectasias and prominent periorbital veins. The technique is the use of 1 mL or less of sclerosant solution for 24 hours after proximal vein ligation with a 6-0 Prolene suture (Ethicon, Somerville, NJ). The suture prevents backflow of the solution into the retro-orbital venous system. This allows vigorous massage of the area and complements immediate compression. Use of a hypertonic solution provides for effective sclerosis of the vein within the concentration gradient of the solution. A detergent sclerosing solution such as STS may travel for many centimeters from the site of injection into areas that should not be sclerosed (see Chapters 7 and 8). This technique demonstrates a 90–100% improvement in 70% of patients after one treatment.[74] No adverse effects have been reported.

Laser technologies, including the long-pulsed, dynamically cooled 1064-nm neodymium-doped yttrium aluminum garnet laser (CoolTouch Varia; CoolTouch/New Star Lasers, Roseville, CA) has been reported to treat periorbital vessels 1–2 mm in diameter with near 100% efficacy.[75] Lasers of lower wavelength would not be expected to deliver sufficient energy at the correct depth to thermocoagulate a vessel of this size without producing excessive cutaneous thermal damage.[76]

SCLEROTHERAPY FOR ESSENTIAL TELANGIECTASIA

Vessels of essential telangiectasia are extremely small, usually measuring less than 0.1 mm in diameter, and are often associated with a feeding arteriolar component (see Chapter 4). Lasers and IPL are the easiest techniques to cause their involution (see Chapter 13). However, sclerotherapy may also be used to decrease the extent of the lesion. Sclerotherapy should be performed with a dilute solution. Lim

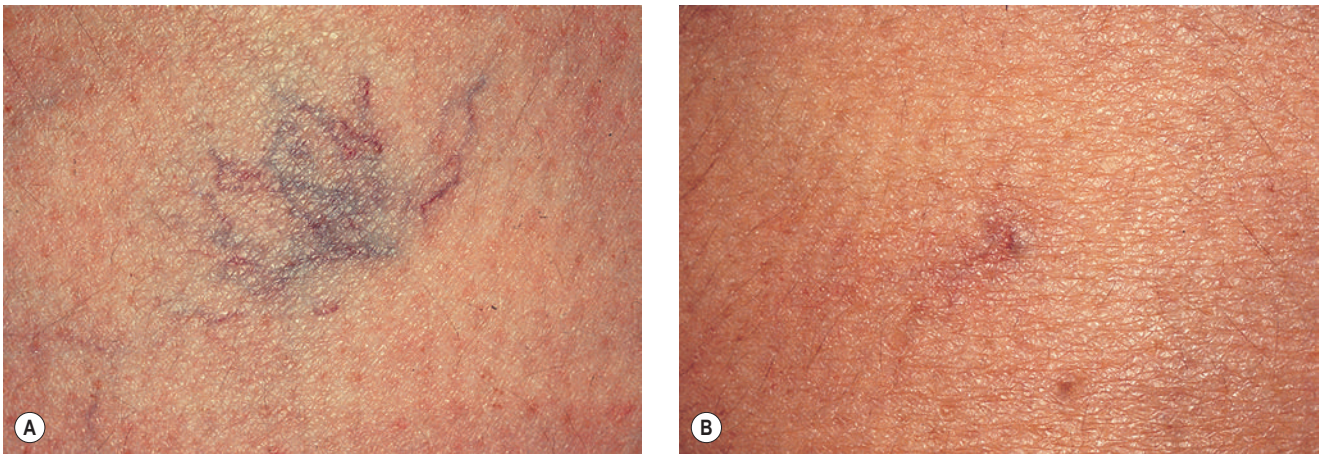

Figure 12.18 Case Study 1. **A,** Telangiectatic patch on posterior medial thigh. **B,** Ten months after treatment.

and Kossard[77] successfully treated a 56-year-old patient with STS 0.08% with good efficacy and no adverse effects.

SCLEROTHERAPY FOR OTHER LESIONS

A variety of other benign microvascular lesions have been treated successfully with sclerotherapy. However, these are mostly limited to single case reports or retrospective case series. These lesions include male varicoceles using 2% POL foam,[78] low flow vascular malformations with POL foam 0.25–3%,[79] reactive vascular lesions with ethanolamine oleate,[80] capillary malformation resistant to pulsed dye laser and IPL,[81] cherry angiomas with STS 3%,[82] pseudocyst of the auricle with STS 1%,[83] digital mucus cyst with STS 1–3%[84] and angiolymphoid hyperplasia with eosinophilia with POL 1%.[85]

CONCLUSIONS

It is clear that sclerotherapy is the 'gold standard' for treating leg telangiectasia. In certain cases, lasers or IPL therapy is also effective and recommended (see Chapter 13). The lay press is filled with descriptions of products that patients can apply to the legs to eliminate leg telangiectasia. A scientific evaluation of one of these products showed conclusively that a vitamin K–containing cream touted to eliminate vessels has no effect compared with placebo when used daily over 33 days.[86] Although we as physicians think of medicine as a science, it is also an art. Therefore, the sclerotherapy technique just mentioned should not be perceived as dogma. Rather, it should serve as a logical outline for the physician in planning individualized treatment.

CASE STUDY 1 Traumatic telangiectatic patch

A 46-year-old woman was accidentally hit by a tennis ball while she was 'playing the net'. A telangiectatic patch on the posterior medial thigh developed after resolution of the bruise 4–6 weeks after the initial injury and did not change in size or color over the following 4 years (Fig. 12.18A). The patch was treated on one occasion only, with injections of POL 0.5% in three locations to blanch the lesion completely. A total of 1 mL was used. A localized pressure dressing with an STD foam pad was placed and secured with adhesive tape for 3 days. Figure 12.18B shows the same area 10 months after initial treatment.

CASE STUDY 2 Unassociated telangiectasia

Figure 12.19A shows the appearance of linear telangiectasia on the medial thigh of a 46-year-old woman, which was noted during her second pregnancy 22 years previously. The area was asymptomatic, and treatment was requested for cosmetic improvement. The appearance 6 months after a single treatment using approximately 3 mL of POL 0.5% is shown in Figure 12.19B. A 30- to 40-mmHg graduated compression stocking was worn for 3 days after the injection. Note some mild hyperpigmentation in one of the treated vessels.

CASE STUDY 3 Reticular vein unassociated with the saphenous system

A reticular vein 2–3 mm in diameter on the popliteal fossa in a 32-year-old woman is shown in Figure 12.20A. The same area 18 months after one treatment with 1 mL of POL 0.75% is shown in Figure 12.20B. The area was compressed for 72 hours after treatment with an STD foam pad under a 30- to 40-mmHg graduated compression stocking, after which the compression stocking alone was worn for 1 more week while the patient was ambulatory. In the intervening 18 months, the patient wore a 20-mmHg graduated compression stocking on a fairly consistent basis while she was ambulatory.

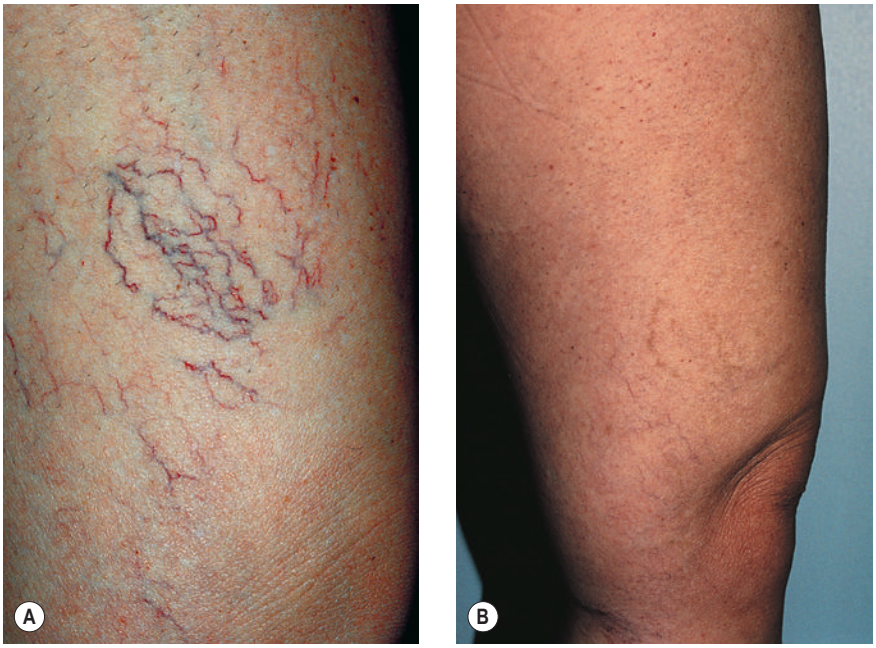

Figure 12.19 Case Study 2. **A,** Linear telangiectasia on medial thigh. **B,** Six months after treatment.

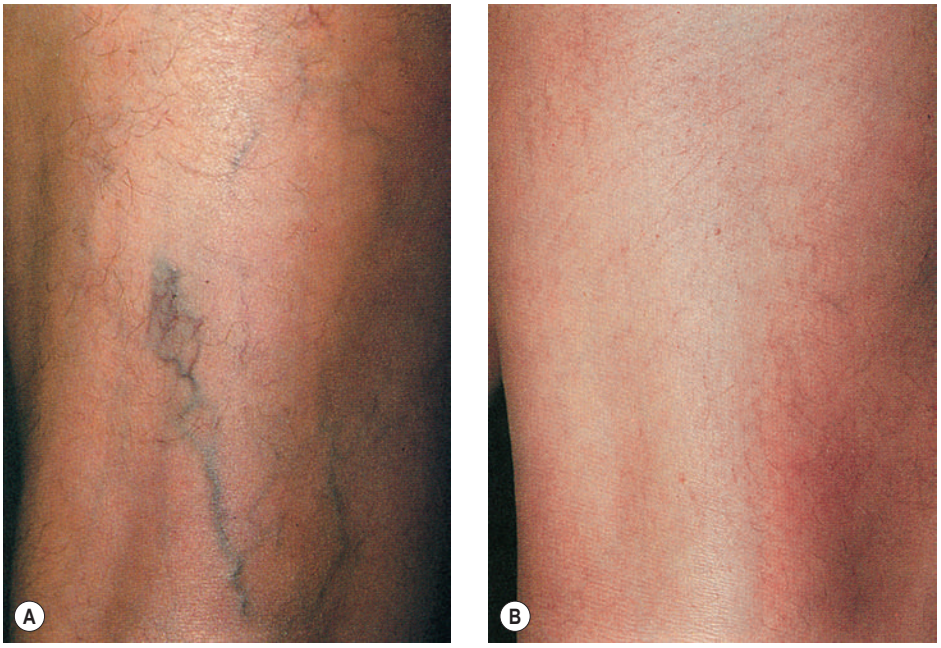

Figure 12.20 Case Study 3. **A,** Reticular vein on popliteal fossa. **B,** Eighteen months after treatment.

CASE STUDY 4 Mixed reticular and telangiectatic veins

Reticular veins approximately 2 mm in diameter associated with multiple telangiectasias on the lateral distal thigh of a 32-year-old woman appeared during her second pregnancy 10 years previously (Fig. 12.21A). The patient requested treatment because of a dull aching that occurred in the area during menses and after prolonged standing. The treated veins are shown immediately after a total injection with 0.5 mL of POL 0.75% in Figure 12.21B, and Figure 12.21C shows the treated area 1 day after injection after removal of the STD pad and a 30- to 40-mmHg graduated compression stocking. Note the ecchymosis induced by the pressure dressing. Figure 12.21D shows the area 1 week after injection. Intravascular thrombi were noted and drained at that time. Eight weeks after injection, the vessels were almost totally resolved. Some mild pigmentation was present in the distal aspect in which thrombosis was most extensive (Fig. 12.21E). Finally, Figure 12.21F shows the area 22 months after initial treatment, demonstrating sustained resolution of the telangiectasia, reticular veins and pigmentation.

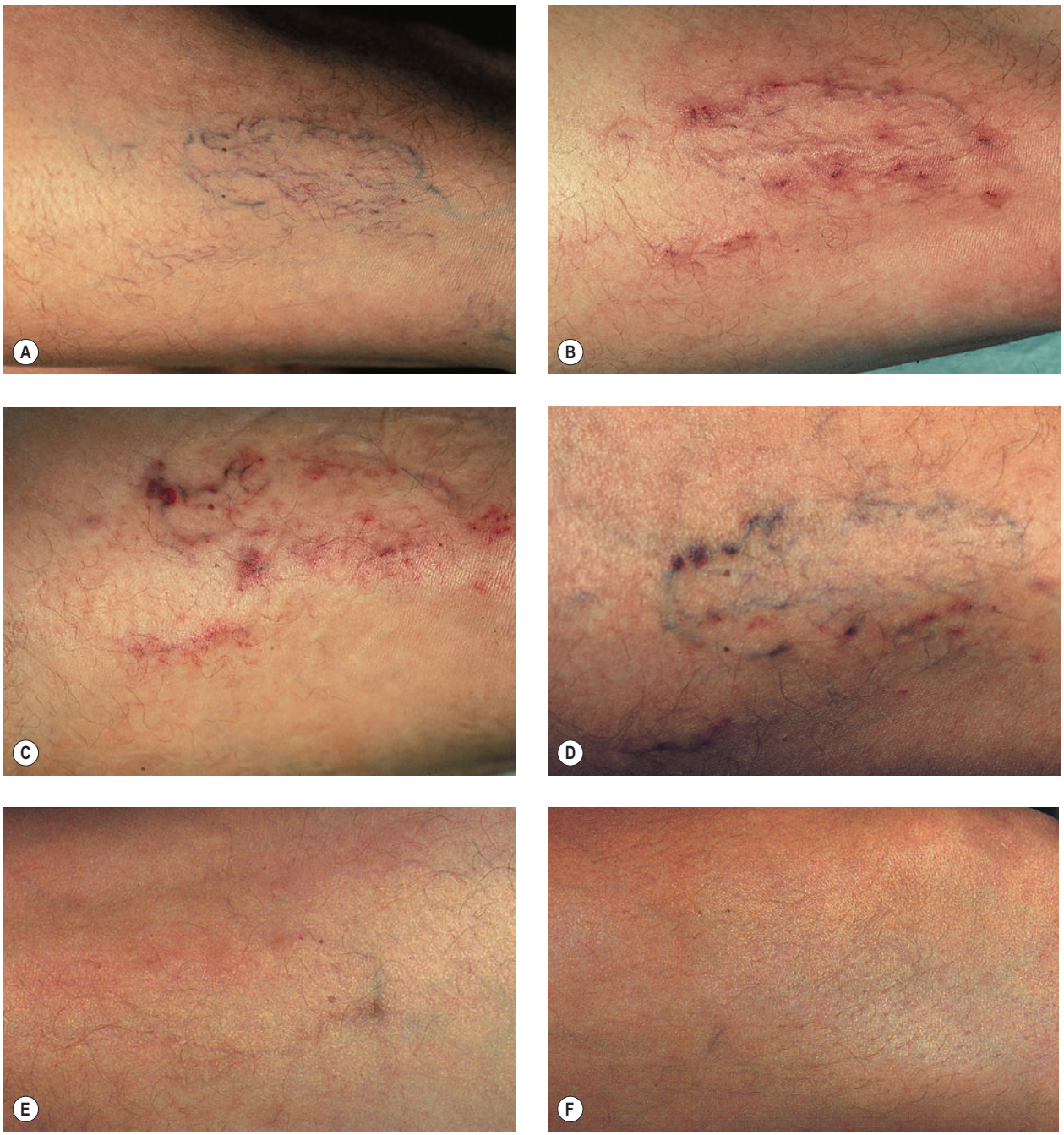

Figure 12.21 Case Study 4. **A,** Reticular veins associated with multiple telangiectasias on lateral distal thigh. **B,** Immediately after injection. **C,** One day after injection and removal of pad and graduated pressure stocking. **D,** One week after injection. **E,** Eight weeks after injection. **F,** Twenty-two months after treatment, with complete resolution.

CASE STUDY 5 Extensive reticular and telangiectatic veins

A 53-year-old woman had a 30-year history of asymptomatic reticular and telangiectatic leg veins that had been stable in appearance since her last of two pregnancies 20 years previously. She sought treatment for cosmetic reasons (Fig. 12.22A). A total of 10 mL of POL 0.75% was injected into all feeding reticular veins on the proximal and distal lateral thigh. Polidocanol 0.5%, 2 mL, was injected into the portion of the telangiectatic mats on the lateral calf and knee, which did not blanch with the previous injection. STD foam pads were placed under a 30- to 40-mmHg graduated support stocking that was worn continuously for 7 days after the procedure. When the stocking was removed, multiple small thrombi were drained. Figure 12.22B shows the appearance of the treated area 25 months after the single treatment session.

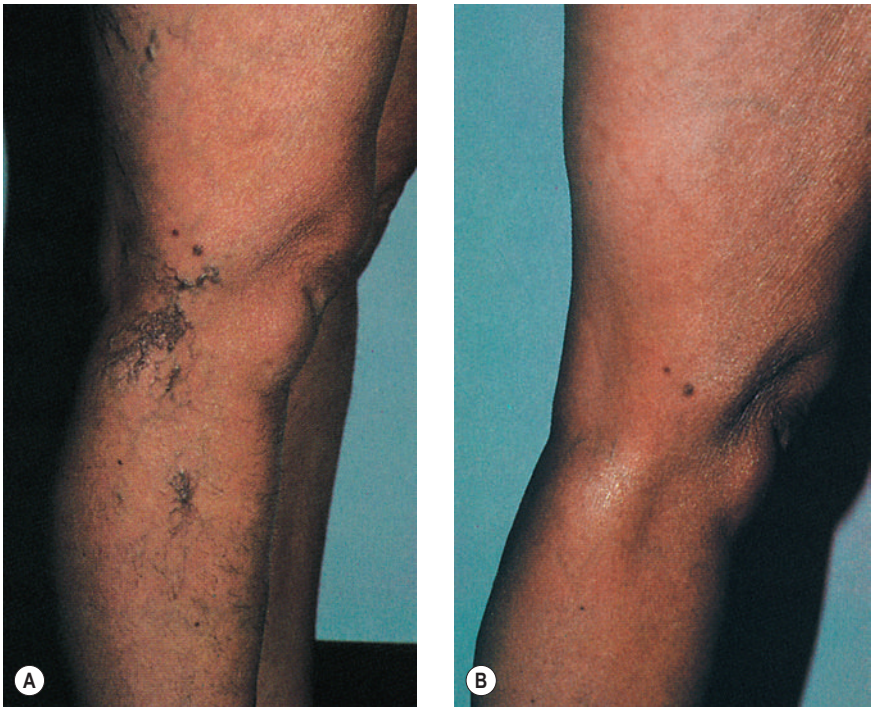

Figure 12.22 Case Study 5. **A,** Reticular veins on the proximal and distal lateral thigh. **B,** Twenty-five months after treatment.

CASE STUDY 6 Treatment of cherry hemangiomas

A 48-year-old woman had multiple cherry hemangiomas on her abdomen and thighs and a 4-mm-diameter hemangioma located on her anterior thigh (Fig. 12.23A). Figure 12.23B shows the appearance 5 months after injection with 0.1 mL of POL 0.75%. Note the slightly indented and hypopigmented scar, which was acceptable to the patient.

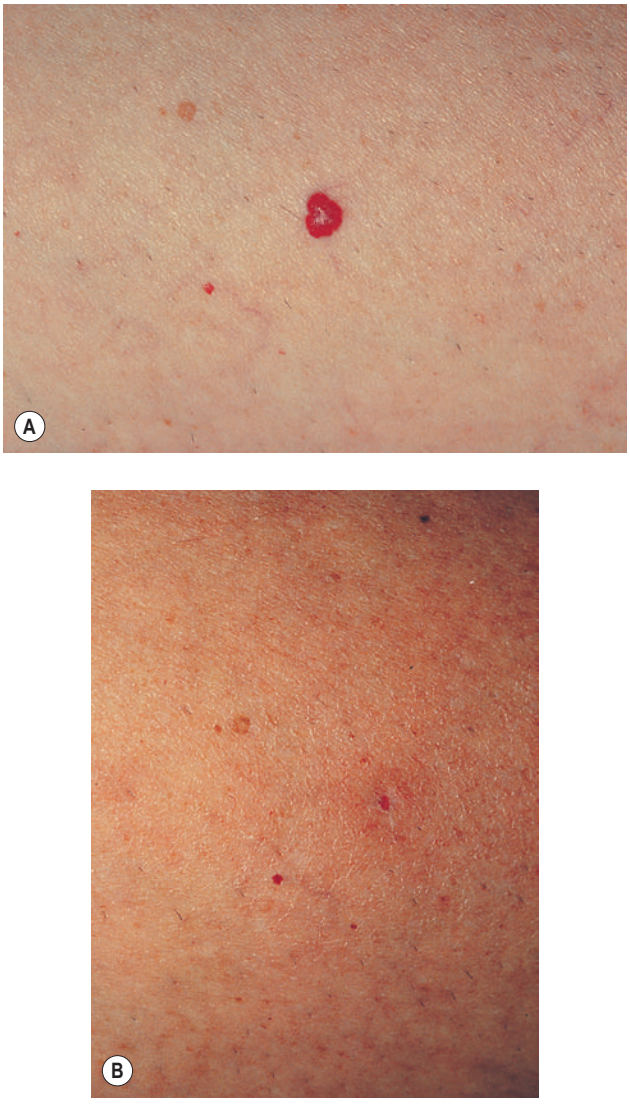

Figure 12.23 Case Study 6. **A,** Multiple cherry hemangiomas on anterior thigh. **B,** Five months after injection.

CASE STUDY 7 Lateral subdermal plexus

A 59-year-old woman was seen initially with a leg ache from the lateral thigh veins that had been increasing in severity over the previous 2 years. Reticular and telangiectatic veins had been present since age 16. The lateral subdermal plexus, noted as having 2- to 3-mm-diameter reticular veins, was incompetent to venous Doppler examination (Fig. 12.24A). Sclerotherapy began with injection of a total of 4 mL of POL 0.75% to all reticular veins on the left leg while the patient was supine. All telangiectasias that did not become inflamed after reticular vein injection were then sclerosed with a total of 6 mL of POL 0.5%. The leg was compressed for 72 hours with a 30- to 40-mmHg graduated compression stocking. A second treatment to the same leg was given 4 months later with 4 mL of POL 0.75% injected into reticular veins and 2 mL of POL 0.5% injected into remaining telangiectasias. The leg was compressed as previously described, and all veins and bruising resolved within 2 months. Figure 12.24B shows total resolution of all veins 1 year after the second treatment.

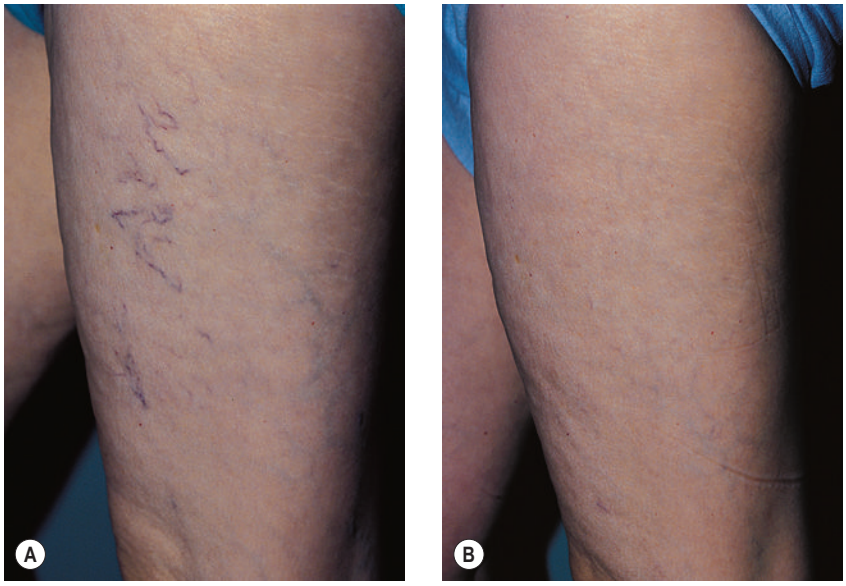

Figure 12.24 Case Study 7. **A,** Clinical appearance before sclerotherapy. **B,** Clinical appearance 1 year after treatment (see text for details).

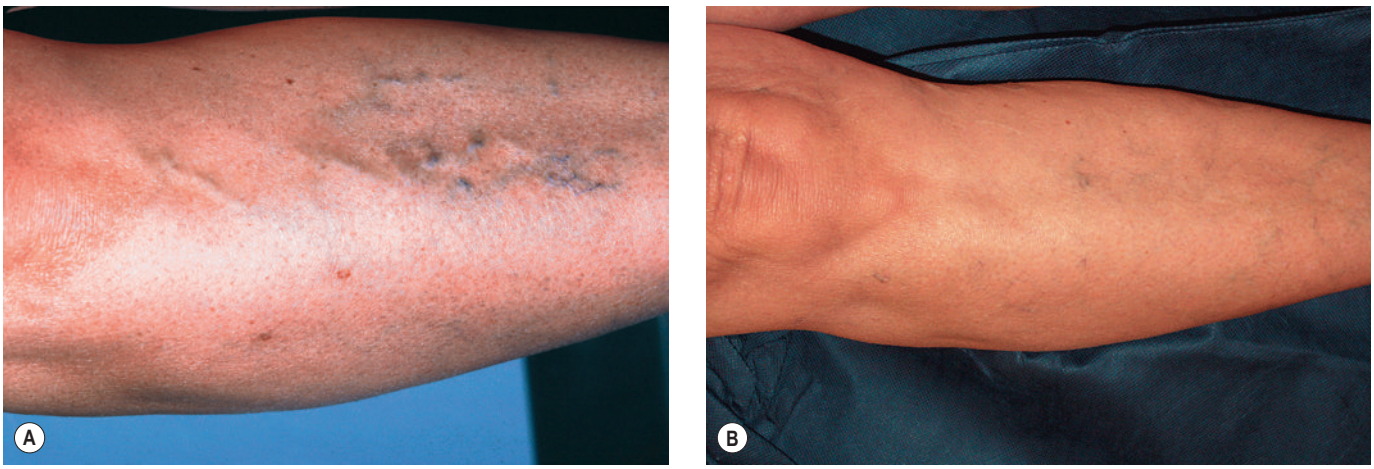

Figure 12.25 Case Study 8. **A,** Dilated pretibial reticular veins. **B,** Presentation with new veins 16 years after treatment.

CASE STUDY 8 Long-term follow-up of sclerotherapy for telangiectasia

A 43-year-old woman presented with dilated pretibial reticular veins 2–4 mm in diameter (Fig. 12.25A). She had a history of playing tennis and working on a hard floor. No evidence of truncal vein incompetence was found. She was treated with one session of sclerotherapy using 2 mL of STS 0.5% and then wore 30- to 40-mmHg graduated compression stockings 24 hours per day for 7 days. She reported complete resolution of her veins after 6–8 weeks and did not recall any posttreatment pigmentation. She presented 16 years later for treatment of new veins on her thighs (Fig. 12.25B).

CASE STUDY 9 Long-term follow-up of sclerotherapy for telangiectasia

A 52-year-old woman presented with scattered telangiectasia in patches without obvious feeding reticular veins on her anterior thigh (Fig. 12.26A). The veins measured 0.2–0.4 mm in diameter. She was treated with one session of sclerotherapy using 1.5 mL of STS 0.25% and then wore 30- to 40-mmHg graduated compression stockings 24 hours per day for 7 days. She reported complete resolution of her veins after 4–6 weeks and did not recall any posttreatment pigmentation. Figure 12.26B, shows the appearance of the treated area 6 years later, when she presented for treatment of new veins on her calves.

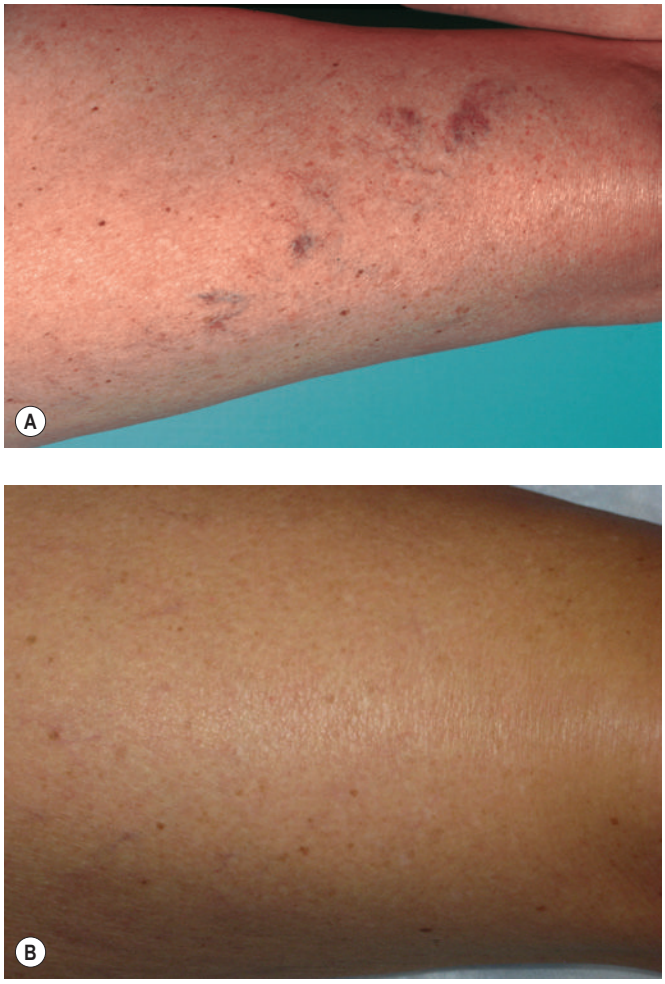

Figure 12.26 Case Study 9. **A,** Scattered telangiectasia in patches without obvious feeding reticular veins on the anterior thigh. **B,** Presentation 10 years later with persistent resolution of the treated veins.

CASE STUDY 10 Treatment of telangiectasia and resulting telangiectatic matting

A 66-year-old woman was seen initially with extensive telangiectasias and venules 0.2–0.6 mm in diameter over the left lateral knee (Fig. 12.27A). These veins developed when she was near 40 years of age after she began estrogen replacement therapy. There was no previous family history of varicose veins. In addition to the cosmetic appearance that was disturbing when she wore shorts while playing golf, her legs ached continuously, especially over the telangiectasias. These vessels were treated with POL 0.5%, 2 mL, with the development of TM 4 weeks after treatment (Fig. 12.27B). Examination 3 months after initial treatment showed a 'feeding' reticular vein in the telangiectatic area. The feeding reticular vein, 2 mm in diameter, was treated with POL 0.75%, 1 mL, and the TM vessels were then treated with CG mixed 1:1 with lidocaine 1% with epinephrine, 1 mL, with resolution occurring in approximately 4 weeks. When the woman was examined 1 year later, the telangiectasia and leg pain had both resolved (Fig. 12.2C).

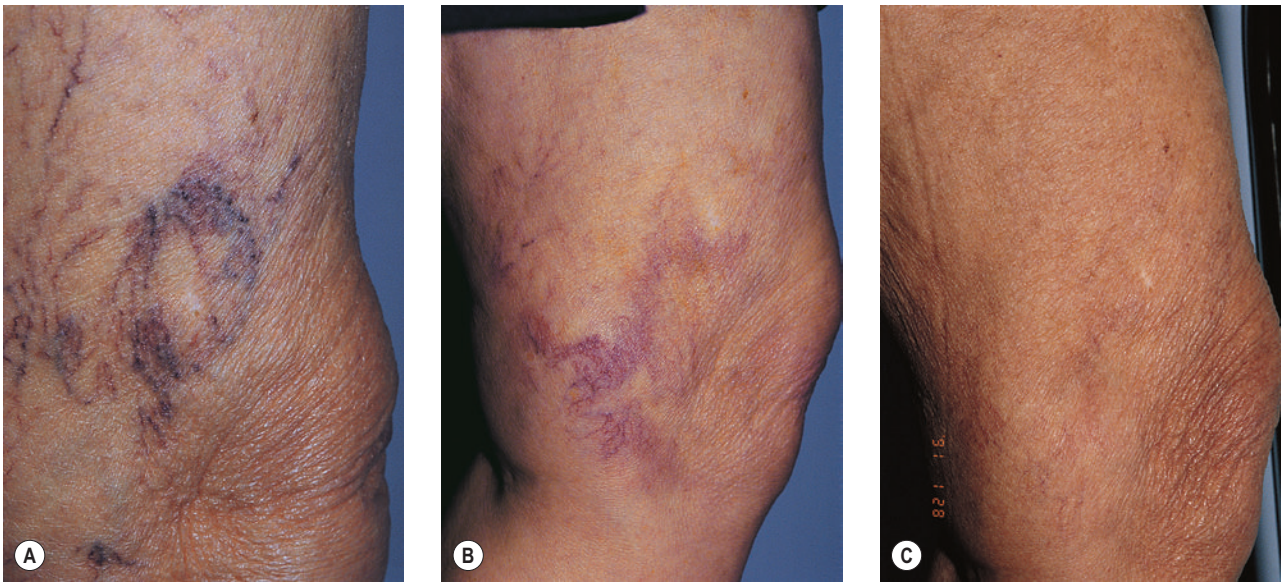

Figure 12.27 Case Study 10. **A,** Clinical appearance before sclerotherapy. **B,** Developmental of telangiectatic matting after sclerotherapy. **C,** Resolution of telangiectasia 1 year after treatment (see text for details).

CASE STUDY 11 Treatment of facial telangiectasia

A 40-year-old man with a 20-year history of a prominent periorbital vein requested treatment (Fig. 12.28A). Physical examination showed a 2-mm venule in the lateral infraorbital region. A 6-0 Prolene suture was placed in the lateral canthal crease to close the vein circumferentially, and 0.2 mL of Sclerodex was injected slowly into the bulging vein. Immediate handheld pressure was applied with an ice pack and maintained by the patient for 5 minutes. The suture was removed the next day. Figure 12.28B shows the appearance 8 weeks after treatment. A tiny coagulum is present in the resolving vein. Follow-up examination 12 years later showed continued elimination of the vein (Fig. 12.28C).

CASE STUDY 12 Treatment of facial telangiectasia

A 65-year-old man presented with prominent perinasal red telangiectasia (Fig. 12.29A). A slow infusion of POL 0.5% was given into the telangiectasia, and the solution was held in place until the vessel went into spasm. A total of 0.5 mL of solution was given in a single treatment session into nasal vessels. Three weeks after treatment, the vessels had resolved (Fig. 12.29B). When the patient was seen in follow-up 15 years later, the treated vessels were not present. New red telangiectasias were present but were not as prominent as before treatment (Fig. 12.29C).

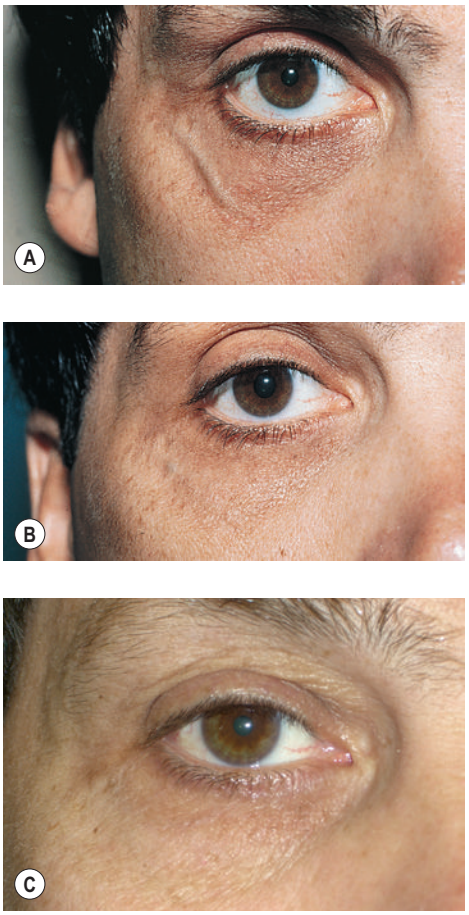

Figure 12.28 Case Study 11. **A,** Periorbital vein before treatment. **B,** Appearance 8 weeks after treatment. **C,** Continued elimination of the vein 12 years after treatment. (From Goldman MP, Weiss RA, Brody HJ, et al. J Dermatol Surg Oncol 19:899, 1993.)

CASE STUDY 13 Facial telangiectasias and venous malformation

An 8-year-old boy had been treated 4 years before for an extensive venous malformation of the right cheek. The initial treatment had included embolization with Ethibloc (Ethicon, Somerville, NJ) and subsequent surgical removal of remaining material. A perilesional network of spider veins outlining the remaining scar was still present (Fig. 12.30A). Injection of 1 mL of 0.5% POL foam in three different points was challenging because the patient had also requested local anesthesia with EMLA cream (lidocaine/prilocaine), inducing a venous spasm. Two sessions led to a nice improvement and patient satisfaction.

CASE STUDY 14 Sclerotherapy of telangiectasias on venous malformation

A 12-year-old girl presented with an extensive venous malformation of the left limb. Lesions were present at birth. One can observe the development of large competent superficial veins: great saphenous vein and accessory anteromedial extrafascial tributary (Fig. 12.31). A wide but light pink port-wine stain extended the length of the limb, but both legs had the same lengths and circumferences. The girl was concerned mainly with the development of telangiectatic and reticular veins on the anterior, medial and lateral aspects of the limb. Because reflux had not been detected in either the deep or superficial venous networks, careful microsclerotherapy with POL 0.5% foam was carried out, improving the lesions with patient satisfaction after four sessions.

CASE STUDY 15 Treatment of reticular chest veins

A 40-year-old woman developed dilated reticulated veins on her chest shortly after undergoing breast augmentation (Fig. 12.32A). Sclerotherapy was performed using STS 0.25% foam made by using 1 mL of STS and 4 mL of air. A total of 8 cm^3 of foam (2 mL of solution) was used to infiltrate the entire anterior chest venous network. Figure 12.32B shows the appearance 3 months after treatment.

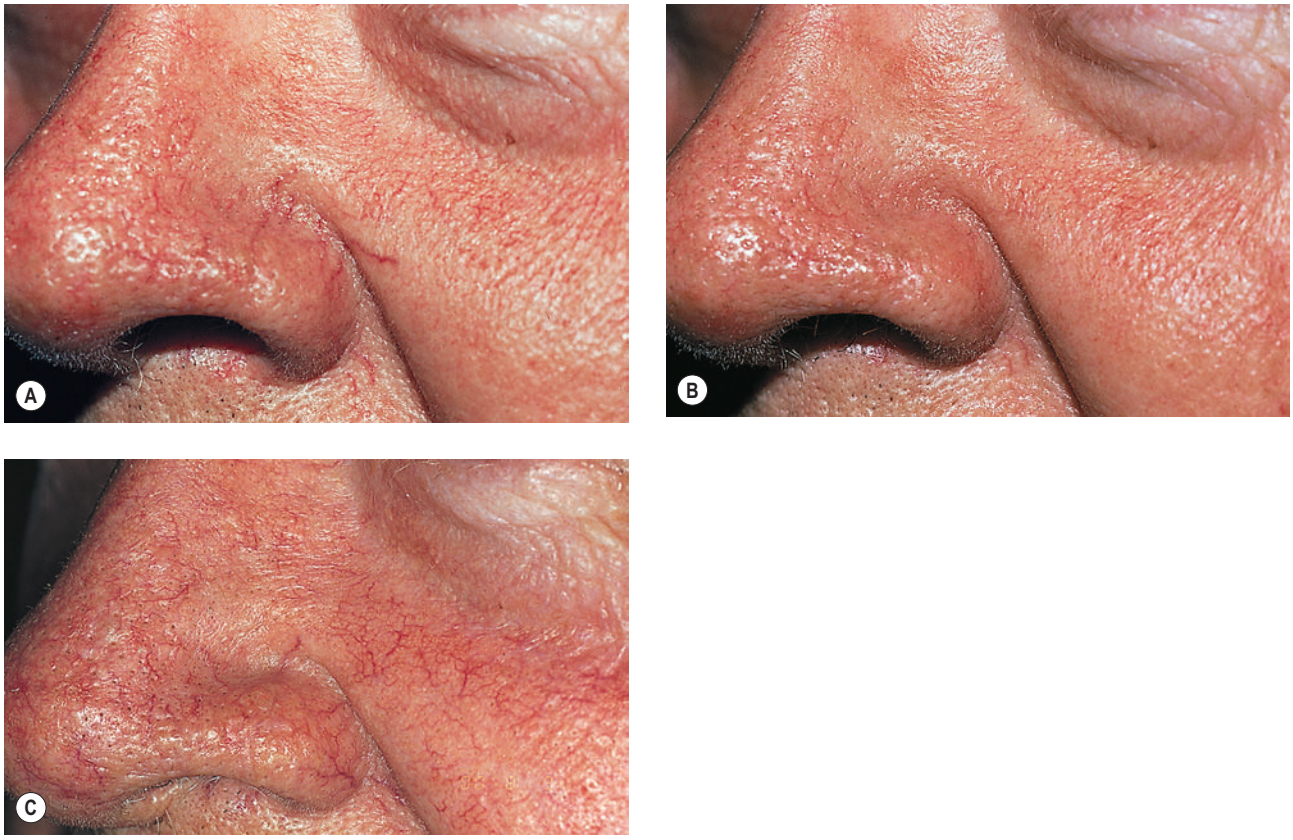

Figure 12.29 Case Study 12. **A,** Perinasal telangiectasia before treatment. **B,** Appearance 3 weeks after one treatment with 0.5 mL of polidocanol 0.5%. **C,** Appearance 15 years after initial treatment. Note persistent resolution of treated telangiectasia with appearance of new telangiectasia.

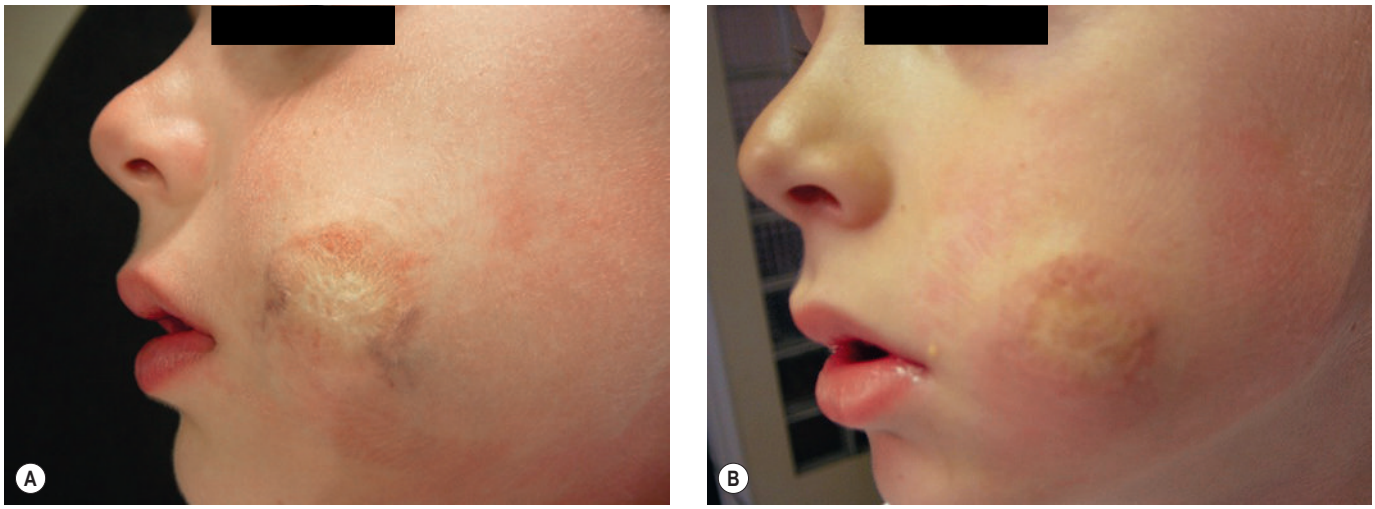

Figure 12.30 Case Study 13. Facial telangiectasias and venous malformation **(A)** before and **(B)** after treatment with polidocanol foam.

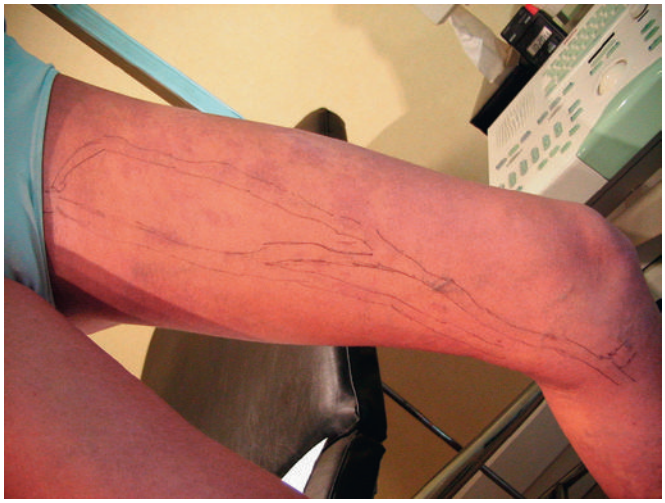

Figure 12.31 Case Study 14. Telangiectasias on venous malformation.

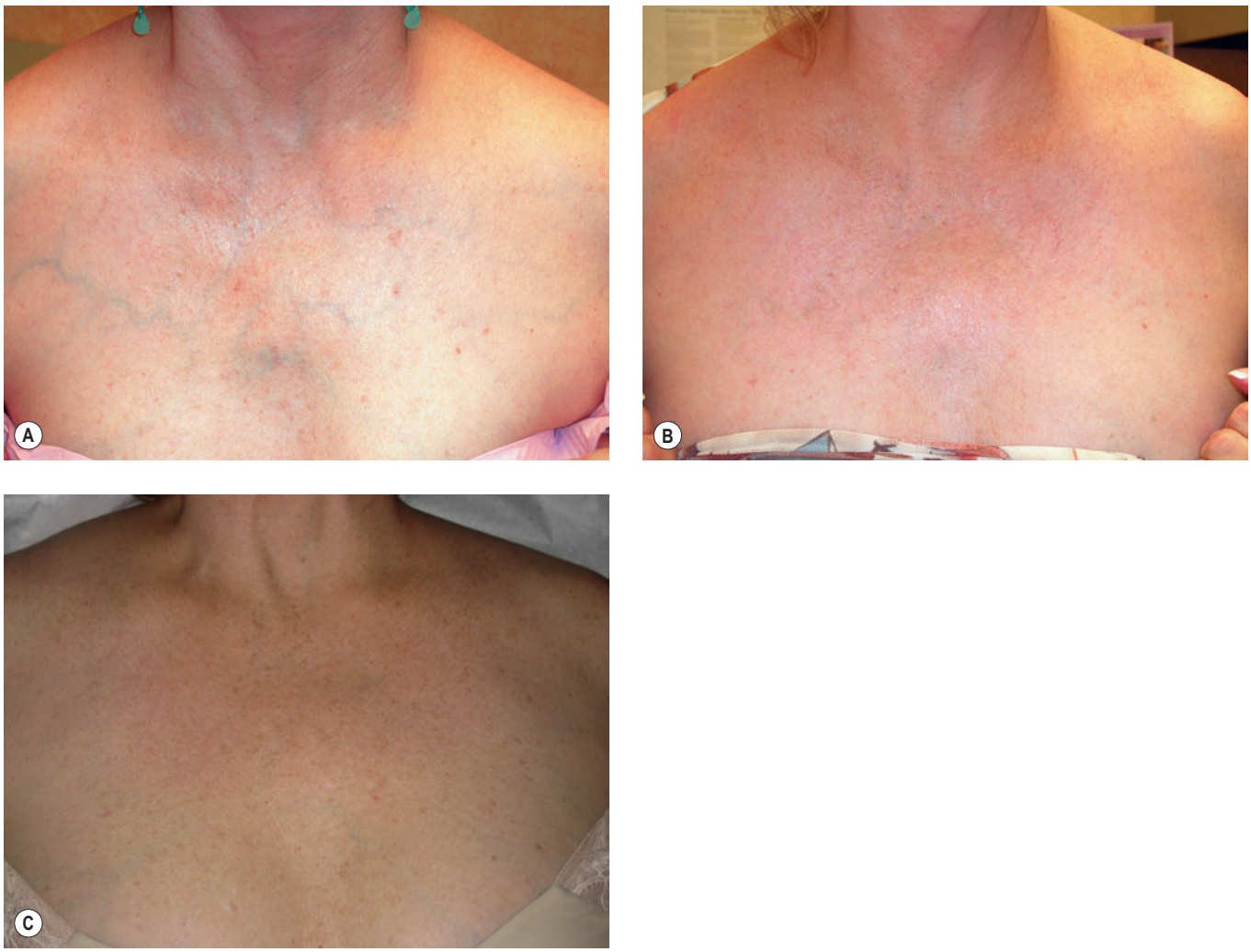

Figure 12.32 Case Study 15. **A,** Dilated reticulated veins on the chest. **B,** Appearance 3 months after sclerotherapy using sodium tetradecyl sulfate 0.25% foam. **C,** Appearance 5 years after treatment. Note persistent resolution of the treated veins.

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13 Treatment of Leg Telangiectasias with Laser and High-Intensity Pulsed Light

Mitchel P. Goldman, with contributions by Cindy Chambers

The laser was first conceived in the imagination of H.G. Wells, who described the use of a light gun in 1896 as an outer-space weapon. Albert Einstein then transformed this vision into a theoretical possibility in the early 1900s. Einstein described the process of stimulated emission as an offshoot in his quest to show the inherent singular nature of the four basic forces of the universe. However, it was not until 1960 that the first laser was actually constructed.

The acronym LASER stands for Light Amplification by the Stimulated Emission of Radiation. In short, a laser emits a beam of monochromic, coherent, collimated photons of a specific wavelength. The emitted wavelength is produced by exciting an atom or molecule to release photons at a wavelength or wavelengths specific for that type of molecule. This ability to produce laser light at a specific wavelength is one key factor in the production of selective damage. By tuning the laser to the absorption spectrum of a particular target, such as oxygenated hemoglobin, theoretically only that target will be affected by the laser energy.

With proper use, lasers are very safe and have not been associated with long-term side effects. Most of the laser radiation used in medicine is within or near the range of visible light in the electromagnetic spectrum. Therefore, its radiant energy level is at a much longer wavelength than that of the high-energy ionizing radiation associated with x-rays and radiation therapy; as such, it is not associated with commonly perceived radiation hazards.[1] In addition to determining the specificity of absorption, each laser's emitted wavelength also dictates the depth of its penetration (Fig. 13.1). (A more thorough discussion of laser physics can be found in other sources.[1,2])

Lasers have been used to treat leg telangiectasias for various reasons.[3] First, lasers have a futuristic appeal. By virtue of their advanced technology, lasers are perceived as 'state-of-the-art'. The general public often equates 'high tech' with treatment safety and superiority. Unfortunately, as described later, this perception by both the general public and the physician has often resulted in unanticipated adverse sequelae (scarring and pain) and higher costs; lasers cost considerably more to purchase and maintain than a needle, syringe and sclerosing solution.

Lasers do however have theoretical advantages compared with sclerotherapy for treating leg telangiectasias including minimizing telangectatic matting, hyperpigmentation associated with hemosiderin deposition and potential allergenic effects. Sclerotherapy-induced pigmentation is caused by hemosiderin deposition through extravasated red blood cells (RBCs) (see Chapter 8). In general, laser coagulation of vessels should minimize this effect. In the rabbit ear model, approximately 50% of vessels treated with an effective concentration of sclerosing solution demonstrated extravasated erythrocytes, compared with a 30% incidence when treated with the flashlamp-pumped pulsed dye laser (PDL) (Goldman MP, unpublished observations). Furthermore, telangiectatic matting (TM), which occurs in a significant percentage of sclerotherapy-treated patients, is less commonly observed after laser treatment of vascular lesions and only seen when excessive inflammation occurs especially with the use of the long-pulsed 1064-nm Nd:YAG laser as described later. Finally, specific allergenic effects of sclerosing solutions are not a concern when treating telangiectasias with a laser.

Both lasers and intense pulsed light (IPL) have been used to treat leg telangiectasias, each acting via thermal energy to induce vessel destruction. Effective lasers and IPL are pulsed so that their effects act within the thermal relaxation times of blood vessels to produce specific destruction of vessels of various diameters based on the pulse duration. This selective thermocoagulation takes advantage of the difference between the absorption of the components in a blood vessel (oxygenated and deoxygenated hemoglobin) and the overlying epidermis and surrounding dermis (as described later). Each wavelength requires a specific fluence to cause vessel destruction. Leg veins are filled with predominantly deoxygenated hemoglobin; in comparison with oxygenated hemoglobin, found primarily in port-wine stains (PWSs) and hemangiomas. Selective wavelengths for deoxyhemoglobin as opposed to oxyhemoglobin include approximately 545 nm, 580 nm and a broad peak between 650 and 800 nm.

Optical properties of blood are mainly determined by the absorption and scattering coefficients of its various oxyhemoglobin components. Oxyhemoglobin has three major absorption peaks at 418, 542 and 577 nm. A less selective and broader absorption peak spans from approximately 750 to 1100 nm. Figure 13.2 shows the oxyhemoglobin absorption and scattering coefficient depth of penetration into blood.[4] The main feature to note in the curve is the strong absorption of oxyhemoglobin and deoxyhemoglobin at wavelengths below 600 nm with less absorption at longer wavelengths. However, in larger vessels (>1 mm in diameter) a much higher absorption of light occurs even at wavelengths longer than 600 nm. This absorption is even more significant for blood vessels 2 mm in diameter. Therefore, use of a light source above 600 nm in vessels greater than 1 mm in diameter results in deeper penetration of thermal

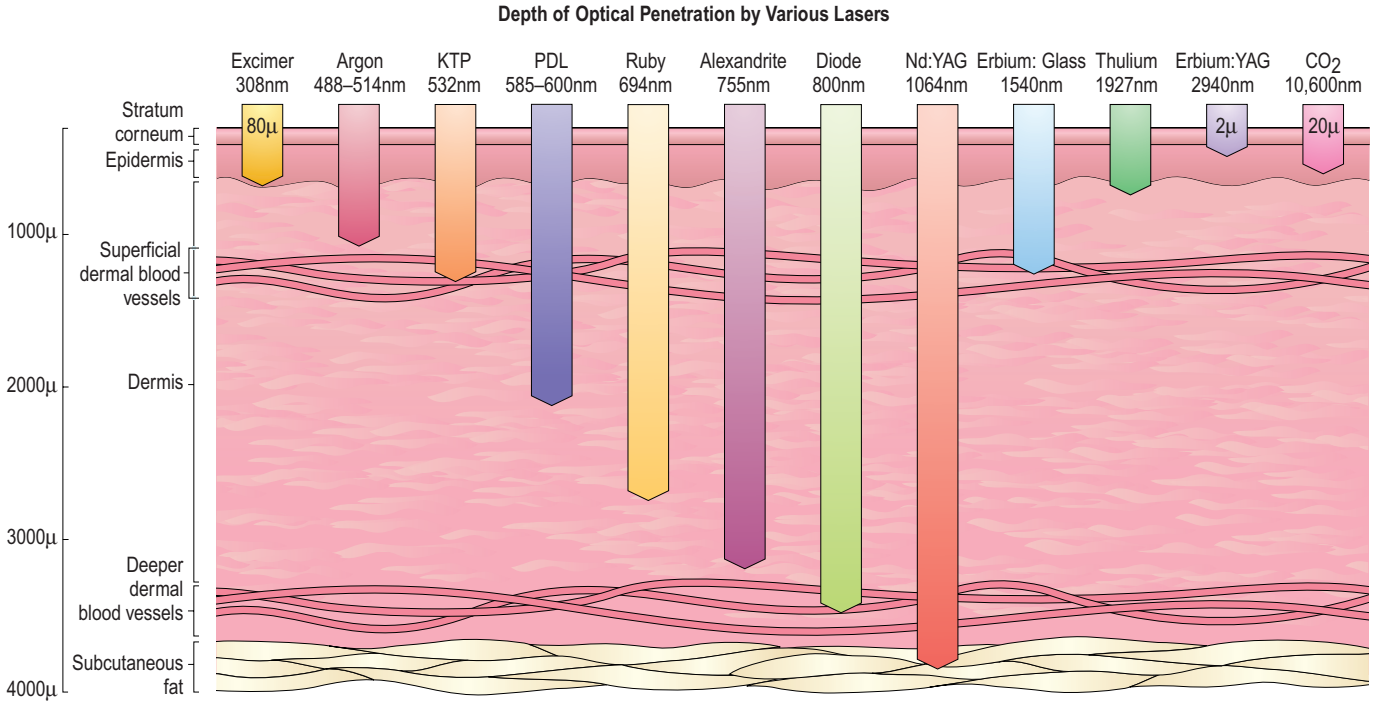


Figure 13.1 Diagram representing approximate levels of penetration for various lasers. (From Bolongia JL, Jorizzo JL, Rapini RP. Dermatology. 3rd ed. St Louis: Mosby Elsevier; 2012.)

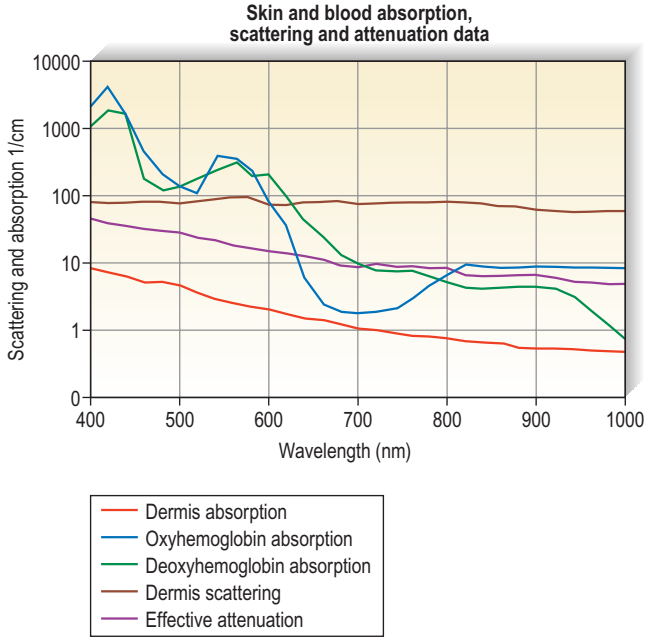


Figure 13.2 Coefficient of blood relative to dermis.

energy without negating absorption by oxyhemoglobin. This occurs because the absorption coefficient in blood is higher than that of surrounding tissue for wavelengths between 600 and 1000 nm (Figs 13.2 and 13.3). Shorter wavelengths heat only the portion of the vessel wall closest to the skin surface, which can result in incomplete thrombosis in larger and deeper vessels.[5] The only caveat is that wavelengths greater than 900 nm are less specific to oxyhemoglobin and also target water. This decrease in specificity requires higher fluences to produce desired effects on the target chromophore, thereby increasing the risk of unnecessary damage to surrounding and overlying tissue unless adequate cooling measures are employed.[6]

Patients seek treatment for leg veins largely for cosmetic reasons and any potential side effect that may compromise the resultant aesthetic outcome of a treatment should be minimized.[7] In a study of 500 consecutive patients (age 20–70 years)[8] presenting for laser removal of lower extremity spider veins (28% <0.5 mm in diameter; 39% <1.5 mm in diameter), TM developed in 56% of patients who had had sclerotherapy (not stated how this was performed). With recent advances in lengthening pulse duration and epidermal cooling, lasers and IPL have become accepted methods for treating telangiectatic vessels and may be appropriate as stand-alone or combination therapy in some circumstances with a minimum of adverse effects. However, for these advanced treatments to be effective and safe, they must be used appropriately.

As detailed in Chapter 8, sclerotherapy has a number of potential adverse effects including postsclerosis pigmentation[9] and/or TM.[10] These adverse effects can occur even with optimal treatment but are more common when an excessive inflammatory reaction occurs. To minimize risks of an inflammatory response, lasers and IPL act by producing thermal damage with the ultimate goal being vaporization of the targeted vessel with minimal impact on the surrounding tissue. When used with appropriate fluences, pulse durations and epidermal cooling, the thermal effects of lasers and IPL present minimal inflammatory response compared with detergent, chemical or osmotic irritation of the vessel wall through sclerotherapy.

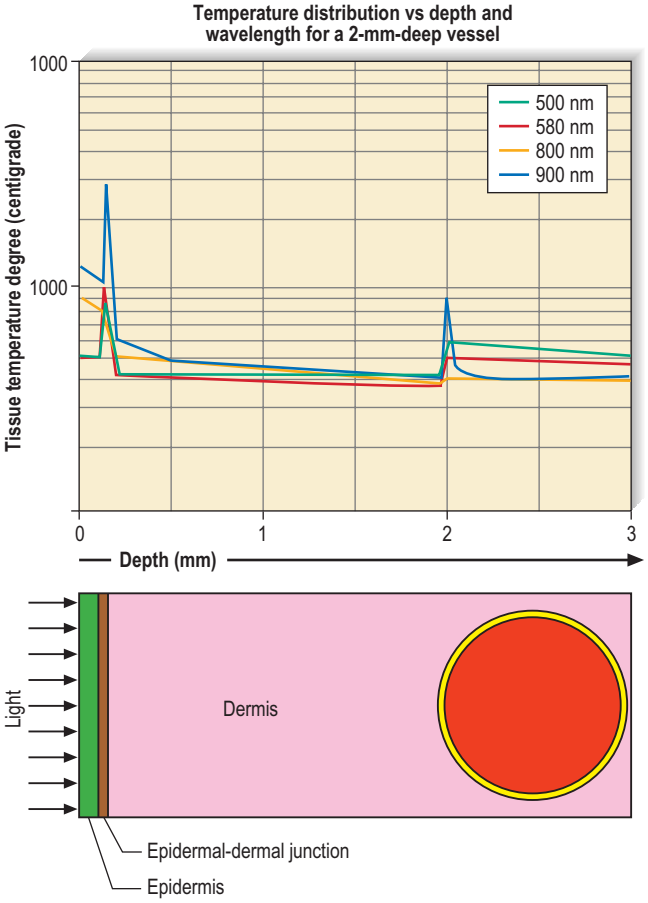


Figure 13.3 Temperature distribution across skin and blood vessel. A 2-mm deep, 1-mm diameter vessel is assumed. A 10-J/cm^2 fluence is assumed at four different wavelengths. The calculation takes into account scattering effects in the epidermis and dermis and fluence enhancement because of scattering. Note the very high temperature on the skin surface and at the epidermal–dermal junction and the shallow penetration for the shorter wavelengths. (Courtesy Shimon Eckhouse, PhD, Energy Systems Corporation, Inc., Newton, MA; from Goldman MP, Fitzpatrick RE. Cutaneous laser surgery. St Louis: Mosby; 1994.)

An understanding of the appropriate target vessel for each laser and/or IPL is important so that treatment is tailored to the appropriate target. As detailed elsewhere in this book, most telangiectasias arise from reticular veins. Therefore, the single most important concept for the treating physician is that feeding reticular veins must be treated completely before treating the telangiectasias. This minimizes adverse sequelae and enhances therapeutic results. When no apparent connection exists between deep collecting or reticular vessels, telangiectasias may arise from a terminal arteriole or arteriovenous anastomosis.[11] In this latter scenario, the telangiectasias may be treated without consideration of underlying forces of hydrostatic pressure. Failure to treat 'feeding' reticular veins and short follow-up periods after the use of lasers may give inflated values to the success of laser treatment.[12] This chapter reviews and evaluates the use of nonspecific and specific laser and light systems in the treatment of leg venules and telangiectasias (Table 13.1).

HISTOLOGY OF LEG TELANGIECTASIAS

The choice of proper wavelength(s), degree of energy fluence and pulse duration of light exposure are all related to the type and size of target vessel treated. Deeper vessels necessitate a longer wavelength to allow adequate penetration. Large diameter vessels necessitate a longer pulse duration to effectively thermocoagulate the entire vessel wall, allowing sufficient time for thermal energy to diffuse evenly throughout the vessel lumen. The correct choice of treatment parameters is aided by an understanding of the histology of the target telangiectasias.

Venules in the upper and middle dermis typically maintain a horizontal orientation. The diameter of the postcapillary venule ranges from 12 to 35 μm.[13] Collecting venules range from 40 to 60 μm in the upper and middle dermis and enlarge to 100 to 400 μm in diameter in the deeper tissues. Histologic examination of simple telangiectasias demonstrates dilated blood channels in a normal dermal stroma with a single endothelial cell lining, limited muscularis and adventitia.[14,15] Most leg telangiectasias measure from 26 to 225 μm in diameter.[14] Electron microscopic examination of 'sunburst' varicosities of the leg has demonstrated that these vessels are widened cutaneous veins.[14] They are found 175 to 382 μm below the stratum granulosum. The thickened vessel walls are composed of endothelial cells covered with collagen, elastic and muscle fibers.

Arteriovenous anastomoses may also be involved in the pathogenesis of telangiectasias and have been demonstrated in 1 of 26 biopsy specimens of leg telangiectasiass.[11] Red telangiectasias have been found to have an oxygen saturation of 76%, compared with blue telangiectasias, which have an oxygen concentration of 69%.[16] Thus each type of telangiectasia may have a slightly different optimal absorption wavelength based on its color in addition to its relative size and depth.

Unlike leg telangiectasias, the ectatic vessels of PWSs are arranged in a loose fashion throughout the superficial and deep dermis. They are more superficial (0.46 mm) and much smaller than leg telangiectasias, usually measuring 10 to 40 μm in diameter. This may explain the lack of efficacy reported by many physicians who treat leg telangiectasias with the same laser and parameters as they do with PWSs.

LASER TREATMENT OF LEG TELANGIECTASIAS

Various lasers have been used in an effort to enhance clinical efficacy and to minimize the adverse sequelae of telangiectasias treatment. Unfortunately, most have also been associated with adverse responses far in excess of those associated with sclerotherapy. This is related both to the nonspecificity of the laser used and failure to treat the hydrostatic pressure from the 'feeding' venous system.

The optimal light source should have a wavelength specific for the vessel treated and should be able to penetrate to the depth of the vessel through its entire diameter. This wavelength has been proposed to be between 600 and 900 nm. Additionally, a light source should have a pulse duration that would allow the light energy to build in the target vessel allowing thermocoagulation of its entire

Table 13.1 Lasers and Light Sources for Leg Veins

Supplier	Product Name	Device Type	Wavelength (nm)	Energy (J)	Pulse Duration (ms)	Spot Diameter (mm)	Cooling
American BioCare	OmniLight FPL	Fluorescent pulsed light	480, 515, 535, 550, 580–1200	Up to 90	Up to 500	External continuous	
Adept Medical	Ultrawave II/III	Alexandrite	755	5–55	5–50	8, 10, 12	None
	Ultrawave	Nd:YAG	1064	5–500	5–100	2, 4, 6, 8, 10, 12	None
Aerolase	LightPod Neo XT	Nd:YAG	1064	Up to 1274	0.65 or 1.5		
Alderm	Prolite	IPL	550–900	10–50	10 × 20, 20 × 25		
Alma (formerly Orion)	Harmony	Fluorescent pulsed light	515–950	5–30	10, 12, 15	40 × 16	None
		Nd:YAG	1064	30–450	10, 15, 45, 60	2, 6	
Asclepion-Meditech	Pro Yellow	CuBr	578	55	300	1.5	None
Candela	Vbeam Perfecta	Pulsed dye	595	Up to 40	0.45–40	Multiple, up to 12	DCD
	Vbeam Platinum	Pulsed dye	595	Up to 40	0.45–40	Multiple	DCD
	Vbeam Aestehtica	Pulsed dye	595	Up to 20	0.45–40	Multiple, up to 10	DCD
	Cbeam	Pulsed dye	585	8–16	0.45	5, 7, 10	DCD
	Gentle YAG VR	Nd:YAG	1064	Up to 600	Up to 300	1.5–3	DCD
	GentleLASE	Alexandrite	755	Up to 100	3	6, 8, 10, 12, 15, 18	DCD
	GentleMax	Alexandrite/ Nd:YAG	755/1064	Up to 600	0.25–300	1.5–18	DCD and Cold air
CoolTouch	Varia	Nd:YAG	1064	Up to 500	300 continuous	2–10	DCD
Cutera	CoolGlide Excel	Nd:YAG	1064	5 to 300	1–300	3, 5, 7, 10	
	CoolGlide Vantage	Nd:YAG	1064	Up to 300	0.1–300	3, 5, 7, 10	Copper contact
	XEO	Nd:YAG and Pulsed light 1064 and 600–850	Up to 300 and 6–40 (Pulsed light)	0.1 to 300 and Automatic (Pulsed light)	10 × 30	None	
	Solera Opus	Pulsed light	500–635	3–24	Variable	6.35	
Cynosure/ Deka	PhotoGenica V	Pulsed dye	585	20	0.45	3, 5, 7, 10	Cold air
	PhotoGenica V-Star	Pulsed dye	585–595	40	0.5–40	5, 7, 10, 12	Cold air
	SmartEpil II	Nd:YAG	1064	1–200	Up to 100	2, 5, 7, 10	Cold air
	Acclaim	Nd:YAG	1064	10–600	0.4–300	3, 5 ,7, 10, 12	Cold air
	Cynergy	Pulsed dye/ Nd:YAG	595/1064	2–40/10–600	0.5–40/0.3–300	1.5, 12, 15	Cold air
	Cynergy with XPL	Pulsed dye/ Nd:YAG/ Pulsed light 595/1064/ 560–950	2–40/10–600	0.5–40/0.3–300/5–50	Cold air		
	Cynosure PL	Pulsed light	560–950	3–10	5–50	46 × 18, 46 × 10	
	PhotoLight	Pulsed light	400–1200	3–30	5–50	46 × 18; 46 × 10	None
	Elite	Alexandrite/ Nd:YAG	755/1064	25–50/ 10–600	0.5–300/ 0.4–300	1.5, 12, 15	Cold air
DDD	Elipse	IPL	400–950	Up to 21	0.2–50	10 × 48	
DermaMed USA	Quadra Q4 (Platinum and Gold Series)	Pulsed light	510–1200	10–20	48	33 × 15	None
	DermaYAG	Nd:YAG	1064	15–300	150	1, 2, 3, 4, 6, 8, 10, 12	
Fotana	Dualis	Nd:YAG	1064	Up to 600	5–200	2–10	None

Continued on following page

Table 13.1 Lasers and Light Sources for Leg Veins (Continued)

Supplier	Product Name	Device Type	Wavelength (nm)	Energy (J)	Pulse Duration (ms)	Spot Diameter (mm)	Cooling
Iridex	Apex-800	Diode	800	5–60	5–100	7, 9, 11	Cooling handpiece
	DioLite^{XP}	KTP	532	250	5–100	0.5, 0.7, 1.0	
	VariLite	KTP/Diode	532/940	250/850	5–100	0.7, 1, 2	
	Lyra i	Nd:YAG	1064	5–900	20–100	1–5 Cont. Adjustable	Cooling handpiece
	Aura i	KTP	532	1–240	1–50	1–5 Cont. Adjustable	Cooling handpiece
	Gemini	KTP	532	Up to 100	1–100	1–5 Cont. Adjustable	Cooling handpiece
		Nd:YAG	1064	Up to 990	10–100	1–5 Cont. Adjustable & 10	Cooling handpiece
LightAge	Epicare	Alexandrite	755	25–40	3–300	7, 9, 12, 15	None
Lumenis	Quantum DL	Nd:YAG	1064	90–150	5–38	6	
	Quantum SR	Pulsed light	560–1200	15–45	6–26	34 × 8	Cooled sapphire crystal
	Vasculite Elite	Pulsed light	515–1200	3–90	1–75	35 × 8	
		Nd:YAG	1064	70–150	2–48	6	Cooled sapphire crystal
	LightSheer	Diode	800	10–100	5–400	9 × 9	
	Lumenis One	Pulsed light	515–1200	10–40	3–100	15 × 35, 8 × 15	Cooled sapphire crystal
		Nd:YAG	1064	10–225	2–20	2 × 4, 6, 9	Cooled sapphire crystal
		Diode	800	10–100	5–400	9 × 9	Cooled sapphire crystal
Med-Surge	Quantel Viridis	Diode	532	Up to 110	15–150		
	ProliteII	Pulsed light	550–900	10–50	N/A	10 × 20, 20 × 25	None
OpusMed	F1	Diode	800	10–40	15–40	5,7	None
Palomar	MediLux	Pulsed light	470–1400	Up to 45	10–100	12 × 12+	None
	EsteLux	Pulsed light	470–1400	Up to 40	10–100	12 × 12	None
	SLP1000	Diode	810	Up to 575	50–1000	DC	
	StarLux	Pulsed light/ Nd:YAG	500–670, 870–1400/ 1064	Up to 60/Up to 700	0.5–500	1.5, 3, 6, 9	
Quantel	Athos	Nd:YAG	1064	Up to 80	3.5	4	None
Sciton	Profile	Nd:YAG	1064	4–400	0.1–200	30 × 30	Contact sapphire
	BBL	Pulsed light	400–1400	Up to 30	Up to 200	15 × 45, 15 × 15	Contact sapphire
	BBL/s	N/A	410–1400	Up to 30	Up to 500	15 × 45, 15 × 15	Contact sapphire
	Profile HMV	Nd:YAG/ Pulsed light	1064/410–1400	Up to 400	0.1–200/1–15	30 × 30, 15 × 45	Contact sapphire
Syneron	eLight SR	Optical energy/RF	580–980	Up to 45/Up to 25	N/A	12 × 25	
	eLight SRA	Optical energy/RF	470–980	Up to 45/Up to 25	N/A	12 × 25	
	eLaser LV	Diode/RF	900	Up to 140/Up to 100	N/A	8 × 5	
	eLaser LVA	Diode/RF	900	Up to 350/10 to 100	N/A	8 × 2	
	Polaris Vascular	Diode/RF	900	Up to 50/Up to 100 RF			
	Galaxy	Diode	580–980	Up to 140/Up to 100 RF	Up to 200	1.5, 3, 5, 7, 10	
WaveLight	Mydon	Nd:YAG	1064	10–450	0.5–90	1.5, 3, 5	Contact or cold air
	Arion	Alexandrite	755	5–40	1–50	6, 8, 10, 12, 14	Cold air

Modified from: Goldman MP. Cosmetic and cutaneous laser surgery. Philadelphia: Elsevier; 2006, and THE Aesthetic Guide Primary Care Edition Autumn 2008 (www.miinews.com).

Table 13.2 Thermal Relaxation Times of Blood Vessels

Diameter of Vessel (mm)	Thermal Relaxation Time (s)
0.1	0.01
0.2	0.04
0.4	0.16
0.8	0.6
2.0	4.0

Presented by RA Anderson at the Annual Meeting of the North American Society of Phlebology, 1996: Washington, DC, November.

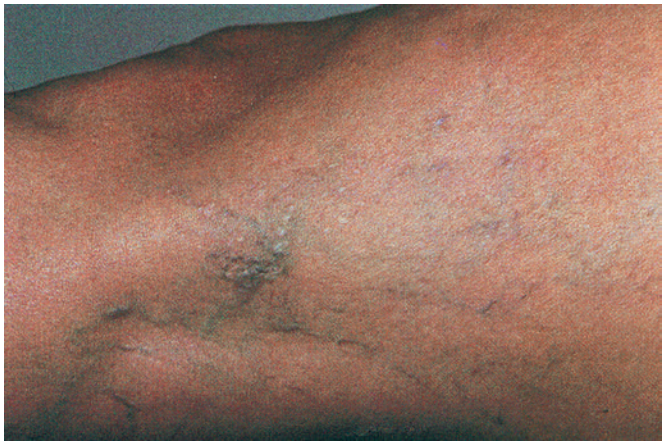


Figure 13.4 Hypopigmented scars with skin textural changes 5 years after treatment of leg telangiectasias with the CO_2 laser.

diameter. Optimal pulse durations have been calculated for various diameter blood vessels (Table 13.2).

During the process of delivering a sufficient packet of energy to thermocoagulate the target vessel, the overlying epidermis and perivascular tissue should also be unharmed. This requires some form of epidermal cooling. A number of different laser and IPL systems have been developed toward this end, as discussed in subsequent sections, though as we will see none perfectly so. In addition to the information presented in the following sections, the reader is encouraged to refer to an excellent summary of various laser treatments for leg veins by Kunishige et al.[6]

CARBON DIOXIDE LASER

The carbon dioxide (CO_2) laser has been used for obliterating venules and telangiectatic vessels.[17–21] One case report described the successful treatment of matted telangiectasias with fractional photothermolysis.[22] The patient underwent five successive monthly treatments with the 1550 Fraxel SR laser (Solta Medical, Hayward, CA), at energies ranging from 10 to 12 mJ, to an area on her medial thigh. At 6 months after the final treatment session, the target areas showed more than 75% improvement. However, because the natural history of matted telangiectasias is usually to spontaneously resolve over the course of a year, it is uncertain how much of the improvement seen in the aforementioned case report was actually a result of 'the tincture of time' as opposed to the CO_2 laser treatment.

The rationale for using the CO_2 laser in the treatment of telangiectasias is to produce 'precise' vaporization without significant damage to tissue structures adjacent to the penetrating laser beam; however, most reported studies demonstrate unsatisfactory cosmetic results. Since the CO_2 laser does not specifically target melanin, it can theoretically be used on those of darker skin types, a subgroup of the population that cannot be safely treated with the PDL. However, with the CO_2 laser, the epidermis and the dermis overlying the blood vessel are destroyed and CO_2 laser disruption of vessels has also been reported to cause occasional brisk bleeding from the vessel, which in one report required pressure bandages for 48 hours.[20] Treated areas have also been described to produce multiple hypopigmented punctate scars with either minimum resolution of the treated vessel or neovascularization adjacent to the treatment site (Fig. 13.4). Pain during treatment is also moderate to severe, but of short duration. Because of this nonselective action, the CO_2 laser is of no advantage over the electrodessication needle and has not been used successfully in treating leg telangiectasias.

ARGON LASER

The argon laser with output at 488 nm and 511 nm has wavelengths somewhat preferentially absorbed by hemoglobin and to a lesser, although significant, extent by water and melanin (Fig. 13.5). Its relatively short wavelength, combined with a spot size of 1 mm, prevents its penetration much beyond 0.5 mm. When the patient is pigmented or tanned, epidermal melanin will selectively absorb the laser energy, preventing penetration below the epidermis and increasing risk of adverse effects. Thus, the argon laser does not have ideal parameters for treating leg veins (Fig. 13.6).

Further, as argon lasers are continuous in nature, they do not allow for selective vessel heating, so scarring commonly occurs.[23] Specifically, argon laser treatment of telangiectasias or superficial varicosities of the lower extremities may cause purple or depressed scars. In a report of 38 patients treated by Apfelberg et al,[18] 49% had either poor or no results from treatment, and only 16% had excellent or good results. In addition, almost half of the patients had hemosiderin bruising. In another series, Dixon et al[24] noted significant improvement in 49% of patients. The authors speculated that after initial improvement, incomplete thrombosis, recanalization or new vein formation produced reappearance of the vessels after 6 to 12 months.

In an effort to enhance therapeutic success with leg vein sclerotherapy, the argon laser has also been used in a combinational approach to interrupt the telangiectasias similar to a 'spot weld' every 2 to 3 cm before injection of a sclerosing agent.[25] In this study, 11 of 16 patients completed treatment. Two patients developed punctate depigmented scars, and three developed hyperpigmentation. Despite this, 93.7% of patients were reported to have 'satisfactory' results.

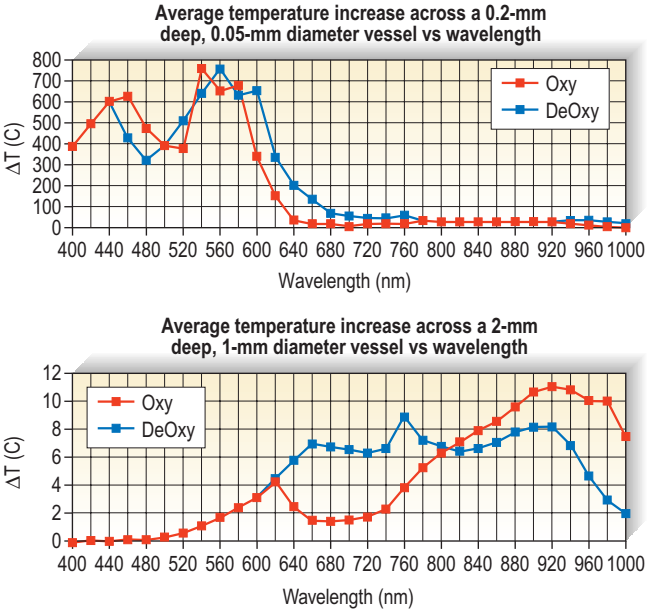


Figure 13.5 Average temperature increase across a cutaneous vessel as a function of wavelength for two cases: a shallow capillary vessel (similar to those found in a port-wine vascular malformation), and a deeper (2 mm) and larger (1 mm) vessel typical of a leg venule. The calculated curves are generated assuming that the main light-absorbing chromophore in the blood is either oxygenated or deoxygenated hemoglobin. The calculation is carried out for a 10-J/cm^2 fluence and does not take into account cooling by heat conductivity. Note the dramatic shift in the optimal wavelength as a function of vessel depth and diameter. Also note the difference between oxygenated and deoxygenated hemoglobin. (Courtesy Shimon Eckhouse, PhD, Energy Systems Corporation, Inc, Newton, MA; from Goldman MP, Fitzpatrick RE. Cutaneous laser surgery. St Louis: Mosby; 1994.)

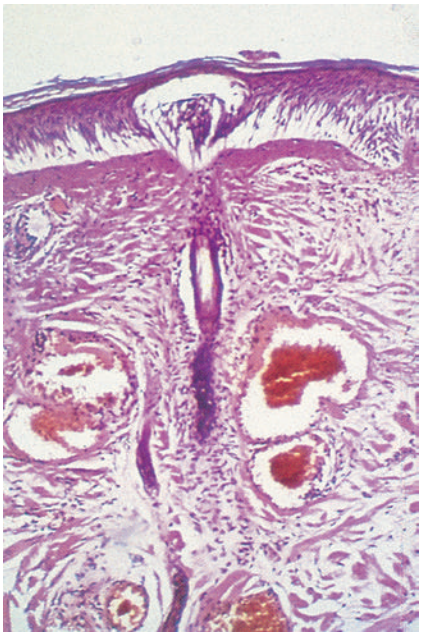


Figure 13.6 Biopsy of a port-wine vascular malformation on the cheek of a 40-year-old man immediately after argon laser treatment at 15 J/cm^2, 1 mm spot diameter, which produced clinical epidermal whitening. Note coagulation of ectatic vessels in the middle and deep dermis with smudging of perivascular collagen. The overlying epidermis shows marked thermal effects with streaming of the epidermal cells and coagulation necrosis of the superficial papillary dermis. (Hematoxylin–eosin, ×200.) (From Goldman MP, Fitzpatrick RE. Cutaneous laser surgery. St Louis: Mosby; 1994.)

Cooling the skin simultaneously with argon or tunable dye (577 nm, 585 nm) laser treatment has been demonstrated to produce improvement in 67% of leg telangiectasias 1 mm in diameter.[26] This may be caused by temperature-related vasomotor changes in blood flow.[27]

ARGON LASER: CONTACT PROBE DELIVERY

Directing the laser energy to the target vessel produces another method for more selective delivery of nonspecific laser energy. Keller[28] reported on the use of a microcontact argon laser probe to treat 'spray telangiectasias' of the leg. Fifteen patients were treated with this device using an argon laser energy of 1 to 2 W with a pulse duration of 0.1 second. This treatment was also performed as 'spot welding' along the course of the blood vessel with a reported 100% effectiveness and no notable complications. We, however, have not achieved the same success rate as Keller,[29] and further reports of this novel form of therapy have not occurred. Thus, at present, argon laser therapy apparently is a satisfactory method for treating selected facial telangiectasias but is much less effective in treating leg telangiectasias and is associated with an unacceptably high risk of adverse sequelae. Box 13.1 summarizes the disadvantages of the argon laser treatment.

Box 13.1 Disadvantages of Argon Laser Treatment

- Partially selective vascular damage
- Hypopigmentation and hyperpigmentation after treatment
- Atrophic and hypertrophic scarring
- Painful procedure

KRYPTON TRIPHOSPHATE AND FREQUENCY-DOUBLED ND:YAG (532 nm)

Modulated krypton triphosphate (KTP) lasers have been reported to be effective at removing leg telangiectasias, using pulse durations between 1 and 50 ms (see Table 13.1). The 532-nm wavelength is one of the hemoglobin absorption peaks (see Fig. 13.5). Although this wavelength does not penetrate deeply into the dermis (about 0.75 mm), relatively specific damage (compared with the argon laser) can occur in the more superficial vascular target by selection of an optimal pulse duration, enlargement of the spot size and addition of epidermal cooling.

Effective results have been achieved by tracing vessels with a 1-mm projected spot size. Typically, the laser is moved between adjacent 1-mm spots with vessels traced at 5 to 10 mm/s resulting in immediate epidermal blanching. Lengthening the pulse duration to match the diameter of the vessel is attempted to optimize treatment (see Table

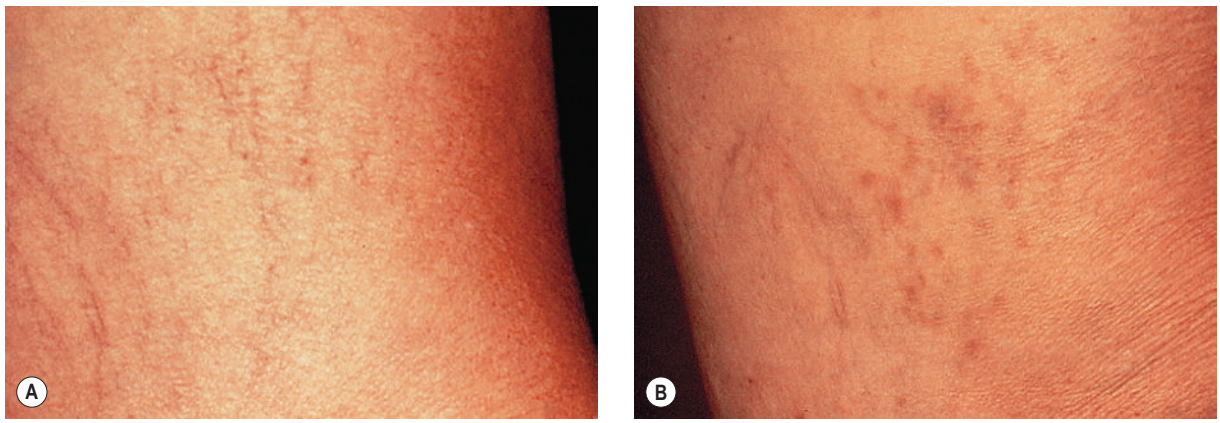


Figure 13.7 **A,** Before treatment. **B,** Three months after treatment there is hyperpigmentation in the telangiectasias treated with the flashlamp-pumped pulsed dye laser at 15 J/cm^2. Of note, the side treated with the KTP (532-nm) laser at 15 J/cm^2 and a 10-ms pulse showed no change. (From West TB, Alster TS. Dermatol Surg 1998;24:221.)

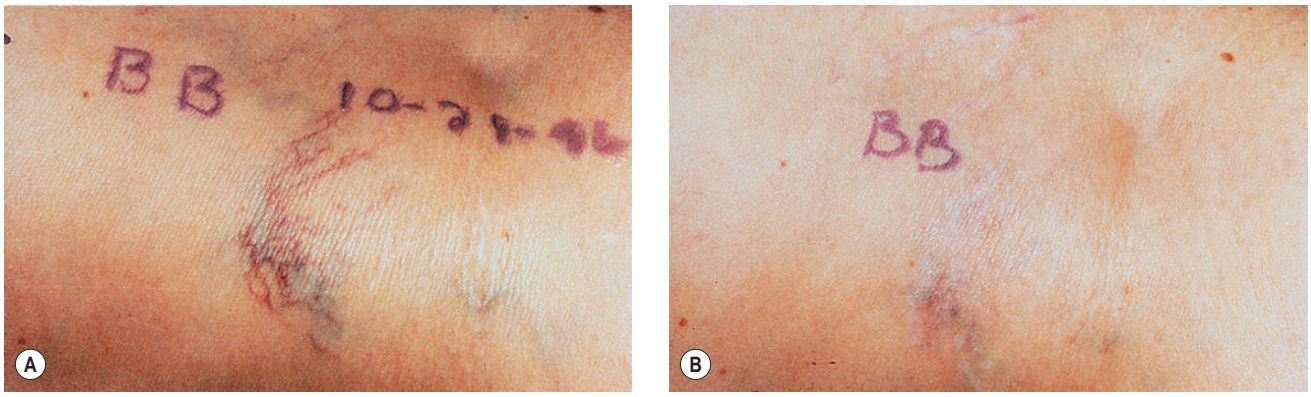


Figure 13.8 **A,** Before treatment. **B,** After one treatment with the VersaPulse at 15 J/cm^2 with a 10-ms pulse through a 3-mm diameter spot with the skin chilled through a 4°C quartz tip. Notice the residual hypopigmentation at the site of the superior most reticular vein seen in A. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (Courtesy Robert Adrian, MD; from Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishers; 1999.)

13.2). West and Alster[30] employed this method in 12 patients with leg telangiectasias using a 1-mm spot size, with a 10-ms pulse (2 pulses per second) at 15 J/cm^2 and found an average improvement of 25% to 50% (Fig. 13.7).

Quintana et al[31] similarly treated 19 leg veins less than 1.5 mm in diameter with the Laserscope KTP Dermastat (Laserscope, San Jose, CA) using a 2-mm diameter handpiece at a fluence of 13 to 15 J/cm^2 and rate of 10 to 15 milliseconds. Patients were treated at 4- to 6-week intervals on four separate visits, with results examined 6 months after the last visit. Of the 28% of patients evaluated, 15% achieved 100% clearance, 40% had 75% clearance, 35% had 50% clearance and 10% had 25% clearance. No scarring was reported; however, 25% had transient hyperpigmentation. Therefore, this laser appears to be somewhat effective but requires multiple treatments.

We and others have found the long-pulse 532-nm laser (frequency-doubled Nd:YAG) (VersaPulse, Lumenis, Palo Alto, CA) to be effective in treating leg veins less than 1 mm in diameter that are not directly connected to a feeding reticular vein.[32] When used with a 4°C chilled tip, a fluence of 12 to 15 J/cm^2 is delivered as a train of pulses in a 3- to 4-mm diameter spot size to trace the vessel until spasm or thrombosis occurs. Notably, some overlying epidermal scabbing is expected with hypopigmentation not uncommonly occurring in dark-skinned patients. While we have found this treatment effective, individual physicians report considerable variation in results described subsequently. Usually, more than one treatment is necessary for maximum vessel improvement, with only rare reports of 100% resolution (Fig. 13.8). A summary of important clinical evaluations of this technology follows.

McMeekin[33] treated 10 patients with 18 sites of leg veins ranging from 0.5 to 1.1 mm in diameter using a VersaPulse with a 3-mm diameter spot, 5.5°C cooling, at 12 and 16 J/cm^2 with one to three passes over each vessel at 2 Hz. The patients were followed for 1 year after a single treatment. Overall, 44% experienced greater than 50% clearance from a single treatment. Six percent of patients had complete clearance, 88% had partial clearance and 6% had no change. Of the partial clearance group more cleared at 16 J/cm^2 than at 12 J/cm^2. At 16 J/cm^2, 37% cleared 25% to 50%, 25% cleared 50% to 75% and 37% cleared 75% to 100%. Importantly, 94% developed hyperpigmentation that

took up to 6 months to resolve and one patient developed blisters and hypopigmented atrophic scars.

Bernstein et al[34] achieved similar efficacy in a study of 15 women (27 treatment sites) with leg telangiectasias less than 0.75 mm in diameter, using a 3-mm spot size, 10-ms pulse duration at 16 J/cm^2 and 4 Hz. Patients were treated with three passes over each vein a total of two times, 6 weeks apart. Computer-based image analysis demonstrated more than 75% clearing. Ten of the 27 sites (37%) cleared completely after one treatment. Two of 15 patients (13.3%) reported blistering with minimal hyperpigmentation noted 6 weeks after treatment.

Using a longer pulse duration and larger spot size, Narukar[35] evaluated patients with leg veins less than 1.5 mm in diameter, using 20- to 50-ms pulses up to 40 J/cm^2 with a 3- to 6-mm diameter spot size. Patients were treated at 6- to 8-week intervals two to three times with an overall clearance of 45%. Interestingly, a 68% clearance was found in patients whose previous sclerotherapy showed a good response and a 32% clearance occurred in patients whose vessels responded poorly to sclerotherapy. At 2-month follow-up, 2% of patients had TM, 4% had hyperpigmentation and 2% had hypopigmentation.

Massey and Katz[36] bettered Narukar's results using a spot size of 5 mm, a pulse width of 50 ms, fluences of 18 to 20 J/cm^2 and a 1.5-Hz repetition rate. A 75% to 100% reduction was achieved in 68% of vessels less than 1 mm and in 44% of vessels 1 to 2 mm after two treatments. These results were obtained with multiple passes to achieve vessel clearance. Hypopigmentation and mild hyperpigmentation, lasting 6 to 8 weeks, were noted in 20% of patients; however, no scarring was observed. Krause[37] also described similar results using a 2-mm diameter spot size, which was reported to produce a narrower band of either hypo- or hyperpigmentation.

A 532-nm KTP laser has also been evaluated in a multipulse mode emission (three stacked pulses of 100, 30 and 30 ms and a delay between pulses of 250 ms), a fluence of 60 J/cm^2 and a 0.75-mm collimated spot without cooling (Virdis Derma, Quantel Medical, France).[38] The authors reported a clearance rates of leg veins 0.5 to 1 mm in diameter treated at 6-week intervals of 53% with one treatment, 78% with two treatments, 85% with three treatments and 93% at 6 weeks following a fourth treatment. It is suggested that the multipulse mode increases intravascular heating in a manner similar to the multipulse mode of IPL (see later) while allowing cooling of the epidermis; however, hypopigmentation lasting 'a few months' was observed in 18% of patients and TM occurred in 7% of patients.

Woo et al,[39] directly compared a 532-nm Nd:YAG at 20 J/cm^2 delivered as a 50-ms pulse through a contact cooling and 5-mm diameter spot to a 595-nm PDL at 25 J/cm^2 with a pulse duration of 40 ms, cryogen spray cooling and a 3 × 10–mm elliptical spot. After one treatment there was 50% to 75% improvement in 2 of 10 patients and greater than 75% improvement in 3 of 10 patients in the 532-nm Nd:YAG group, and 50% to 75% improvement (6 of 10 patients) in the PDL group, which overall performed better.

In another study, a 532-nm diode laser with a 1-mm diameter spot at fluences of 2 to 32 J/cm^2 was compared with a 1064-nm Nd:YAG laser at 1- to 20-ms pulses through a 3-mm diameter spot at 130 to 160 J/cm^2 in the treatment of TM vessels less than 0.3 mm in diameter that did not respond to sclerotherapy.[40] Two to three passes were needed to close the vessels with each laser. Overall, 39% of vessels treated with the 532-nm laser and 55% of those treated with the 1064-nm laser had better than 50% lightening.

More recently, Ozden et al[41] compared the 532 KTP laser with the 1064-nm Nd:YAG laser in 16 patients with sized-matched superficial leg veins in three consecutive monthly treatments evaluating a total of 64 leg vein sites. Fluence and pulse width treatment parameters for treated vessels less than 1 mm in diameter were 15 to 25 J/cm^2 and 15 to 20 ms for the KTP 532 laser and 300 to 500 J/cm^2 and 20 to 50 ms for the 1064-nm Nd:YAG laser, respectively. Fluence and pulse width treatment parameters for treated vessels 1 to 3 mm in diameter were 15 to 22 J/cm^2 and 10 to 20 ms for the KTP 532 nm laser and 250 to 350 J/cm^2 and 50 to 60 ms in the 1064-nm Nd:YAG laser group, respectively. Response to treatment was graded on a quartile system: 0 = no clearing; 1 = 1–24% clearing; 2 = 25–49% clearing; 3 = 50–74% clearing; 4 = 75–94% clearing; and 5 = 95–100% clearing. Average clinical improvement scores in the thin (<1 mm) and thicker (1–3 mm) treatment sites were 1.94 and 1.25 for the KTP and 3.38 and 3.50 for the Nd:YAG lasers, respectively. Following the third treatment session, average improvement scores improved to 2.44 and 1.31 in the KTP group and 3.75 and 3.23 in the Nd:YAG groups, respectively. Although no adverse effects were reported, pain was significantly higher in the Nd:YAG treated group. This study further elucidates that although both the KTP and Nd:YAG lasers demonstrate reasonable efficacy in smaller more superficial vessels, as would be anticipated by its shorter wavelength and more superficial tissue penetration, the KTP laser has very low efficacy with vessels larger than 1 mm.[41]

Bernstein et al[42] subsequently evaluated the effectiveness of a novel dual-wavelength 532/1064 laser (Excel V, Cutera, Brisbane CA) for the treatment of lower extremity telangiectasias. Twenty female subjects (Fitzpatrick skin types I–III) were treated in 79 sites using the 532-nm wavelength with fluences ranging from 13 to 15 J/cm^2, pulse duration of 40 ms and a 5-mm-diameter spot size. Two treatments were performed at 12-week intervals resulting in an average 2.5/5 point improvement. All patients tolerated the procedure well (mean pain sore 2.9/10) with no serious adverse effects reported. Postinflammatory hyperpigmentation was seen in 2% (1/64 patients).

In short, the 532-nm, long-pulsed, cutaneous, chilled Nd:YAG laser is effective in treating more superficial leg telangiectasias but has overall poor efficacy in deeper vessels because of limited penetration. As summarized previously, efficacy is technique dependent, with excellent results achievable. Patients need to be informed of the possibility of prolonged pigmentation at an incidence similar to that with sclerotherapy, as well as temporary blistering and hypopigmentation that is predominantly caused by epidermal damage in pigmented skin (type III or above, especially when tanned) (Fig 13.9).

COPPER BROMIDE 578 nm

In a single study evaluating the efficacy of the 578-nm copper bromide laser, 46 women with red leg telangiectasias

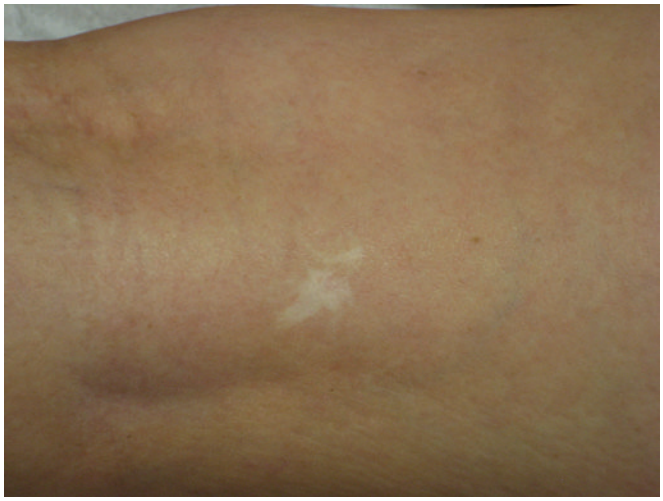


Figure 13.9 A 6-year post LaserScope 532 nm Aura Laser treatment 2 mm, 12 J, 15 ms to leg veins causing third degree burn.

less than 1.5 mm in diameter were treated with 1 minute of precooling to the skin followed by laser pulses at 50 to 55 J/cm^2 through a 1.5-mm diameter spot size generated with a 300-ms pulse, with a 75-ms delay between pulses.[43] Treatments were given through a circulating cooling window at 1° to 4°C. Up to three treatments were given at 6-week intervals. An average of 1.7 treatments produced greater than 75% improvement in 72% of patients. While relatively effective this devise is limited by its long warm-up time (15–20 minutes) and small 1.5-mm diameter spot size leading to longer treatment time and overall reduced efficiency limiting use in clinical practice.

FLASHLAMP-PULSED DYE LASER, 585 OR 595 nm

The PDL has been demonstrated to be highly effective in treating cutaneous vascular lesions consisting of very small vessels, including PWSs, hemangiomas and facial telangiectasias.[44] The depth of vascular damage is estimated to be 1.5 mm at 585 nm and 15 to 20 μm deeper at 595 nm. Therefore, penetration to the typical depth of superficial leg telangiectasias may be achieved, but not the deeper larger veins.[45] In comparison with PWS, hemangiomas and facial telangiectasias, lower extremities telangiectasias in general have not responded as well, with less lightening and more posttherapy hyperpigmentation.[46] This may be caused by the larger diameter of leg telangiectasias as compared with dermal vessels in PWS and larger diameter feeding reticular veins, as described previously.

Vessels that should respond optimally to PDL treatment are predicted to be red telangiectasias less than 0.2 mm in diameter, particularly those vessels arising as post-sclerotherapy TM. This is based on the time of thermocoagulation produced by this relatively short pulse laser system (see Table 13.2). The PDL produces vascular injury in a histologic pattern that is different than that produced by sclerotherapy. In the rabbit ear vein, approximately 50% of vessels treated with an effective concentration of sclerosant demonstrated extravasated RBCs, whereas with PDL treatment, extravasated RBCs were apparent in only 30% of vessels treated (unpublished observations). Thus, the PDL may produce less posttherapy pigmentation because of a decreased incidence of extravasated RBCs (Figs 13.10–13.14).

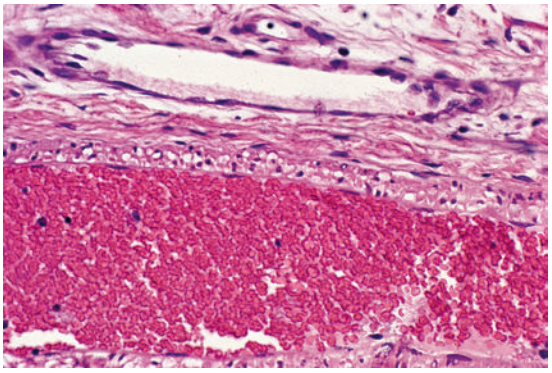


Figure 13.10 Vessel 1 hour after treatment with flashlamp-pumped pulsed dye laser alone at 8 J/cm^2. Endothelium is vacuolated. (Hematoxylin–eosin, original magnification ×200.)

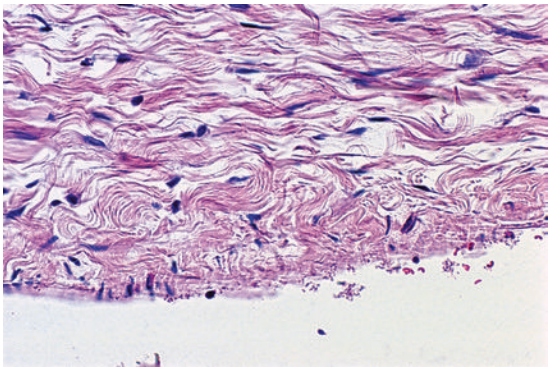


Figure 13.11 Vessel 1 hour after treatment with flashlamp-pumped pulsed dye laser alone at 9.5 J/cm^2. There is focal endothelial necrosis with adherence of platelets to damaged endothelium. (Hematoxylin–eosin, original magnification ×400.) (Reprinted from Goldman MP et al. J Am Acad Dermatol 1990;23:23, with permission from American Academy of Dermatology.)

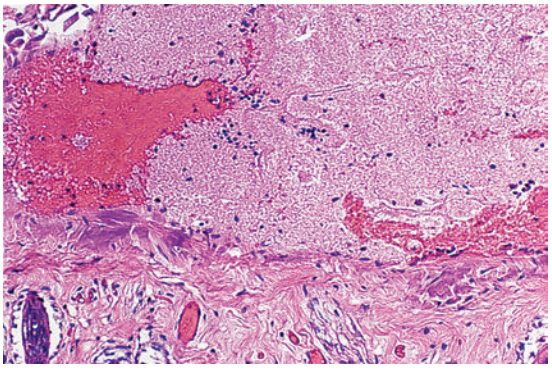


Figure 13.12 Vessel 1 hour after treatment with flashlamp-pumped pulsed dye laser alone at 10 J/cm^2. Perivascular heat denaturization of collagen is apparent. There is also extensive homogenization of red blood cells with intravascular fibrin deposition. (Hematoxylin–eosin, original magnification ×200.) (Reprinted from Goldman MP et al. J Am Acad Dermatol 1990;23:23, with permission from American Academy of Dermatology.)

The etiology of TM is unknown but has been thought to be related either to angiogenesis[47] or to a dilation of

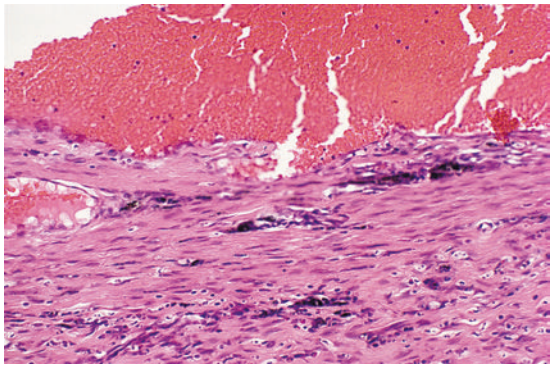


Figure 13.13 Vessel 2 days after treatment with flashlamp-pumped pulsed dye laser alone at 9.5 J/cm^2. Focal endothelial necrosis and thrombus formation are present along with margination of white blood cells. (Hematoxylin–eosin, original magnification ×200.) (Reprinted from Goldman MP et al. J Am Acad Dermatol 1990;23:23, with permission from American Academy of Dermatology.)

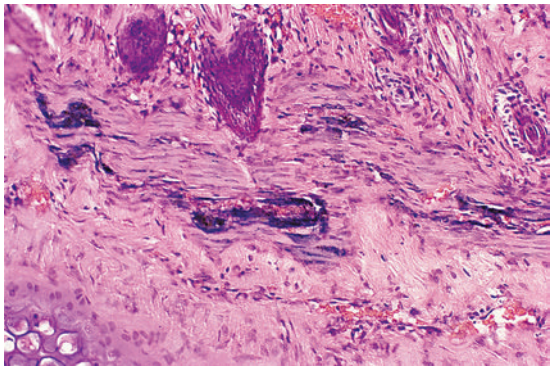


Figure 13.14 Vessel shown 10 days after treatment with flashlamp-pumped pulsed dye laser alone at 10 J/cm^2. Advanced endosclerosis is present within organizing thrombosis. (Hematoxylin–eosin, original magnification ×200.) (Reprinted from Goldman MP et al. J Am Acad Dermatol 1990;23:23, with permission from American Academy of Dermatology.)

existing subclinical blood vessels by promoting collateral flow through arteriovenous anastomoses.[48] One or both of these mechanisms may occur. Obstruction of outflow from a vessel (which is the end result of successful sclerotherapy) is one of the most important factors contributing to angiogenesis.[49] In addition, endothelial damage leads to the release of histamine and other mast cell factors and vasokines, which promote both the dilation of existing blood vessels and angiogenesis.[50,51] Sclerotherapy by its mechanism of endothelial destruction thereby provides the means for new blood vessel formation to occur. Indeed, it is remarkable that physicians do not see a higher incidence of post-treatment TM associated with sclerotherapy.

TM has not been reported to be a side effect of argon or PDL, in the treatment of vascular disorders. This may be caused by the production of intravascular fibrin that occurs during laser treatment.[52–54] Fibrin develops through thermal alteration of fibrin complexes or proteolytic cleavage of fibrinogen. Unlike laser, sclerotherapy-induced vascular injury has not been associated with the appearance of fibrin strands (unpublished observations M Goldman). This is explained by limitation of angiogenesis by factors other than those associated with the absence of fibrin deposition, or by intravascular consumption of fibrin-promoting factors in laser treatment of cutaneous vascular disease.

Multiple factors associated with inflammation have been demonstrated to promote both a dilation of existing blood vessels and angiogenesis.[51] Rabbit ear vein treatment with the PDL decreases perivascular inflammation compared with vessels treated with sclerotherapy alone.[54] Thus, another possible mechanism for absence of TM in laser-treated blood vessels is a decrease in perivascular inflammation.

The pulse duration of the first generation of PDL was 450 μs, optimal for the 50- to 100-μm diameter of PWS vessels. This pulse duration, similar to the KTP discussed earlier is most effective for treating leg telangiectasias that are less than 1 mm in diameter. Unfortunately, many studies failed to demonstrate satisfactory efficacy with the PDL at these parameters, which may be a result of failure to recognize the importance of high-pressure vascular flow from feeding reticular and varicose veins and treatment of these before treating the distal telangiectasias. A summary of the literature detailing investigations of the flashlamp-pumped PDL (585/595) follows.

Polla et al[46] treated 35 superficial leg telangiectasias with the PDL. The exact laser parameters were not given, except that vessels were treated an average of 2.1 times with a maximum of four separate treatments. These vessels were described as being either red–purple and raised, or blue and flat. No mention was made regarding the association of reticular or varicose veins or vessel diameter. Fifteen percent of treated vessels had greater than 75% clearing, with 73% of treated areas showing little response to treatment. The only lesions that responded at all were red–pink tiny telangiectasias and almost 50% of the treated patients developed persistent hypopigmentation or hyperpigmentation.

Goldman and Fitzpatrick[55] subsequently treated 30 female patients with red leg telangiectasias of less than 0.2 mm in diameter. Thirteen of 101 telangiectatic patches were noted to have an associated reticular 'feeding' vein between 2 and 3 mm in diameter that was not treated. Seven patients with 25 patches of TM after previous sclerotherapy were also treated. PDL 5-mm diameter spots were overlapped slightly with every effort made to treat the entire vessel. After treatment, a chemical ice pack (Kwik Kold, American Pharmaseal, Valencia, CA) was applied to the treated area until the laser-induced sensation of heat resolved (5–15 minutes). Thirty-nine telangiectatic patches, chosen randomly, were treated with laser energies between 7.0 and 8.0 J/cm^2 and compressed with a rubber 'E' compression pad (STD Vascular Products, Bristol, UK) fixed in place with Microfoam 100 mm tape (3 M Medical-Surgical Division, St Paul, MN). A 30- to 40-mmHg graduated compression stocking was then worn over this dressing continuously for approximately 72 hours. The most effective fluence appeared to be between 7.0 and 8.0 J/cm^2. With these parameters, approximately 67% of telangiectatic patches completely faded within 4 months (Figs 13.15–13.18). As hypothesized, TM and persistent pigmentation did not occur with PDL treatment of leg telangiectasias and post-PDL hyperpigmentation completely resolved within 4 months. There were no episodes of cutaneous ulceration, thrombophlebitis or other complications; however, hypopigmentation occurred in some

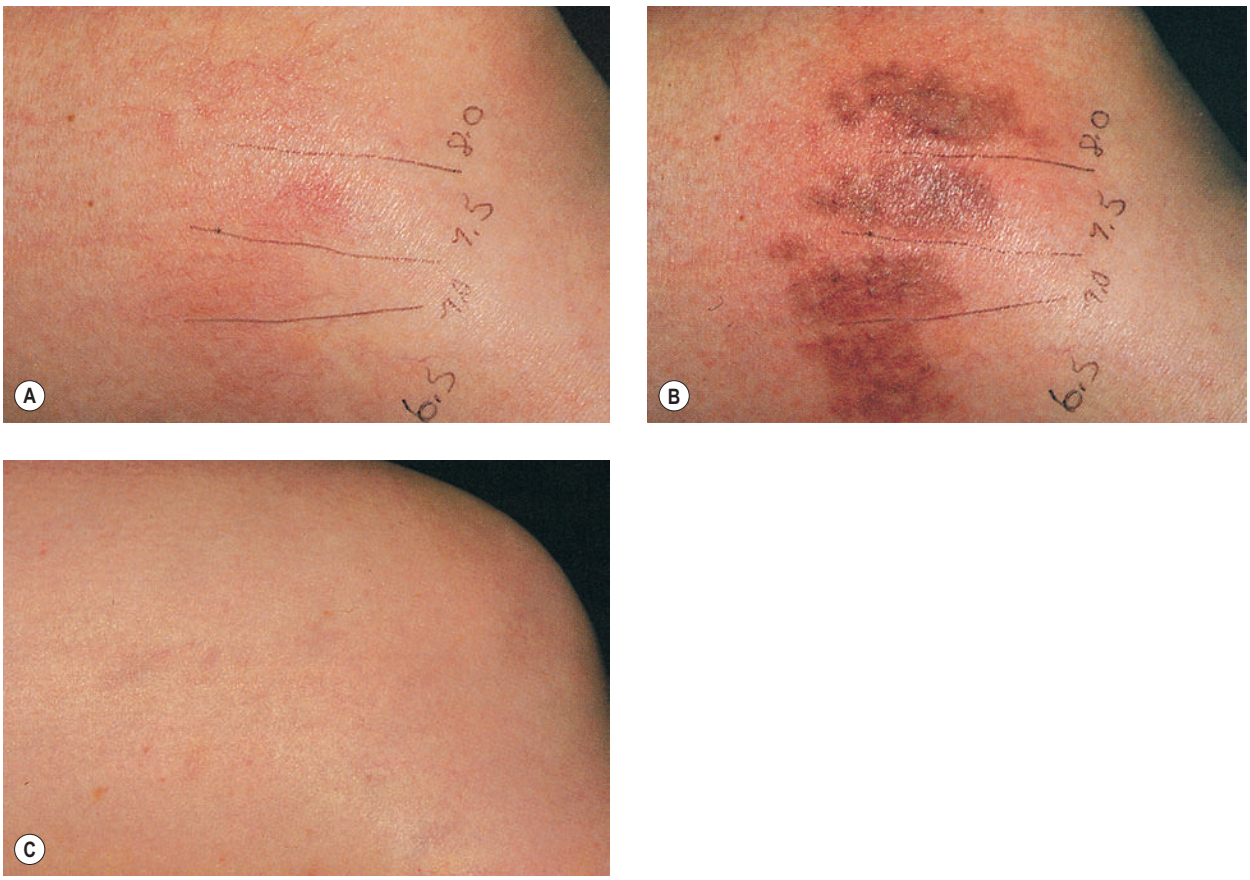


Figure 13.15 Photographic record of false resolution of flashlamp-pumped pulsed dye laser (PDL)-treated leg veins. **A,** Treatment site at medial distal thigh with parameters of experimental treatment marked. **B,** Immediately after PDL treatment; note extent of purpura. **C,** Same treatment site immediately before marking the skin with laser parameters (taken at different F-stop exposure). Note 'false' clearing of vessels.

patients with tanned skin (Fig. 13.19). The laser impact sites usually remained hypopigmented for years and in many cases were thought to be permanent.

Interestingly, there appears to be no difference in the response to PDL treatment between linear leg telangiectasias and TM vessels. In the seven patients with 25 sites treated (mentioned earlier in this section), 72% of the treated sites completely faded at laser fluences between 6.5 and 7.5 J/cm^2. Matted vessels did not respond to treatment in only one patient with four areas of TM, and less than 100% resolution occurred in 16% of treated areas (Fig. 13.20).

Like TM vessels, essential telangiectasias represent a network of fine red telangiectasias usually less than 0.2 mm in diameter. This condition responds well to the PDL at fluences of 7 to 7.25 J/cm^2.[56] Treatment, however, is tedious, with more than 2000 5-mm diameter pulses sometimes necessary to cover the entire affected area.

The reason for greater efficacy of treatment in Goldman and Fitzpatrick's report in comparison with others[46,57] may be a result of the rigid criteria by which patients were selected for treatment. Patients who responded well to treatment had red telangiectasias less than 0.2 mm in diameter without associated 'feeding' reticular veins.

Many physicians have found that vessel location may affect treatment outcome, with vessels on the medial thigh being the most difficult to completely eradicate. However, with the PDL, vessel location appears to be unrelated to treatment outcome if telangiectatic patches with untreated associated reticular veins are excluded. In addition, there appears to be no obvious difference in efficacy between telangiectatic patches that are treated with compression and those that are not (Fig. 13.21). Sadick et al[58] conducted a study that further supported the notion that graduated compression stocking use for 7 days starting immediately after treatment of class I–II venulectasia with PDL yielded no additional therapeutic efficacy.

LONG-PULSE FLASHLAMP-PUMPED PULSED DYE LASER

In an effort to thermocoagulate larger diameter blood vessels, a second generation of PDL with a longer pulse duration, lengthened to 1.5 to 40 ms, and longer wavelength, increased to 595 600 nm, was released in 1996[6] (see Table 13.1). The longer wavelength theoretically permits more thorough heating of larger vessels at greater depths allowing effective treatment of vessels 1 mm in width and 1 mm in depth.[59] A summary of the literature detailing the study of long pulsed flashlamp-pumped PDL is detailed later.

Using a 595-nm PDL at 1.5 ms, Hsai et al found more than 50% clearance of leg veins at a fluence of 15 J/cm^2 and approximately 65% clearance using a fluence of 18 J/cm^2.[60]

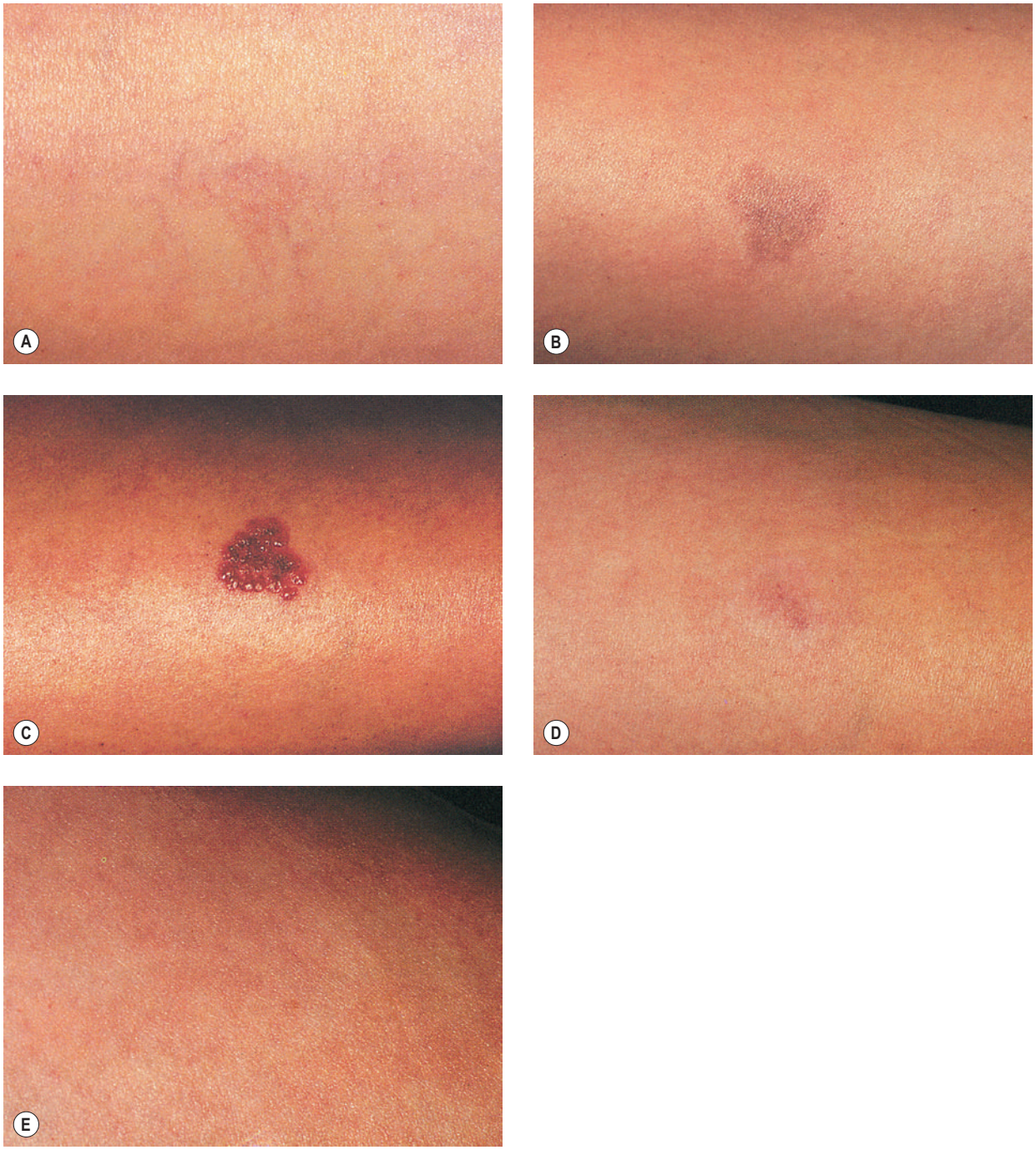


Figure 13.16 Photographic follow-up of telangiectatic patch on the medial thigh treated with the flashlamp-pumped pulsed dye laser at 7.5 J/cm^2, 15 pulses. **A,** Immediately before treatment. **B,** Immediately after treatment. **C,** Two days after treatment. Note some nonspecific vesiculation of the skin. **D,** Vessel shown 11 days after treatment. Note some hypopigmentation and fading of the telangiectasias; purpura is no longer present. **E,** Eleven months after treatment, showing complete vessel elimination without pigmentary or textural skin changes.

In this limited study of 18 patients, vessels ranging in diameter from 0.6 to 1 mm were treated with an elliptical spot size of 2 × 7 mm through a transparent hydrogel-based wound dressing. No adverse sequelae were noted at the 5-month follow-up visit (Fig. 13.22).

Another study evaluated the use of the 595-nm long-pulse PDL on 35 sites of lower extremity spider veins in 15 subjects.[61] This laser used 8 pulselets spread over the selected pulse duration, up to 40 ms. Treatments were administered three times, at 6-week intervals, using a 3 × 10–mm spot size, an average fluence of 20.4 J/cm^2 and a dynamic cooling device. At 8 weeks following the final treatment, clearance rates ranged from 65% to 75% when measured by the treating physician, and approximately 40% to 50% when assessed by blinded observers. Of note, one subject developed severe posttreatment hyperpigmentation, which persisted long enough to delay subsequent treatment by 6 weeks. At 8 weeks following the final treatment, 9 of 28 sites receiving

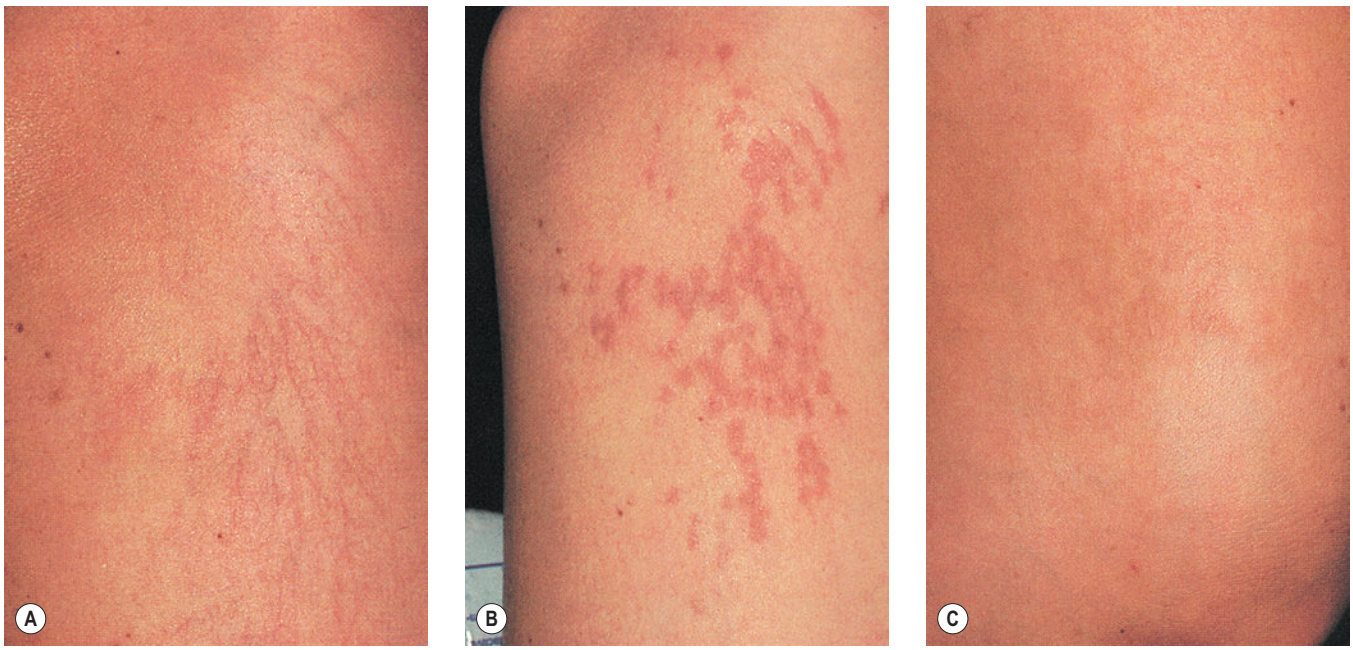


Figure 13.17 Photographic follow-up of telangiectatic flare on the lateral thigh treated with flashlamp-pumped pulsed dye laser at 7 J/cm^2, 125 pulses. **A,** Immediately before treatment. **B,** Immediately after treatment; note the characteristic, localized urticarial response. **C,** Six weeks after treatment; note slight hyperpigmentation and total resolution of telangiectasias. Pigmentation resolved over the subsequent 2 to 4 weeks.

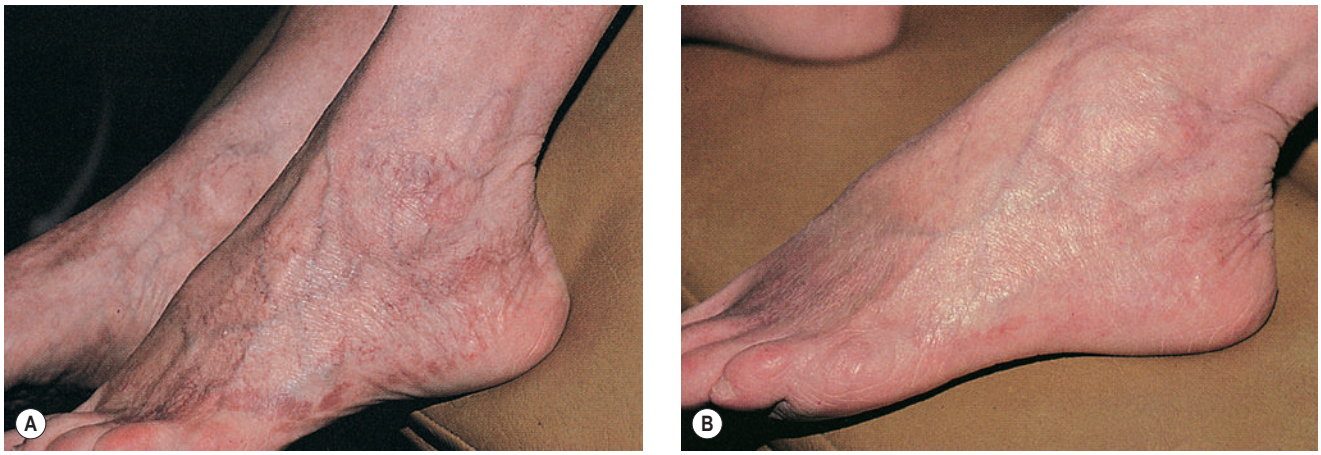


Figure 13.18 Photographic follow-up of extensive pedal telangiectasias treated on two occasions with the flashlamp-pumped pulsed dye laser at 7.25 J/cm^2, 84 pulses and 115 pulses. **A,** Before treatment. **B,** Six months after initial treatment; 3 months after second treatment. (Courtesy Richard Fitzpatrick, MD.)

three treatments showed residual hyperpigmentation as assessed by the treating physician; and blinded observers using digital photographic assessment noted a 25% incidence of hyperpigmentation at this same time point.

Lee and Lask[62] treated 25 women with leg telangiectasias less than 1 mm in diameter with the long-pulse PDL (LPDL) (Sclerolaser, Candela, Wayland, MA). Each patient had four areas treated; two at a wavelength of 595 nm with fluences of 15 or 20 J/cm^2, with two additional areas treated with a 600-nm wavelength at 15 or 20 J/cm^2, respectively. A maximum of three treatments were performed at 6-week intervals. All patients had improvement, although the 595-nm wavelength at 20 J/cm^2 gave the best results. Treatment response was variable and unpredictable, with some patients having complete resolution and some having only slight improvement. Most patients experienced purpura and hyperpigmentation that resolved after several weeks and three patients had superficial scabbing that resolved without apparent scarring.

West and Alster[30] treated 12 patients with leg telangiectasias with a 590- or 595-nm pulse at 15 J/cm^2 citing an average improvement of 75%. However, persistent hyperpigmentation was noted in 71% of patients at the 12-week follow-up period.

Bernstein et al[63] demonstrated similar results in their study of 10 women (Fitzpatrick skin type I and II) with leg telangiectasias less than 1.5 mm in diameter treated with a 1.5-ms, 595-nm LPDL at fluences of 15 and 20 J/cm^2. Patients were treated through a hydrogel dressing that resulted in a 9% energy loss, three times at each site at

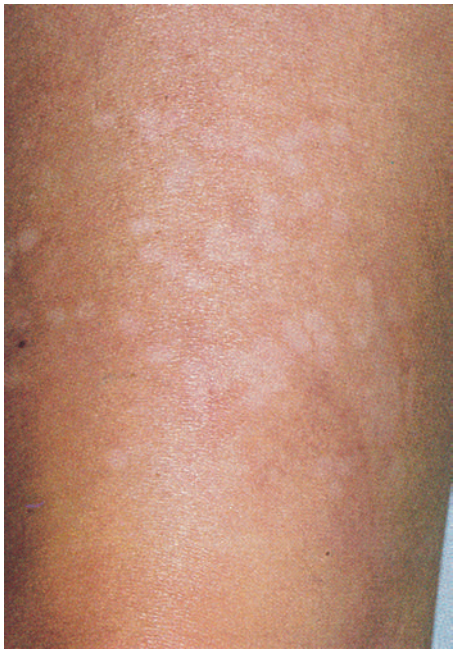


Figure 13.19 Temporary hypopigmentation, lasting for 6 months in this 32-year-old woman with type III tan skin treated on the anterior thigh with the flashlamp-pumped pulsed dye laser at 7.5 J/cm^2.

6-week intervals. Computer-based image analysis demonstrated at least 50% clearing in 80% of treated areas. Twenty percent of treated sites had hypopigmentation and 40% had hyperpigmentation 6 weeks after the final treatment.

Reichert[59] performed the largest study on the use of the LPDL by evaluating 80 patients with more than 250 treatment sites of telangiectasias not associated with feeding reticular veins. Treatment parameters were a 1.5-ms pulse at 16 to 22 J/cm^2 with a 2 × 7–mm or a 7-mm diameter spot at a 590-nm wavelength for red telangiectasias than 0.5 mm in diameter and a 595- to 600-nm wavelength for larger vessels. Ice cooling of the skin was performed both before and after treatment. A hydrogel was used during treatment and was cooled to 8°C when fluences exceeded 20 J/cm^2. A clearance rate of almost 100% was achieved at the 4- to 6-month follow-up time after one to two treatments in 95% of vessels up to 0.5 mm in diameter. Eighty percent of telangiectasias 0.5 to 1 mm in diameter faded in about 80% of sites after four treatments. Hyperpigmentation was present for 'months' in 40% of treated sites, with 10% having hypopigmentation. 'Frequent epidermal sloughing followed by crusting and gradual re-epithelization over 2 to 3 weeks' was reported when high fluences were used. Although this study had poor statistical and evaluation analysis, it does indicate that with optimal technique, specific types of leg telangiectasias will respond to the LPDL.

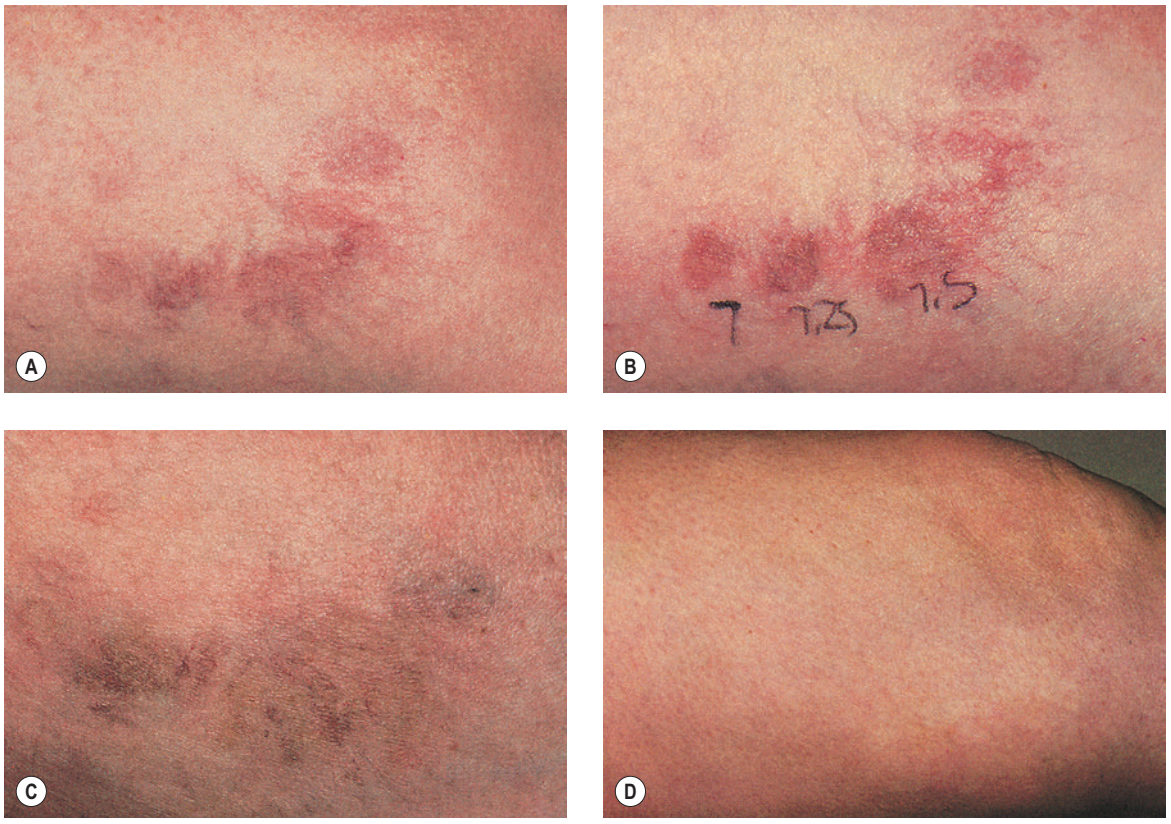


Figure 13.20 Telangiectatic matting 9 months after sclerotherapy treatment of leg telangiectasias on the medial thigh. **A,** Immediately before treatment. **B,** Immediately after patch tests were performed with the flashlamp-pumped pulsed dye laser (PDL), 9 pulses to each site. **C,** Two months after patch test treatment; note complete vessel resolution in areas treated at laser parameters of 7.25 and 7.5 J/cm^2. Only partial resolution occurred at 7.0 J/cm^2. Some hyperpigmentation is noted. **D,** One year after treatment of the entire area with LPDL at 7.25 J/cm^2, 46 pulses; note complete resolution of prior telangiectatic matting without pigmentary or textural skin changes.

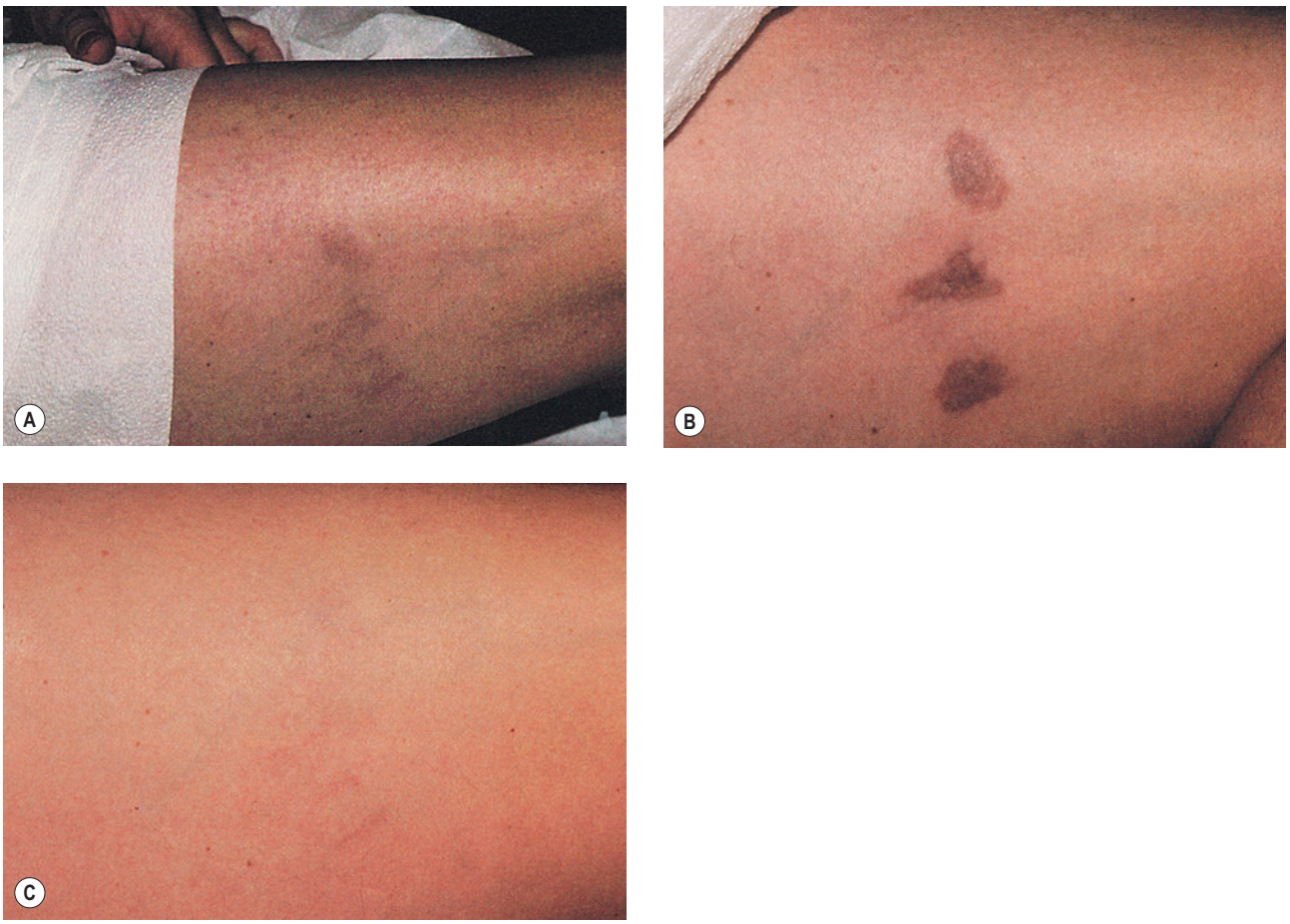


Figure 13.21 Telangiectatic patches with a feeding reticular vein 2 mm in diameter on the lateral thigh. **A,** Immediately before treatment. **B,** Immediately after treatment with the flashlamp-pumped pulsed dye laser, 20 pulses to each patch: 7.25 J/cm^2, superior patch; 7.5 J/cm^2, medial patch; 7.75 J/cm^2, inferior patch. **C,** 9 months after treatment. Note only partial resolution of the treated areas with persistence of the untreated reticular vein. (Courtesy Richard Fitzpatrick, MD.)

Hohenleutner et al[64] treated 87 patients with telangiectasias that were less than 1 mm in diameter with the LPDL using either ice cube or gel cooling. They did not treat feeding reticular veins when they were of 'no hemodynamic significance'. Vessels greater than 1 mm in diameter did not respond to treatment parameters and were excluded from study. They found that cooled Vigilon gel decreases fluence by 35% in addition to decreasing skin temperature by 5°C for 1 minute. Ice cube cooling produced a 15°C decrease in skin temperature for 1 minute. With ice cube cooling, 20% of patients with veins less than or equal to 0.5 mm in diameter and 0% of patients with veins between 0.5 and 1 mm in diameter achieved greater than 95% clearing treated at 600 nm with 18 J/cm^2. A 50% to 95% clearance occurred in 82% of veins less than 0.5 mm in diameter and in 50% of veins between 0.5 and 1 mm in diameter at a fluence of 20 J/cm^2. Hyperpigmentation and/or hypopigmentation occurred in 32% of treated areas and resolved within 6 months. When fluence was increased to 20 J/cm^2, however, hyperpigmentation occurred in 48% of treated areas. Thus, cooling with ice cubes enhances clinical efficacy and improves safety of this laser.

Ultralong pulse PDLs have been developed with pulse widths of 2 to 40 ms at a wavelength of 595 nm (Cynosure, Chelmsford, MA and Candela, Wayland, MA). The 2- to 40-ms pulse durations are created by using two separate laser beams each emitting a 2.4-ms pulse. These lasers operate at 595 nm with an adjustable pulse duration from 0.5 to 40 ms delivered through a 5-, 7- or 10-mm diameter spot size or a 3 × 10–mm or 5 × 8–mm elliptical spot. Dynamic cooling with a cryogen spray is also available, with the cooling spray adjustable from 0 to 100 ms, given 10 to 40 ms after the laser pulse, or as continuous 4°C air-cooling at a variable speed. A fluence of 10 to 25 J/cm^2 can be delivered through a 3 × 10–mm or a 5 × 8–mm elliptical spot.

Twenty-seven women with leg telangiectasias that were less than 1 mm in diameter were evaluated in one clinical study. Each patient had three areas treated. There was no difference in vessel response between a 4-ms 16-J/cm^2 pulse, a 4-ms 20-J/cm^2 pulse and a 1.5-ms 14- or 16-J/cm^2 pulse. Little or no improvement was seen in 50% and 33% of patients, respectively, after one treatment. Hyperpigmentation and hypopigmentation lasting about 12 weeks was seen in 40% to 67% and 20% to 27% of veins, respectively.[65] It is unclear why this specific study proved much less effective than previous studies on similar telangiectasias. The authors of this study were particularly objective in their treatment evaluation, with subtle improvements being

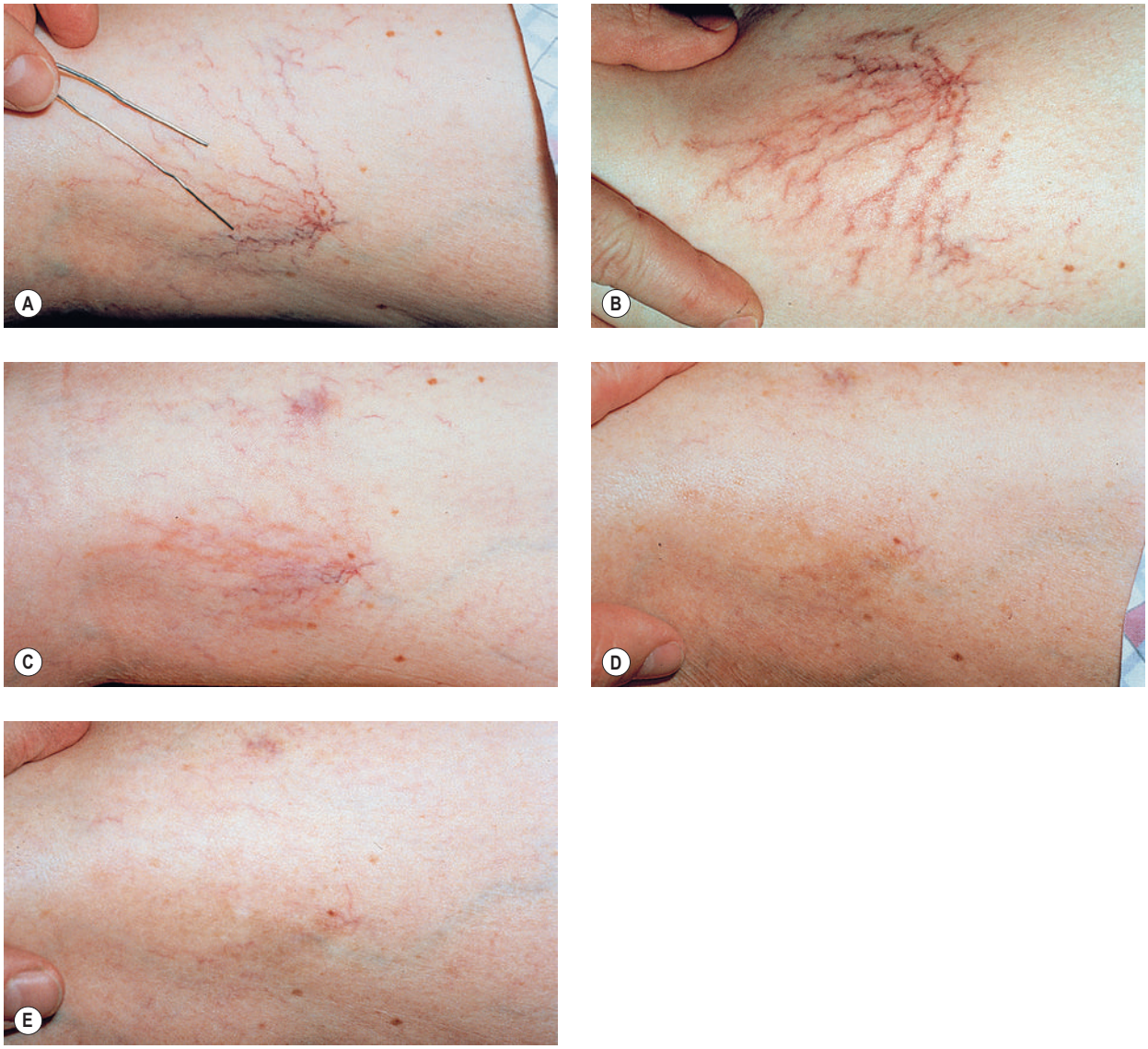


Figure 13.22 Treatment of leg telangiectasias with the long-pulse flashlamp-pumped pulsed dye laser. **A,** Before treatment. **B,** Immediately after treatment at 595 nm, 25 J/cm^2. **C,** Eight weeks after treatment. **D,** Eight weeks after second treatment at identical parameters. **E,** Six months after second treatment. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (Courtesy CS Burton III, MD; from Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishers; 1999.)

less noticeable in photographic analysis by independent evaluators.

Polla[66] also evaluated the Candela LPDL on 40 patients with leg veins 0.05 to 1.5 mm in diameter using a 6- or 20-ms pulse with a 7- or 10-mm diameter spot at 10 to 13 J/cm^2 and 6 to 7 J/cm^2, respectively, with a dynamic cooling device (DCD) setting of 30 ms, 10 ms delay. One to seven treatments were performed at 3-week intervals. Optimal results were obtained after two sessions, with 8% total clearance and 67% experiencing clearance above 40%. All patients had purpura for 7 to 10 days; 33% had pigmentation for less than 2 months and 15% for over 2 months.

Weiss and Weiss[67] had similar results using the Cynosure LPDL on 20 patients with sclerotherapy-resistant TM. They performed a single treatment with a 20-ms pulse and a 7-mm diameter spot at 7 J/cm^2 for a total of three stacked pulses with simultaneous cold air-cooling. Eighteen of 20 patients had at least 50% improvement at 3 months post-treatment. Purpura occurred in only 25% of patients and lasted 10 days.

A longer pulse duration of 40 ms was used on 10 patients with leg telangiectasias up to 1 mm in diameter at 595 nm with DCD cooling at 25 J/cm^2.[68] In this study, six patients had 50% to 75% improvement and 2 of 10 had hyperpigmentation lasting over 3 months.

Finally, Kono et al studied the DCD LPDL in a population of 14 Asian patients with 38 leg veins, distinguishing between veins less than 0.2 mm in diameter, 0.2 to 1 mm in diameter and 1 to 2 mm in diameter.[69] Vessels less than 0.2 mm in diameter were treated twice at 8-week intervals with 1.5- or 3-ms pulses through a 3 × 10–mm elliptical spot at 4 to 25 J/cm^2 and demonstrated total resolution. Vessels between 0.2 and 1 mm in diameter were treated with a pulse duration of 3 to 10 ms, with 91% having greater than 75%

improvement. Vessels between 1 and 2 mm in diameter were treated with a pulse duration of 10 to 20 ms, with 55% of veins having better than 50% clearing. Mild hyperpigmentation was present in nearly 50% of treated areas at 3-month follow-up.

Our experience is similar to that reported earlier. We use the LPDL at pulse durations matching the thermal relaxation time of the leg veins as detailed by Kono et al.[69] The energy fluence used is just enough to produce vessel purpura and/or spasm. Like Weiss and Weiss,[67] we use stacked pulses to achieve this clinical endpoint. We have used both LPDL systems and find them comparable. Because of the necessity for multiple treatments and the significant occurrence of long-lasting hyperpigmentation, like Weiss and Weiss[67] and Kono et al,[69] we reserve the use of the LPDL for sclerotherapy-resistant, red telangiectasias that are less than 0.2 mm in diameter.

LONG-PULSE ALEXANDRITE (755 nm)

The long-pulse alexandrite laser was initially developed to treat hair; however, it soon became apparent that the wavelength, fluence and pulse duration could also be used for telangiectasias (see Table 13.1). The 755-nm wavelength penetrates 2 to 3 mm beneath the epidermis and is effective in thermocoagulating blood vessels in clinical and histologic studies as summarized in the following.[70–72]

One study of leg telangiectasias in 28 patients treated three times every 4 weeks at fluences ranging from 15 to 30 J/cm^2 found that a single-pulse technique with 20 J/cm^2, 5-ms pulse duration yielded the best resolution when combined with sclerotherapy using 23.4% hypertonic saline (HS)[71] (Fig. 13.23). When this technique was used without epidermal cooling with a chill tip at 4°C, focal crusting and scabbing was noted. With laser treatment alone, telangiectasias smaller than 0.2 mm in diameter improved by 23%, vessels between 0.4 and 1 mm improved by 48% and telangiectasias of 1 to 3 mm improved by 32%.

Kauvar and Lou[73] treated 20 women with 54 patches of leg veins measuring 0.3 to 2 mm in diameter with a single treatment of a 3-ms alexandrite laser at 60 to 80 J/cm^2 through an 8-mm diameter spot with dynamic epidermal cooling. Multiple passes were given until vessel clearance (averaging 1.9 passes). At 12-week follow-up, 65% of 51 treated areas showed greater than 75% clearance; however, hyperpigmentation was observed in 35% of treated areas.

An additional study using an alexandrite laser at 90 J/cm^2 with a 3-ms pulse through a 3 × 10–mm spot size and dynamic cooling with an 80-ms cryogen spray was performed on leg telangiectasias 0.3 to 1.3 mm in diameter.[74] The pain of treatment ranged from mild to severe. Almost all treated areas had purpura, edema and erythema. Most vessels showed clearance of 50% to 75%, with hyperpigmentation in 15 of 20 subjects at 12 weeks. The authors speculated that the high pigmentation rate, three times that of Kauvar and Lou's study,[73] was a result of the increased fluence used.

Ross et al[75] set out to determine the optimal fluence and pulse width for the treatment of leg telangiectasias with the long-pulse 755-nm alexandrite laser. Fifteen patients with leg telangiectasias ranging in diameter from 0.2 to 1.0 mm were treated with pulse durations ranging from 3 to 100 ms. For each pulse duration, test spots were performed to determine optimal radiant exposures, which elicited persistent bluing and/or immediate stenosis as clinical endpoints. The optimal settings for each patient were then used to treat larger areas of similar-sized vessels. Follow-up evaluations were performed 12 weeks after the treatment. Overall, the optimal pulse duration was 60 ms for most patients, with a clearance of approximately 65% after the single treatment session. Furthermore, the average radiant exposure necessary for vessel closure was 89 J/cm^2. Using these optimal long-pulse alexandrite settings not only achieved satisfactory vessel clearance but also resulted in minimal side effects.

A study by Eremia et al,[76] comparing the alexandrite laser to the 810-nm diode laser and the 1064-nm Nd:YAG laser in the treatment of leg telangiectasias 0.3- to 3-mm in diameter on 30 women, however, did not show as promising results as those previously mentioned. These authors found that the 3 × 10–mm spot size was difficult to use and the study was performed with an 8-mm diameter spot with 60 to 70 J/cm^2, a 3-ms pulse and an 80- to 100-ms cryogen spray after an 80-ms delay. With the alexandrite laser, greater than 75% improvement occurred in only 33% of sites and greater than

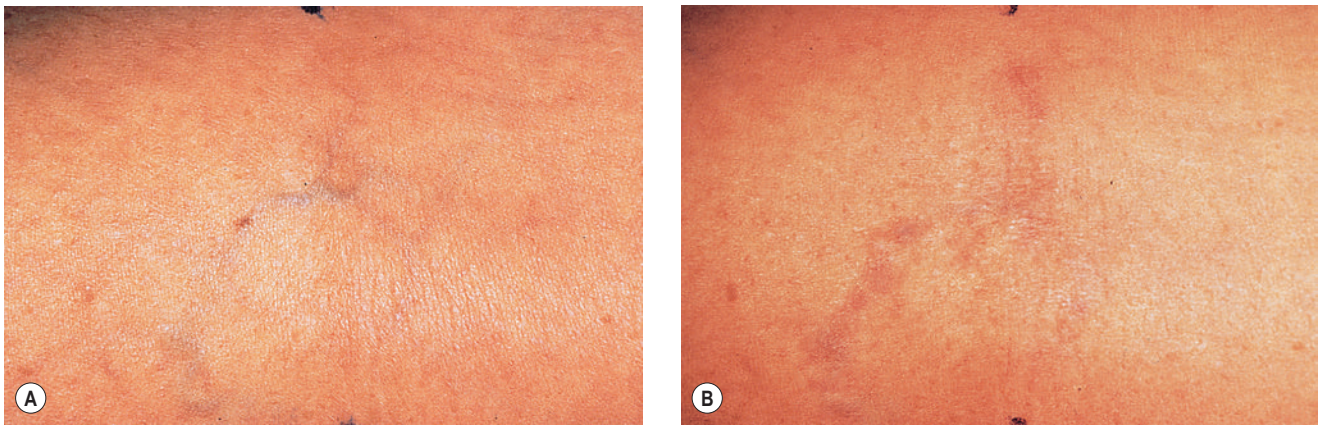


Figure 13.23 Treatment of leg telangiectasias with the long-pulse alexandrite laser. **A,** Before treatment. **B,** Seven weeks after treatment. Note the postinflammatory hyperpigmentation remaining at treatment sites. This likely cleared over the ensuing weeks to months. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (Courtesy McDaniel DH, MD; from Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishers; 1999.)

50% improvement in 58% of sites after two treatments. Ten of 22 patients developed TM, pain was a significant problem and almost all patients demonstrated marked posttreatment inflammation for 1 to 2 weeks. The 1064-nm Nd:YAG and 810-nm diode lasers were better tolerated, having little to no adverse effects, with greater than 75% improvement occurring in 88% of the Nd:YAG-treated veins and 29% of the diode-treated veins. The 1064-nm Nd:YAG was used with a 6-mm diameter spot size, 150 J/cm^2, with a 25-ms pulse duration for small vessels and a 100-ms pulse for larger vessels, with a 30-ms postcontact cryogen spray.

The bottom line is that the alexandrite laser is more painful, no more effective and probably produces more adverse effects than other lasers at the parameters stated by the studies mentioned earlier.

DIODE LASERS

Multiple diode-pumped lasers are now available, including a 532-nm, an 800-nm, an 810-nm (gallium-arsenide) and a 940-nm diode laser (see Table 13.1). Diode lasers generate coherent monochromatic light through excitation of small diodes. These devices are therefore lightweight and portable, with a relatively small desktop footprint.

Dierickx et al[77] evaluated an 800-nm diode laser (LightSheer, Lumenis, Santa Clara, CA) on eight areas of leg veins. The laser was used at 15 to 40 J/cm^2 given in 5- to 30-ms pulses as double or triple pulses separated by a delay of 2 seconds. Veins were treated every 4 weeks for three sessions and evaluated 2 months after the last treatment. Optimal parameters were 30-ms pulses at 40 J/cm^2. At these parameters, vessels 0.4 to 1 mm in diameter showed 100% clearing in 22%, 75% clearing in 42% and 50% clearing in 32%.

Trelles et al[78] evaluated both the subjective as well as the objective efficacy of an 800-nm diode laser for leg vein clearance in 10 women of various ages and skin types. Investigators used a sequence of five to eight stacked pulses with a pulse duration of 50 ms, a delay of 50 ms and a 3-mm spot size. Treatments were administered at 2-month intervals until complete clearance occurred, and final efficacy was assessed 6 months following each patient's final treatment. To reach complete clearance, 50% of patients needed three treatment sessions and the remaining 50% needed less than three. Although treated leg veins varied from 1 to 4 mm in diameter, the best results were ultimately seen in those vessels that had initially measured 3 to 4 mm. Treatment of vessels located on the thigh as well as those in patients with Fitzpatrick skin type III also yielded superior efficacy. Of note, no correlation was found between patient age and efficacy of treatment.

Garden et al[79] also used an 810-nm diode laser with a 750-μm spot size at 40 W and 50-ms pulses for a total of 453 J/cm^2 of fluence delivered. Twelve patients with 58 vessels 0.2 to 0.5 mm in diameter were treated with three to four passes until vessel spasm occurred. Patients were retreated every 2 to 4 weeks resulting in a mean clearance of 60% after 2.2 treatments. Eighteen vessels had greater than 70% clearance after three treatments. When a scanner was incorporated into the diode laser so that 15- to 20-mm-long passes could be given, efficacy increased. In 11 patients treated with the scanner diode in two sessions 2 to 4 weeks apart, 18% of vessels had 75% to 90% clearance, 21% had 50% to 75% clearance, 18% had 25% to 50% clearance and 36% had up to 25% clearance.

In another study, 35 patients with spider leg veins were treated with an 810-nm diode laser with a 12-mm diameter spot, 60-ms pulse duration and 80 to 100 J/cm^2 with a cooled handpiece.[80] Fifteen of the 35 patients had complete disappearance of the spider veins; however, at 6 month follow up 7 patients had had a relapse in their leg veins, with an additional patient having a relapse at 1-year follow-up and two of the 35 patients had scarring.

A 940-nm diode laser has also been used in the treatment of blue leg telangiectasias less than 1 mm in diameter without Doppler evidence of refluxing feeding veins.[81] Twenty-six patients were treated with 300 to 350 J/cm^2 with a 40- to 70-ms pulse and 1-mm diameter spot, with a clearance of greater than 50% in 20 patients and greater than 75% in 12 patients. Slight textural changes were seen in five patients and pigmentation taking several months to resolve in four patients. No cooling was provided except for ice packs after treatment. In a follow-up of these patients 1 year later, 75% of patients had greater than 75% clearance.[82]

These outstanding long-term results were not seen in a separate study using the same laser but with a variety of pulse durations (10–100 ms) and fluences (200–1000 J/cm^2) through a 0.5-mm diameter spot for vessels less than 0.4 mm in diameter, a 1-mm diameter spot for vessels 0.4 to 0.8 mm in diameter and a 1.5-mm diameter spot for vessels 0.8 to 1.4 mm in diameter.[83] Fluences were adapted to have complete vessel clearance without epidermal blanching. No cooling device was used and patients were evaluated at 1 year. The largest diameter vessels had the highest clearance rates, with only 13% of vessels that were less than 0.4 mm in diameter clearing by more than 75% as opposed to 88% of vessels that were 0.8 to 1.4 mm in diameter. In this study, laser therapy was more painful than sclerotherapy in 31 of 46 patients, with equal efficacy noted by the patients who had had both forms of treatment.

Additionally, combination diode laser with radiofrequency (RF) delivered at levels up to 100 J/cm^3 has been used to treat leg telangiectasias. Chess[84] treated 25 patients with 35 leg veins 0.3 to 5 mm in diameter with a 915-nm diode laser at fluences ranging between 60 and 80 J/cm^2 as well as RF energy at 100 J/cm^3 through a 5 × 8–mm elliptical spot size, with 5°C contact cooling, in up to three sessions every 4 to 10 weeks. The authors found 77% of treated sites exhibited greater than 75% improvement at 6 months with an average discomfort rating of 7 out of 10. Three sites on three different patients developed eschar formation without permanent scarring. In a similar study, leg telangiectasias 1 to 4 mm in diameter were treated with 60 to 80 J/cm^2 fluence and 100 J/cm^3 RF energy through a 5 × 8–mm elliptical spot size with 5°C contact cooling in three separate sessions at 2- to 4-week intervals.[85] Overall, 75% of vessels had greater than 50% improvement and 30% had greater than 75% improvement at 2-month follow-up with almost no complications. Trelles et al also evaluated the efficacy of a combined 900-nm diode laser with a bipolar RF device in the treatment of 1 to 4 mm leg veins in 40 patients with skin types II–IV with no evidence of venous insufficiency.[86] Treatments were administered at 2-week intervals, for a maximum of three treatments. The diode laser reached an average fluence of 60 J/cm^2 with a 250-ms exposure time.

Radiofrequency energy was delivered at 100 J/cm^3, with 5°C contact cooling. The majority of patients required one or two treatment sessions. Clinical photography coupled with computer generated data minimized subjectivity in follow-up improvement assessments, which demonstrated that 82.5% of subjects achieved over 50% clearance in target vessels at 6 months. Interestingly, treatments on thicker vessels (>2 mm) and those performed on patients of darker skin types showed the greatest efficacy. However, even in those patients with lighter, type II, skin, a vessel clearance rate of greater than 50% was seen in 66%. The posttreatment telangiectatic matting that developed in less than 10% of patients had completely or almost completely resolved in each by the 6-month assessment. Overall, very few additional side effects were noted.

Prieto et al evaluated the dermal histologic and immunohistochemical changes induced by exposure of leg telangiectasias to either a combination 915-nm diode laser and RF or to a 1064-nm Nd:YAG laser.[87] Three patients with 0.1- to 2.0-mm telangiectasias each had one leg treated with the combination diode and RF device, and the opposite leg treated with the Nd:YAG laser. Punch biopsies from treated areas were taken 7 days after laser/RF exposure. Tissue from each treatment type showed intermediate-sized vessels with complete thrombosis and hemorrhage within the dermis as well as the subcutis with focal full-thickness necrosis seen in the overlying epidermis. A single treatment session of both the combination diode and RF device as well as the Nd:YAG, yielded an average of 50% to 75% clinical clearing, respectively. Thus, when comparing results from both treatment modalities, the similar degree of improvement in the clinical appearance of the telangiectasias was supported by histologic examination of tissue specimens.

In summary, although relatively efficacious in the treatment of leg telangiectasias, standard diode laser use is limited by treatment pain and adverse effects. Given the thicker, deeper nature of telangiectatic leg veins associated with high hydrostatic pressures, a relatively high fluence is required to achieve a sufficient increase in vessel temperature. Higher radiant exposures, however, are associated with increased risk of adverse effects as noted earlier. In an effort to reduce radiant exposure and subsequent adverse effects while maintaining or improving clinical outcomes, Klein et al[88] studied the effect of addition of indocyanine green (ICG), a light-absorbing dye with maximal absorption in blood at 800 to 810 nm. In an initial proof-of-concept trial, ICG (2 mg/kg) was administered IV to 15 female patients (skin type II to III) with telangiectatic leg veins (0.25–3 mm) without evidence of underlying chronic venous insufficiency immediately followed by diode laser with different radiant exposures (50–110 J/cm^2) applied in a single treatment. Both legs were randomly allocated to either PDL as control (Sclerolaser plus TM, Candela, Wayland, MA) or diode laser therapy (MeDioStar, Asclepion, Jena, Germany). PDL laser parameters included: wavelength 595 nm, radiant exposure 16 J/cm^2, elliptical spot 2 × 7 mm and pulse duration: 1.5 mm. Before administration of the ICG, 11 patients received a test spot with the diode laser alone (808 nm, spot size 4 or 6, radiant exposure 75–110 J/cm^2, pulse duration 26–87 ms). The same laser parameters were applied for diode alone and ICG plus diode laser with the exception of addition of double pulses for the later. Diode laser therapy was initiated within 2 min of ICG injection due its short half-life. The ICG + Diode Laser Group was divided into 3 subgroups (A, B and C) with progressive increases in pulse duration and radiant exposure as follows: group A: mean radiant exposure 64.07 J/cm^2, mean pulse duration 26.65 ms, spot size 4 mm; group B: mean radiant exposure 96 J/cm^2, mean pulse duration 54.8 ms with 4- and 6-mm handpiece; group C: mean radiant exposure 107 J/cm^2, mean pulse duration 85.8 ms and spot size of 6 mm as well as double pulses for the last two patients. Mean clearance rating at 3 months for PDL therapy was 2.07 ± 1 (moderate clearance) (patient assessed) and 0.78 ± 0.78 (blinded investigator) compared with 0.6, 1.25 and 2.6 (patient assessment) and 0, 0 and 2.6 (blinded investigator assessment) for the ICG-Diode groups A, B and C, respectively. Side effects included transient urticarial reactions confined to treated vessels and transient postinflammatory hyperpigmentation in PDL treated patients in addition to a burning sensation (mild 7, moderate 2). ICG + DL did not induce any noted side effects in group A and B; however, transient purpura as well as transient local urticaria occurred in all patients in group C immediately following therapy but resolved within a few hours. Group C also included four patients with mild transient postinflammatory hyperpigmentation, one case of TM and one case of hypopigmentation, still visible at 5 months follow-up (also observed in the PDL and diode laser alone treated areas in same patient). Burning sensation in group C was rated as (mild 5, moderate 3, severe 1) with an overall pain score of 5.6.

In a follow up randomized controlled trial (RCT) using the same technology, Klein et al[89] evaluated the efficacy of ICG + DL (810 nm, 60–110 J/cm^2, 48–87-ms pulse duration, 6-mm spot size; total ICG dose 4 mg/kg) compared with Nd:YAG (1064 nm, 160–240 J/cm^2, 65-ms pulse duration, 5-mm spot size) in 29 patients (skin types I–III) in a side-by-side comparison in one single treatment with histological evaluation in 4 participants. Investigator rated clearance of ICG + DL vs. Nd:YAG was 3.4 ± 8 vs. 2.2 ± 1.1 (Scale: 0, no clearance, to 4, excellent clearance, 3 months after treatment, $P < 0.001$). Participant rated clearances were 3.4 ± 0.7 for ICG + DL vs. 2.3 ± 0.7 for Nd:YAG ($P < 0.001$). Of note, both the ICG + DL and Nd:YAG laser treatments achieved slightly better clearance rates for medium-sized vessels (mean clearance 3.5 and 2.3, respectively) than for small vessels (3.2 and 2.1, respectively). Early side effects present in both groups included burning (Nd:YAG 76%, ICG + DL 90%), blistering (Nd:YAG 10%, ICG + DL 10% both mild) and edema (Nd:YAG 90%, ICG + DL 91%). Adverse events in the Nd:YAG group additionally included two ulcerations in a single patient who developed scarring as well as hyperpigmentation (45% of cases at 6 weeks, improved to 21% at 3 months), hypopigmentation (4 cases at 6 weeks) and residual slight scarring in 3 patients present at 3 months. ICG + DL adverse events included hyperpigmentation at 6 weeks in 62% of participants (compared with 45% in Nd:YAG group), which improved to 41% at 3 months (compared with 21% at the same time interval in the Nd:YAG group), one case of hypopigmentation and one erosion at 6 weeks as well as one case of TM at 3 months.

Though most apparent in target vessels larger than 1 to 2 mm in diameter, the addition of RF to the diode appears to yield vessel clearance at lower diode fluences than would

be necessary to achieve the same results if the diode was used alone. The addition of ICG to diode laser treatment appears to offer additional benefit with improved outcomes compared with Nd:YAG treatment in a single study; however, this combinational approach may be associated with a slight increase in adverse effects including postinflammatory hyperpigmentation and treatment associated pain.

RADIOWAVE COAGULATION (RFA)

Tepavcevic et al[90] studied the efficacy of RFA (Elman surgyton, blood vessel electrode, coagulation impulse 2 units) compared with Nd:YAG (1064 nm, fluence: 110–150 J/cm^2, pulse duration: 20–40 ms, 3–6 mm spot size) and sclerotherapy (1 mL of 0.5% Ra aethoxysklerol) for the treatment of 0.1- to 0.2-mm leg telangiectasias and found relatively disappointing results for the RFA technology; 66.7% of patients were rated at 3 months to have had no change in vessel clearance in the RFA group compared with 30% in the laser group and 0% in the sclerotherapy group. Conversely only 3.3%, 3.3% and 0% of patients obtained 50% to 75%, 75% to 100% and 100% clearance in the RFA group compared with 16.7%, 13.3% and 0% in the laser group and 13.3%, 30.0% and 13.3% of patients in the sclerotherapy group, respectively. Further, moderate to severe pain was significantly higher, 70% in the RFA group compared with 56.67% and 10% in the laser and sclerotherapy groups, respectively. Overall poor efficacy and high treatment-associated pain make this a poor choice for the treatment of lower leg telangiectasias at this time.

FIBER-GUIDED LASER COAGULATION

Trelles et al reported another method for treating leg veins with fiberoptic transmission of argon or tunable dye laser into the vessel (International Society of Cosmetic Laser Surgeons, Palm Desert, CA, February 1993). With this technique, a vessel is cannulated with a 0.840-mm hypodermic needle, and a 200-mm optical fiber is passed through the needle into the vein. Two to four pulses of laser light (514, 570, 585 and 620 nm) are delivered with a pulse duration of 100 to 300 ms at 1.5 to 5 W, adjusted to coagulate the vessel. Because of nonspecific thermal heating related to long pulse durations, the skin is cooled with ethyl chloride. Out of 175 patients, 111 were satisfied with treatment. However, 9 of the 175 developing a depressed or pigmented scar.

A stronger endoluminal laser was subsequently developed to treat larger diameter veins, including the great saphenous vein (GSV). Bone Salat[91] treated 44 patients, 38 with incompetent GSVs, with endoluminal laser thermocoagulation. In this technique, the fiber is inserted through either a phlebectomy or a percutaneous approach into the GSV. The first laser used in this treatment was the 810-nm LaserLite A100 diode laser (Diomed, Andover, MA) with energy emission powers of 0.5 to 30 W. Using an optical fiber of 300 to 600 μm in diameter, the practitioner used 5 to 10 W with 3- to 4-second pulses to thermocoagulate vessels ranging from 7 to 22.5 mm in diameter. Treated limbs were then compressed with bandages or graduated compression stockings and evaluated at 1 and 2 weeks and at 3 to 6 months with duplex. No adverse effects were reported. All but one patient had resolution of reflux.

HIGH-INTENSITY PULSED LIGHT

The high-intensity pulsed light (IPL) source was developed as an alternative to lasers to maximize efficacy in treating leg veins (PhotoDerm VL, ESC/Sharplan now Lumenis, Santa Clara, CA). This device permits sequential rapid pulsing, longer duration pulses and penetrating longer wavelengths compared with other laser systems (Fig. 13.24).

Theoretically, a phototherapy device that produces a noncoherent light as a continuous spectrum longer than 550 nm should have multiple advantages over a single-wavelength laser system. First, both oxygenated and deoxygenated hemoglobin absorb at these wavelengths. Second, blood vessels located deeper in the dermis are simultaneously affected. Third, thermal absorption by the exposed blood vessels should occur with less overlying epidermal absorption, because the longer wavelengths penetrate deeper and are absorbed less by the epidermis, including melanin (Fig. 13.25).

With the theoretical considerations just mentioned, IPL emitting in the 515- to 1000-nm range has been used at varying energy fluences (5–90 J/cm^2) and various pulse durations (2–25 ms) to treat venectasias 0.4 to 2.0 mm in diameter. The IPL allows treatment through a quartz crystal of 8 × 35 mm or 8 × 15 mm (up to 2.8 cm^2) that can be decreased in size to match the clinical area of treatment. Clinical trials using various parameters with the IPL, including multiple pulses of variable duration, demonstrated efficacy ranging from over 90% to total clearance in vessels less than 0.2 mm in diameter, 80% in vessels 0.2 to 0.5 mm in diameter and 80% in vessels 0.5 to 1 mm in diameter.[92–94] The incidence of adverse sequelae was minimal, with hypopigmentation occurring in 1% to 3% of patients, resolving within 4 to 6 months. Tanned or darkly pigmented Fitzpatrick type III patients were likely to develop hypopigmentation and hyperpigmentation in addition to blistering and superficial erosions; however, these all cleared over a

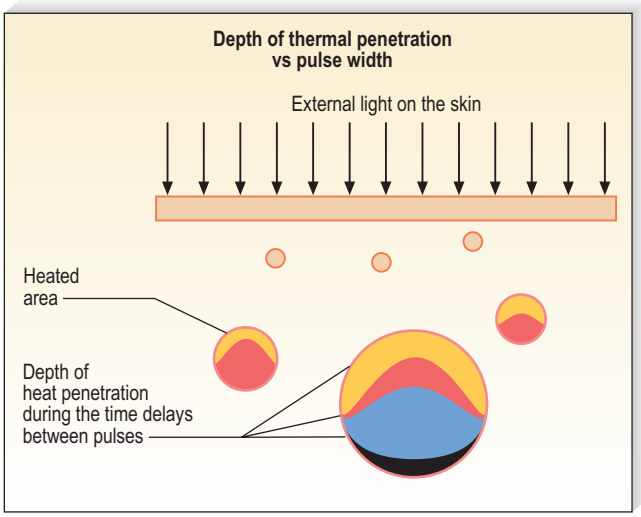
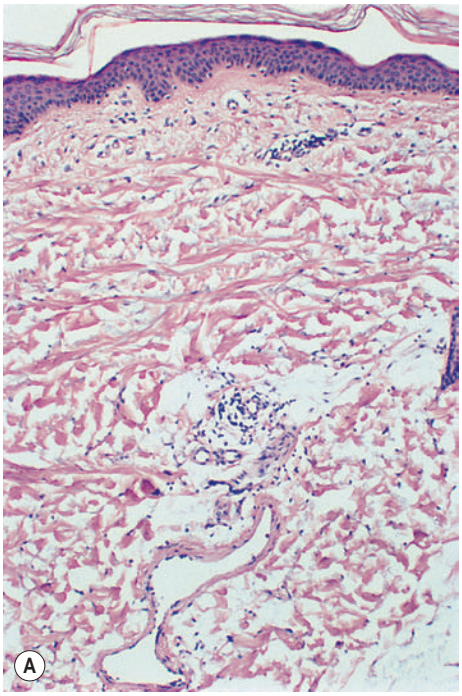


Figure 13.24 Diagram of the effect of repetitive pulses of the PhotoDerm light source on a 2-mm vessel 1 mm below the epidermis. (Courtesy Shimon Eckhouse, PhD, Energy Systems Corporation, Inc, Newton, MA.)



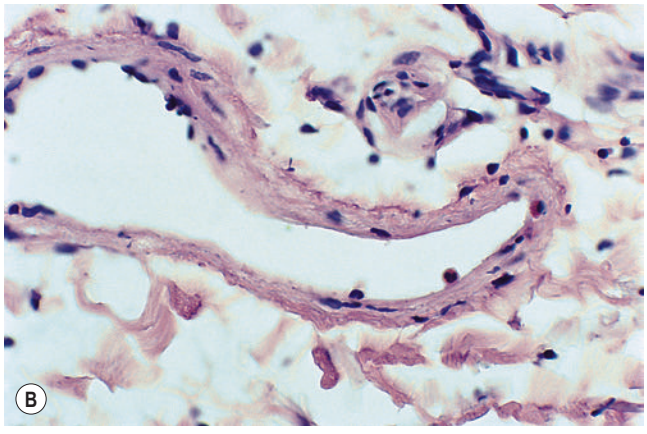


Figure 13.25 Appearance of venule 1 mm in diameter stained with hematoxylin–eosin 48 hours after treatment with the PhotoDerm VL at 26 J/cm^2, delivered in a double pulse 6 and 15 ms long separated by 50 ms. **A,** Note size and depth of vessel, which appears collapsed from biopsy and processing artifacts but devoid of blood; original magnification ×50. **B,** Same vessel as in A. Note intravascular margination of mast cell and lymphocytes with partial destruction of endothelium and vessel wall; original magnification ×200.

few months. Treatment parameters found to be most successful for vessels less than 0.2 mm in diameter ranged from a single pulse of 22 J/cm^2 in 3 ms to a double pulse of 35 to 40 J/cm^2 given in 2.4 and 4.0 ms with a 10-ms delay. Vessels between 0.2 and 0.5 mm were treated with the same double-pulse parameters or with a 3.0- to 6.0-ms pulse at 35 to 45 J/cm^2 with a 20-ms delay time. Vessels above 0.5 mm were treated with triple pulses of 3.5, 3.1 and 2.6 ms with pulse delays of 20 ms at a fluence of 50 J/cm^2 or with triple pulses of 3, 4 and 6 ms with a pulse delay of 30 ms at a fluence of 55 to 60 J/cm^2. The choice of a cut-off filter was based on skin color, with a 550-nm filter used for light-skinned patients and a 570- or 590-nm filter used for darker-skinned patients (Figs 13.26 and 13.27).

Weiss and Weiss[95] reported improved efficacy by increasing the pulse durations to a maximum of 10 ms as two consecutive pulses separated by a 20-ms delay with a 570-nm cut-off filter and fluences of 70 J/cm^2. They have achieved response rates of 74% with two-treatment sessions, with an 8% incidence of temporary hypopigmentation or hyperpigmentation. By combining a shorter pulse (2.4–3 ms) with a longer pulse (7–10 ms), it is theoretically possible to ablate smaller and larger vessels overlying one another in the dermis (Fig. 13.28).

In a European multicenter study, 40 women with leg telangiectasias up to 1 mm in diameter were treated with IPL using the following parameters.[92] For vessels less than 0.2 mm in diameter, a 3-ms pulse of 22 J/cm^2 was used, for vessels of 0.2 mm to 0.5 mm a double pulse of 2.4 ms each, separated by 20 ms, with 35 J/cm^2 was given, and for vessels 0.5 mm to 1 mm a triple pulse of 3.5, 3.1 and 2.6 ms was used, with delays of 20 ms and a fluence of 50 J/cm^2 The authors reported a clearance rate of 92% in vessels less than 0.2 mm in diameter, 80% in vessels less than 0.5 mm in diameter and 81% in vessels less than 1 mm in diameter with no evidence of recurrence at 1-year follow up. Associated side effects included 11 cases of temporary hyperpigmentation., one case of temporary hypopigmentation and two nonscarring blisters.

Schroeter and Neumann[96] have reported a similar success rate in treating 40 patients with leg telangiectasias. For veins less than 0.2 mm in diameter the authors used a single pulse of 3 to 4 ms with a 550-nm cut-off filter between 22 and 28 J/cm^2 and for veins 0.2 to 2 mm in diameter a 570-nm cut-off filter with a double-pulse technique of 2.4 ms each with a 10- to 20-ms delay between pulses at 24 to 30 J/cm^2 was employed. With these parameters they achieved over 80% clearance that was maximal at 1-month follow-up. Even with these parameters, which are more conservative than those used by Weiss or Goldman, hyperpigmentation was seen in 20 of the 40 patients, with two of 40 having blistering and three of 40 having hypopigmentation.

Although most authors have reported satisfactory results with IPL in treating leg telangiectasias, this opinion is not universal. Green[97] has not seen effective results when he used the IPL and attributes this to having a different objectivity in evaluating his patients compared with those authors previously discussed, citing low clearance rates with unacceptable side effects.[98]

Treatment of essential telangiectasias, especially on the legs, is efficiently accomplished with the IPL, however (see Figs 13.26–13.28). This condition, responds well to PDL, but can be time consuming and expensive. With IPL, large areas of involvement can be treated quickly and effectively with many different parameters (Fig. 13.29).[99] We recommend testing a few different parameters during the first treatment session and using the most efficient and least painful parameter on subsequent treatments. Of note, one study of 14 patients, one of whom had leg telangiectasias, found that a single pulse of 30 J/cm^2 delivered through a 550-nm cut-off filter in 5 ms was 100% effective.[99]

The use of IPL to treat leg veins has produced encouraging results, but these are far from easily reproduced. This technology requires significant experience to produce good results and minimize adverse effects. Various parameters must be matched both to the patient's skin type as well as

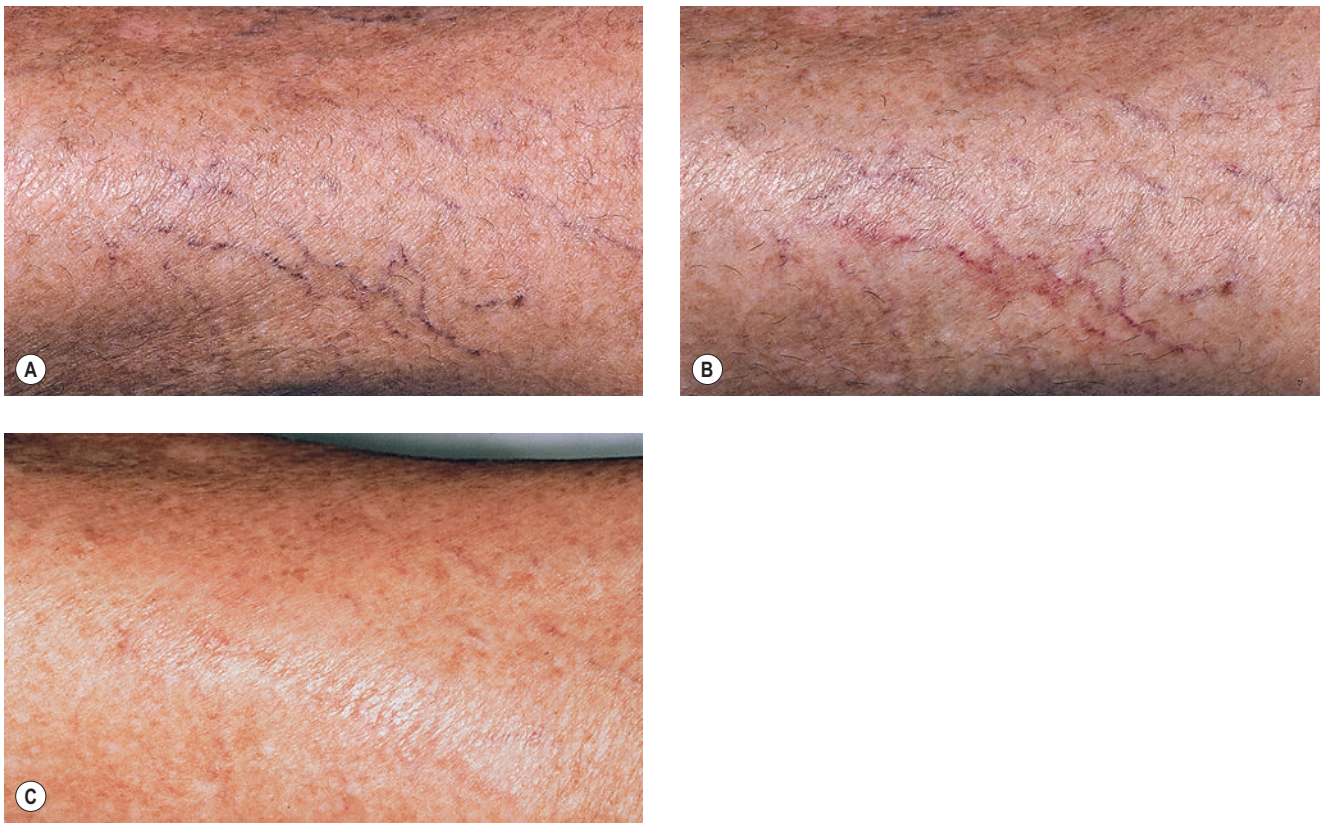


Figure 13.26 **A,** Clinical appearance of a 0.6-mm-diameter vessel on the distal calf before treatment. **B,** Immediately after treatment with the PhotoDerm VL with a 590-nm cut-off filter, 41 J/cm^2 given as a double pulse of 6.5 and 15 ms with a 10-ms delay time. **C,** Ten weeks after treatment, with complete resolution. (From Goldman MP. Laser and noncoherent pulsed light treatment of leg telangiectasias and venules. In: Goldman MP, Bergan JJ, editors. Ambulatory treatment of venous disease. St Louis: Mosby; 1996.)

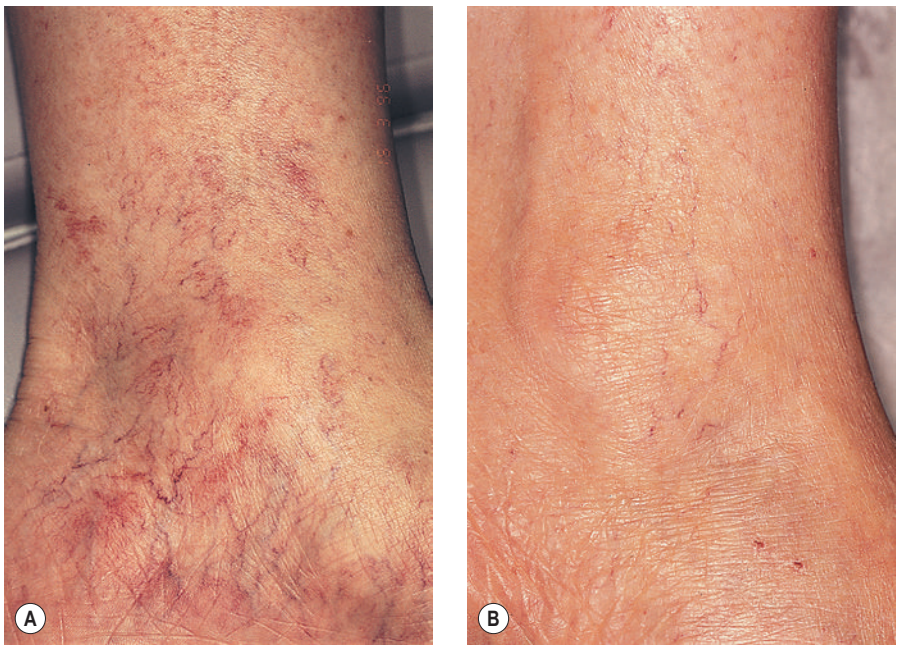


Figure 13.27 **A,** Ankle telangiectasias before treatment. **B,** Six weeks after a single treatment with the PhotoDerm VL at 40 J/cm^2 given as a double pulse of 2.4 and 4.0 ms duration with a 10-ms delay. (From Goldman MP, Fitzpatrick RE. Cutaneous laser surgery: the art and science of selective photothermolysis. 2nd ed. St Louis: Mosby; 1998.)

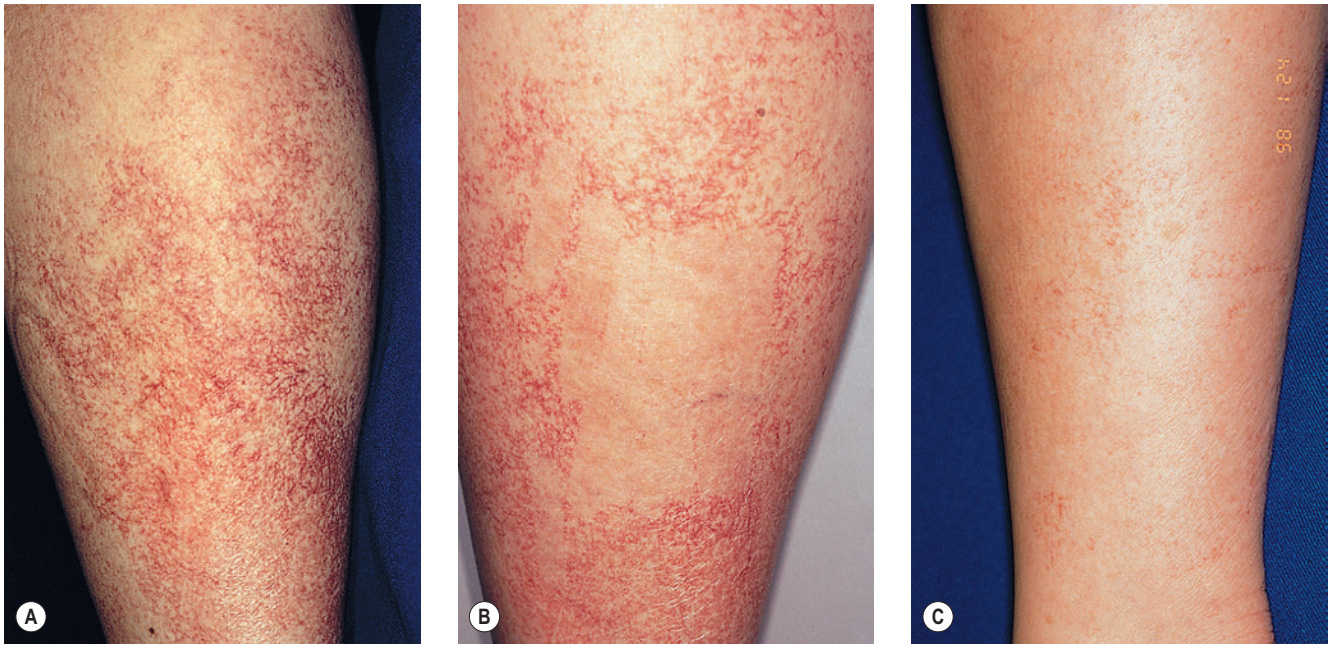


Figure 13.28 Tanned, skin type III, 63-year-old female with isolated telangiectasias without associated varicosities. Previous attempt with sclerotherapy yielded no improvement. **A,** Before treatment. **B,** Ten minutes after treatment with intense pulsed light. Parameters were a double pulse of 2.4 and 7 ms with a 10-ms delay using a 570-nm filter, at 44 J/cm^2. **C,** Resolution 2 months after second treatment. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishers; 1999.)

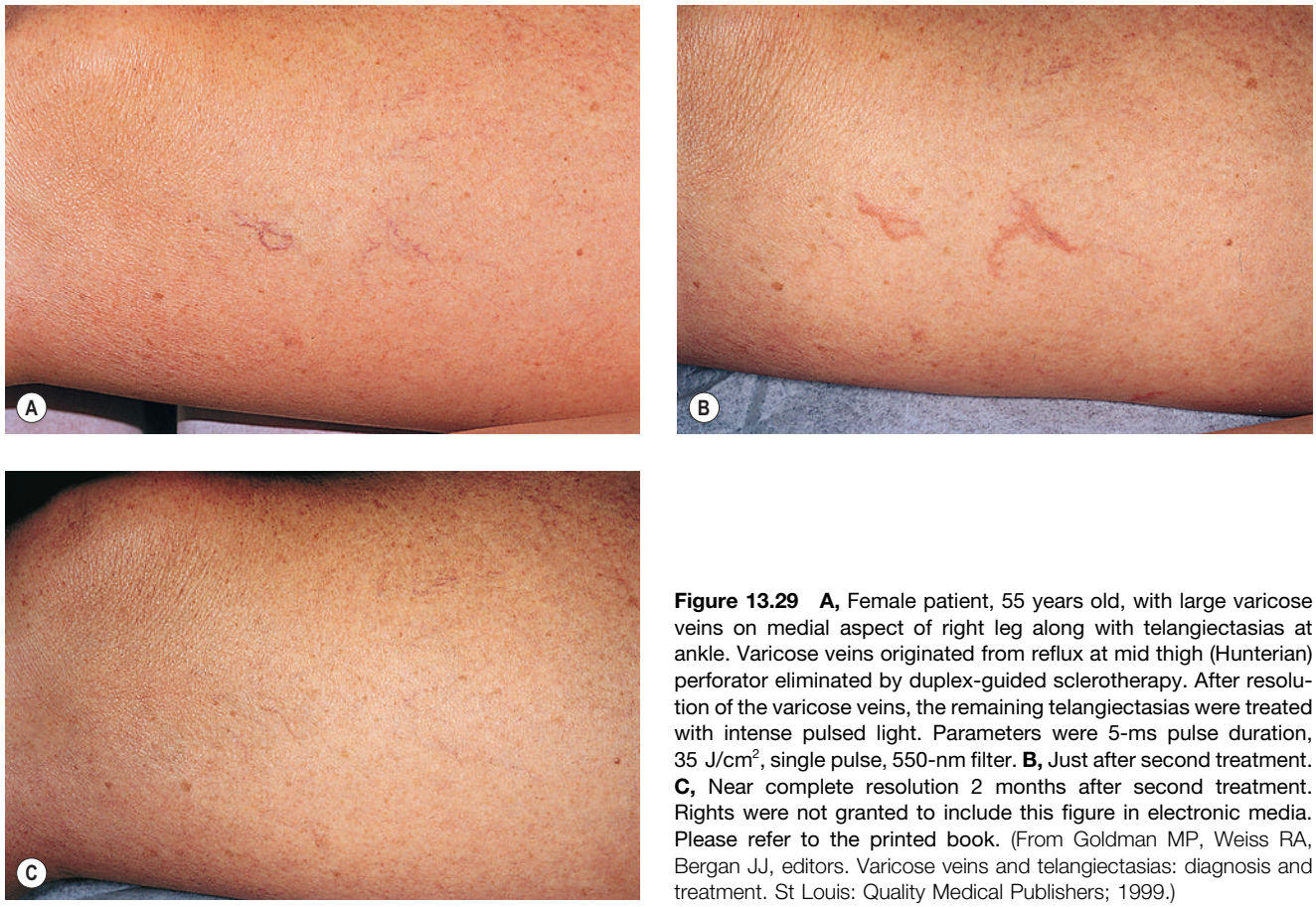


Figure 13.29 **A,** Female patient, 55 years old, with large varicose veins on medial aspect of right leg along with telangiectasias at ankle. Varicose veins originated from reflux at mid thigh (Hunterian) perforator eliminated by duplex-guided sclerotherapy. After resolution of the varicose veins, the remaining telangiectasias were treated with intense pulsed light. Parameters were 5-ms pulse duration, 35 J/cm^2, single pulse, 550-nm filter. **B,** Just after second treatment. **C,** Near complete resolution 2 months after second treatment. Rights were not granted to include this figure in electronic media. Please refer to the printed book. (From Goldman MP, Weiss RA, Bergan JJ, editors. Varicose veins and telangiectasias: diagnosis and treatment. St Louis: Quality Medical Publishers; 1999.)

diameter, color and depth of leg veins. With older machines that do not have integrated cooling through sapphire crystals, a cold gel must be placed between the IPL crystal and skin surface to provide optimal elimination of epidermal heat and reduce potential adverse effects.

ND:YAG LASER, 1064 nm

The Nd:YAG, 1064 nm laser, is probably the most effective and well-studied laser available to treat leg telangiectasias and was first used for this purpose in 1987.[18] The average depth of penetration in human skin is 0.75 mm, and reduction to 10% of the incident power occurs at a depth of 3.7 mm.[100] A narrow therapeutic fluence range, which reduces both its efficacy and safety, is associated with the 1064-nm wavelength.[72] This narrow range may be largely attributed to the formation of methemoglobin (metHb), an oxidized form of hemoglobin that appears during laser-induced blood vessel heating.[101] At 1064 nm, metHb shows a significantly stronger absorption than either hemoglobin or oxyhemoglobin. Theoretically, this metHb formation effect is less pronounced at 755 nm.

In an effort to deliver laser energy to the depths of leg veins (often 1–2 mm beneath the epidermis) with thermocoagulation of vessels 1 to 3 mm in diameter, 1064-nm lasers with pulse durations of between 1 and 250 ms have been developed. However, because of the poor absorption of Hb and HbO_2 with a 1064-nm wavelength as discussed earlier, higher fluences must be used. Whereas a fluence of 10 to 20 J/cm^2 is sufficient to thermocoagulate blood vessels when delivered at 532 nm or 585 nm, a fluence of 70 to 150 J/cm^2 is required to generate sufficient heat absorption at 1064 nm.

Depending on the amount of energy delivered, the epidermis must be protected to minimize damage to pigment cells and keratinocytes. Three mechanisms are available to minimize epidermal damage through heat absorption. First, the longer the wavelength, the less energy will be absorbed by melanocytes or melanosomes (Fig. 13.30). This will allow darker skin types to be treated with minimum risks to the epidermis caused by a decrease in melanin interaction. Second, delivering the energy with a delay in pulses greater than the thermal relaxation time for the epidermis (1–2 ms) allows the epidermis to cool conductively between pulses. This cooling effect is enhanced by the application of cold gel on the skin surface, which conducts away epidermal heat more efficiently than air. Finally, the epidermis can be cooled directly to allow the photons to pass through without generating sufficient heat to cause damaging effects (discussed in more detail as follows).

In 2005, Parlette et al evaluated 21 female patients (27–82 years old, Fitzpatrick skin type I to IV) to investigate a range of pulse durations to determine an optimal pulse duration for clearance of leg veins (0.1–1.6 mm in diameter).[102] Patients were treated with a 1064-nm Nd:YAG, (Candela, Wayland, MA) using progressively increasing fluences for each spot size and pulse duration. Fluences ranged from 80 to 200 J/cm^2, 200 to 300 J/cm^2 and 280 to 580 J/cm^2 for the 6-, 3- and 1.5-mm spot sizes, respectively. Treatment endpoints were immediate vessel disappearance or visible intravascular thrombosis. No posttreatment compression

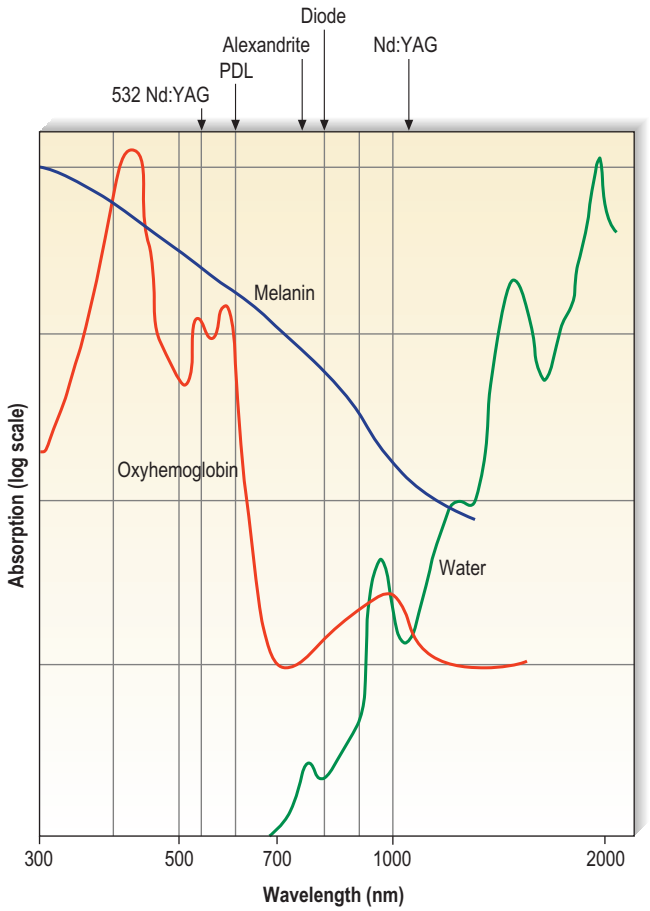


Figure 13.30 Oxyhemoglobin, water and melanin absorption curves as a function of wavelength. (Adapted from Boulnois JL. Lasers Med Sci 1986;1:47.)

was used. Optimal pulse duration for each patient was determined from test sites and defined as the pulse duration using the lowest fluence to achieve the greatest vessel elimination with the least side effects. In general, as spot size decreased from 6 to 3 to 1.5 mm, 1.7× the fluence was required to achieve equivalent immediate reactions to like-sized vessels. Side effects included hyperpigmentation seen in 48% of patients following test sites. Treatment-associated purpura correlated strongly with moderate to severe hyperpigmentation, which was more common with shorter pulse durations (3–20 ms), larger spot sizes and immediate vessel rupture or thrombus formation. In this series, an objective clearance of 71% following a single treatment was noted by three blinded observers. Overall patient satisfaction with treatment was high (4.2/5) which correlated well with patient subjective assessment of improvement (3.8 out of 5). The authors determined that although short pulse durations (<20 ms) were effective in confining heating to the lumen and endothelial lining, the associated rapid, extreme heating lead to purpura and vessel rupture, both of which were associated with increased rates of adverse effects. Conversely longer pulse durations (80–100 ms) caused increased thermal diffusion leading to excessive perivascular heating and scarring. The authors concluded that the 60-ms pulse duration appeared to demonstrate the most efficient vessel elimination with least adverse effects and

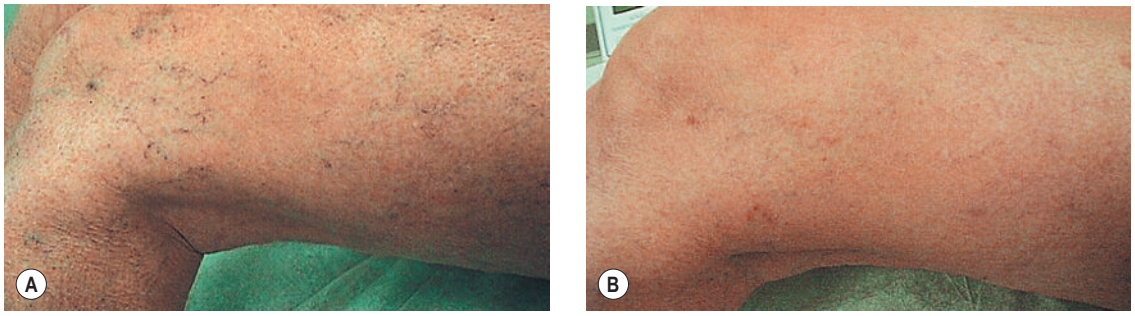


Figure 13.31 Treatment of leg telangiectasias with the Vasculight at parameters specified. **A,** Before treatment; **B,** Six days after treatment. (Courtesy Robert Weiss, MD.)

encouraged use in clinical practice of the smallest fluence and spot size necessary to achieve complete immediate vessel stenosis.

Various 1064-nm lasers are currently available that meet the criteria for selectively thermocoagulating blood vessels, such as Lumenis One and Vasculite (Lumenis, Santa Clara, CA), Varia (CoolTouch, Roseville, CA), Lyra (Laserscope, San Jose, CA), GentleYAG (Candela, Wayland, MA), SmartEpil II (Cynosure, Chelmsford, MA), Harmony (Orion Lasers, FL), Profile (Sciton, Palo Alto, CA), Mydon (WaveLight, Erlangen, Germany) and CoolGlide (Cutera, Burlingame, CA) (see Table 13.1). It is important to note that all long-pulse 1064-nm Nd:YAG lasers are not the same. Variables include the spot size, laser output in both fluence as well as how the extended time of the laser pulse is generated, pulse duration and epidermal cooling. In addition, although many claims are made by the laser manufacturers, few well-controlled peer-reviewed medical studies are available. Because of the variability between the 1064-nm Nd:YAG lasers, a review of the clinical studies with each system will be presented separately.

VASCULITE

The Vasculite was the first long-pulsed, 1064-nm laser to be approved by the U.S. Food and Drug Administration (FDA) for vascular treatment. The Nd:YAG 1064-nm laser is combined with IPL technology. Individual pulses up to 16 ms in length can be delivered as single, double or triple synchronized pulses with a total maximum fluence of 150 J/cm^2. The laser beam is generated in the handpiece and delivered through a sapphire crystal 6, 9 or 3 × 6 mm in diameter. Weiss and Weiss,[103,104] Sadick,[105] and Goldman[106] have reported excellent results in treating leg telangiectasias from 0.1 to 3 mm in diameter. Application of a cool gel to the skin and synchronization of pulses allows epidermal cooling and protection. In addition, synchronized timing between pulses can be tailored to thermal relaxation times of blood vessels.

Weiss and Weiss[104] treated 30 patients who had been dissatisfied with previous leg vein treatments with either sclerotherapy or other laser lights or IPLs. A single 14- to 16-ms pulse at 110 to 130 J/cm^2 was given to treat vessels 1 to 3 mm in diameter. A double pulse of 7 ms separated by 20 to 30 ms at a fluence of 90 to 120 J/cm^2 was used to treat vessels 0.6 to 1 mm in diameter. A triple synchronized pulse of 3 to 4 ms at a fluence of 80 to 110 J/cm^2 was used to treat vessels 0.3 to 0.6 mm in diameter. Immediate contraction of the vessel was used as an endpoint of treatment followed by urtication and immediate bruising from vessel rupture in 50% of vessels. At 3 months after treatment the majority of sites had improved by over 75% (Fig. 13.31). Hyperpigmentation was noted in 28% of patients at the 3-month follow-up period. In short, this report demonstrated successful treatment on otherwise difficult vessels and mirrors the authors' experience. Weiss and Weiss[107] also reported on 3-year results in the treatment of leg telangiectasias 0.3 to 3 mm in diameter at slightly higher fluences of 110 to 150 J/cm^2 and found an average of 75% improvement in 2.38 treatments. Sixteen percent of patients developed pigmentation, which resolved at 6 months, and 4% developed TM.

Sadick[108] reported on 12-month follow-up in 25 patients with leg veins, with a fluence of 120 J/cm^2 given through a 6-mm diameter spot in a 7-ms double pulse to vessels 0.2 to 2 mm in diameter and as a single pulse of 14 ms and a fluence of 130 J/cm^2 to vessels 2 to 4 mm in diameter. Using these parameters, 64% of patients achieved 75% or greater clearance in three treatments. Two of the 25 treated patients who had less than 25% vessel clearance developed a recurrence of the veins within 6 to 12 months. Sixteen percent of patients developed pigmentation, which lasted 4 months, and 8% developed TM.

Slightly higher fluences were used by Trelles et al[109] in treating 40 patients with leg veins up to 4 mm in diameter: 130 J/cm^2 given as a double pulse of 7 ms and 140 J/cm^2 given as a 14-ms triple pulse was used on vessels less than 2 mm and 2 to 4 mm in diameter, respectively. The authors used a computerized objective assessment tool to determine efficacy; however, the percentage improvement was not noted, only that 80% of patients were satisfied with treatment.

COOLTOUCH VARIA

The CoolTouch Varia combines a multiple train of pulses to generate a pulse width from 10- to 300-ms bursts generating fluences up to 150 J/cm^2. A 3- to 10-mm diameter beam is delivered through a fiberoptic cable. Dynamic cooling is given with a cryogen spray that can be delivered before, during and/or after the laser pulse. The cooling spray can be varied from 5 to 200 ms and can be given in 5- to 30-ms bursts in 5-ms intervals before and/or after the laser pulse. In this manner, in the treatment of larger or deeper vessels, the postcooling quenching cryogen spray can be given 20 to 30 ms after the laser pulse to coincide with conduction of

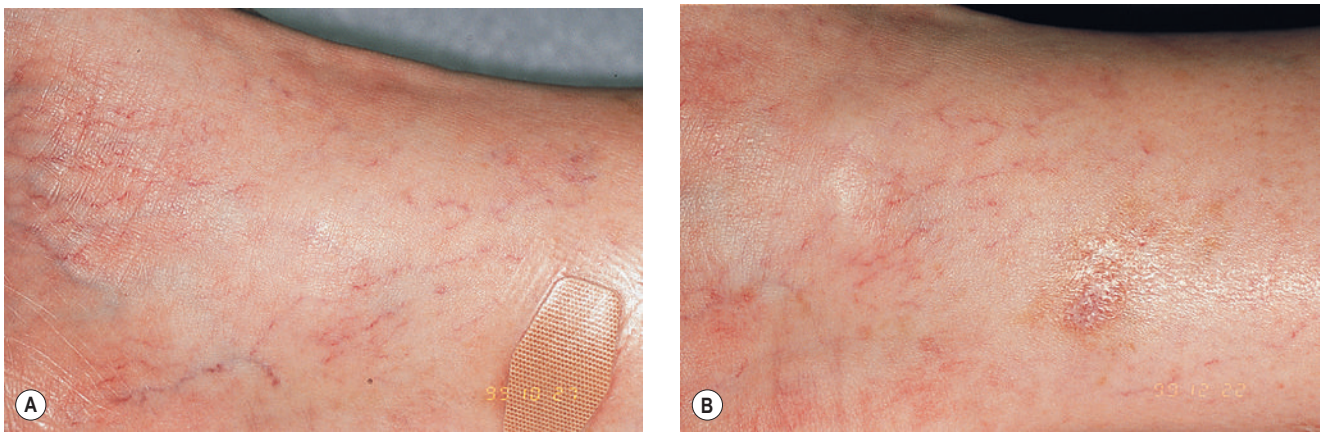


Figure 13.32 **A,** After sclerotherapy an ulceration occurred that is covered with an occlusive dressing. **B,** After treatment of a foot telangiectasias with the CoolTouch Varia at 150 J/cm^2 with a 50-ms pulse and 5 ms of precooling 10 ms before the laser pulse, followed by a 10-ms cooling burst 10 ms after the laser pulse. Note complete clearing 60 days after treatment.

heat absorbed by the vessel propagating back to the epidermis. More superficial and smaller vessels require a shorter delay in the postlaser cooling spray of 5 ms. The authors have found this laser to be therapeutically beneficial in treating leg telangiectasias 0.1 to 2 mm in diameter (Fig. 13.32). A comparative study of two long-pulsed 1064-nm Nd:YAG lasers was performed on 11 patients with leg telangiectasias without (or with previously treated) feeding reticular veins. The CoolTouch Varia was used with a 6-mm diameter spot size at a fluence of 135 J/cm^2 with a 25-ms pulse and precooling of 5 ms, with post cooling of 15 ms. The CoolGlide laser was used with a 5-mm diameter spot, 25-ms pulse at 200 J/cm^2 and contact cooling. Both lasers produced comparable clearing of 75% in all treated vessels; however, the CoolGlide laser was significantly more painful.[110]

In 2001 and 2002 two papers were published on the same 23 of 30 leg vein patients (completing the study) treated with the CoolTouch Varia, noting 75% improvement at 85% of treated sites.[111,112] In these trials, patients received up to two treatments 4 to 6 weeks apart. Fluences of 150 J/cm^2 were used for all diameter veins with a 25-ms pulse duration on veins less than 1.5 mm in diameter and 50- to 100-ms on veins 1.5 to 3 mm in diameter. One to three passes were required to blanch the targeted vessels. Laser spot diameters and the time of pre- and/or postcooling was not noted in either of the two papers. Transient pigmentation was noted in 6 of 23 patients, with TM in 1 of 23 patients. In these studies, patients who had previously had treatment with non-HS sclerotherapy preferred sclerotherapy to laser, citing increased pain with laser treatment.

A direct comparison of the CoolTouch Varia with sclerotherapy utilizing sodium tetradecyl sulfate (STS) was also performed on 20 patients with size-matched superficial leg telangiectasias 0.5 to 1.5 mm in diameter.[113] Laser parameters included a 5.5-mm diameter spot at 125 to 150 J/cm^2 with a 25-ms pulse duration. Precooling ranged from 0 to 5 ms and postcooling ranged from 20 to 50 ms with a delay of 5 to 20 ms. The endpoint of laser treatment was vessel contraction. Sclerotherapy with STS 0.25% was followed by 48-hours' wear of 20- to 30-mmHg graduated compression stockings. In this head-to-head trial, sclerotherapy-treated patients had a significantly better response in fewer treatments with comparable adverse effects.

Of note, the CoolTouch Varia is especially useful in treating periorbital telangiectasias and reticular veins. Although these veins may be treated with sclerotherapy (see Chapter 12), we have had near 100% success without adverse effects in treating these vessels with the CoolTouch Varia (Fig. 13.33).

COOLGLIDE

The CoolGlide can deliver fluences up to 100 J/cm^2 through a 10-mm diameter spot. The pulse duration can be varied continuously from 10 to 100 ms. Unlike the other systems, which can deliver each burst at a 1-Hz frequency, the CoolGlide can deliver pulses at 2 Hz. Cooling is provided by a contact system that glides in front of the laser beam so that 2 cm of skin is precooled before the laser aperture glides over the treatment site. The authors have also found this system to be effective in treating leg telangiectasias 0.1 to 3 mm in diameter (Fig. 13.34).[110] However, the lack of effective, reproducible cooling can lead to the production of epidermal scars, more so than with the other 1064-nm laser systems, as well as an increase in procedural pain (Fig. 13.35).

Fifteen women with 21 sites of leg telangiectasias 0.25 to 4 mm in diameter were treated twice, separated by an interval of 6 to 8 weeks, with the CoolGlide using a 7-mm spot, fluence of 90 to 160 J/cm^2 and pulse durations of 10 to 50 ms.[114] Significant improvement was seen in 71% of sites but hyperpigmentation was present in 61% of sites at 3-month follow-up. A second study of 20 patients with reticular veins 1 to 3 mm in diameter was performed using 100 J/cm^2 and a 50-ms pulse without mention of the laser spot diameter.[115] Although 66% of the vessels cleared by more than 75% with one treatment at 3 months, pain was significant, especially without the use of EMLA cream (a eutectic mixture of lidocaine and prilocaine) applied for 1 hour. Unfortunately, longer follow-up was not reported.

LYRA

The Lyra long-pulse 1064-nm Nd:YAG laser has been studied in 20 patients with leg telangiectasias 0.5 to 5 mm in diameter with 100 to 200 J/cm^2 at 50 to 100 ms with a

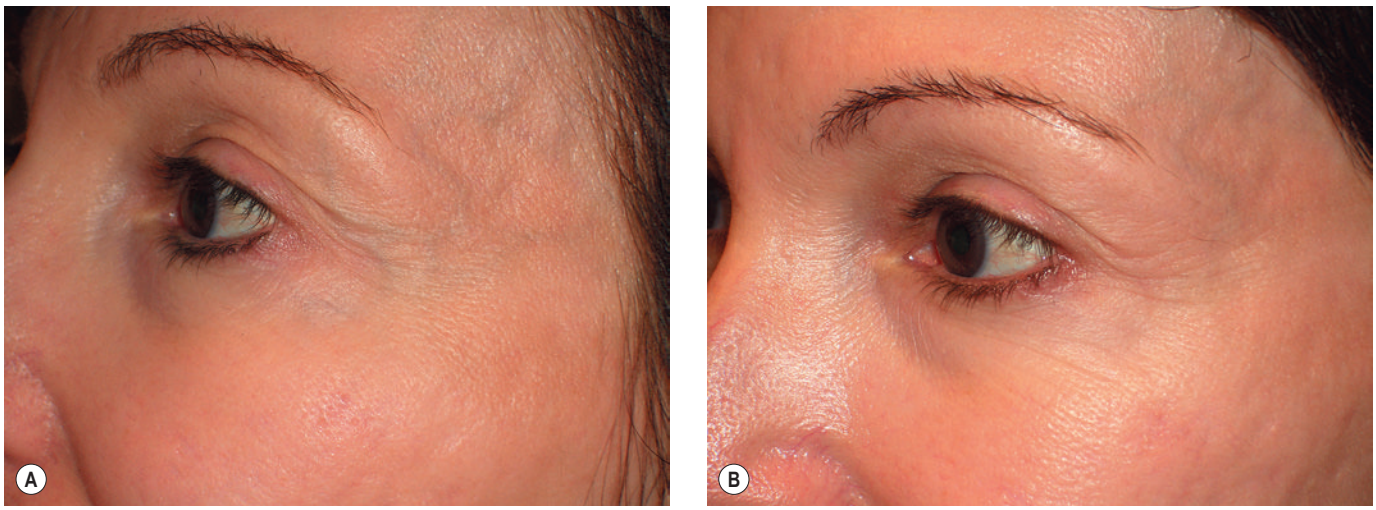


Figure 13.33 **A,** Appearance of dilated reticular vein 2 mm in diameter in the lateral canthal and infraorbital region before treatment. **B,** Appearance 4 weeks after a treatment using the CoolTouch Varia at 210 J/cm^2 with a 3.5-mm diameter spot size and a 25-ms pulse duration with 30 ms of cryogen spray cooling immediately after the laser pulse.

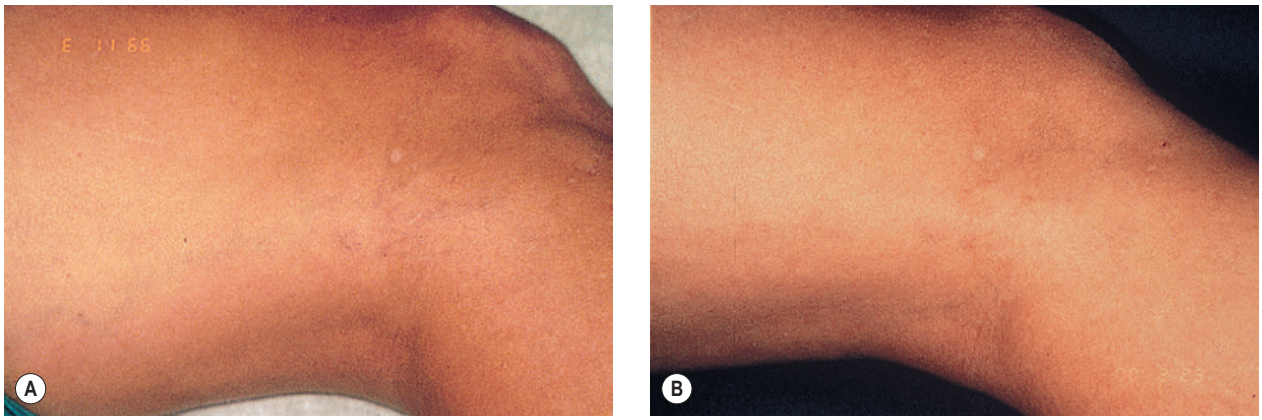


Figure 13.34 **A,** Reticular vein 2 to 3 mm in diameter on the medial thigh feeding into an area of telangiectasias. **B,** Complete resolution 16 weeks after treatment with the CoolGlide laser with multiple pulses until vessel spasm occurred at a fluence of 80 J/cm^2, 30-ms pulses with epidermal contact cooling.

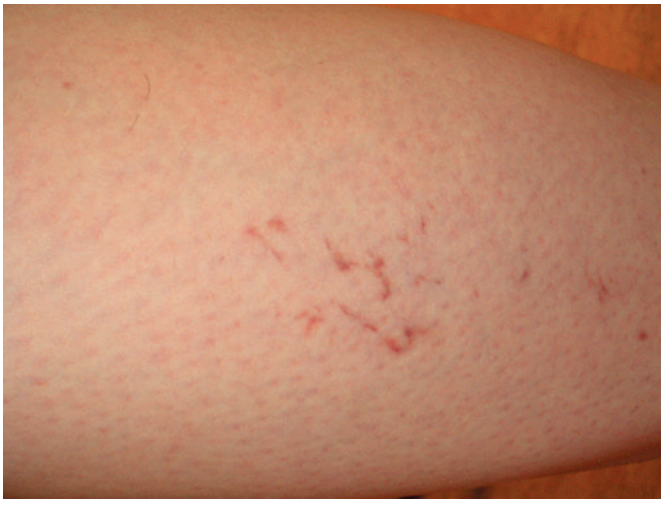


Figure 13.35 A lack of effective, reproducible cooling can lead to an increase in procedural pain as well as the production of epidermal scars (seen here), more so than with the other 1064-nm laser systems.

3- to 5-mm diameter spot and one to four treatments.[116] Comparable telangiectasias on the same patient received a single sclerotherapy treatment with STS 0.6%; however, no compression was used. Even at these parameters with excessive concentration of STS without compression and four laser treatments versus one sclerotherapy treatment, adverse effects and treatment efficacy were not statistically different between the two treatment modalities. Patient surveys found that 35% preferred laser and 45% preferred sclerotherapy.

Sadick[117] also evaluated the Lyra in a limited evaluation of 10 patients using a 30- to 50-ms pulse duration, 1.5-mm diameter spot, 400 to 600 J/cm^2 for red vessels and a 50- to 60-ms pulse, 1- to 3-mm diameter spot, 250 to 370 J/cm^2 for blue vessels. Patients were treated through a 4°C cold window for three treatments. At 6 months, 80% of vessels had greater than 75% clearance. Two of the 10 patients studied had pigmentation lasting up to 6 months and TM occurred in 1 patient. Moderate discomfort was experienced by all patients.

GENTLEYAG

Ozyart et al[118] retrospectively analyzed 255 patients (189 female, 66 male, median age 35, Fitzpatrick skin type II–V) treated with the 1064-nm Nd:YAG laser (GentleYAG, Candela) for spider angiomas (26 patients), facial telangiectasias (130 patients) and lower extremity telangiectasias (99 patients). Patients were treated at 4-week intervals for 5 months. Laser parameters including spot size, pulse duration and starting fluence for leg telangiectasias were 1.5 mm, 20 to 40 ms, 360 J/cm^2 for telangiectasias less than 0.5 cm; 3 mm, 40 to 60 ms, 220 J/cm^2 for vessels less than 1.0 cm; 3 mm, 40 to 60 ms, 200 J/cm^2 for vessels less than 1.5 cm; and 3 mm, 180 ms, 180 J/cm^2 for leg vessels 1.5 to 3.0 mm. The authors reported a clearance of 80.8% (80/99 patients) for leg telangiectasias compared with 100% clearance of spider angiomas and 97% clearance of facial telangiectasias. Interestingly, larger leg telangiectasias (1.5–3 mm) responded better (45%) after the first session of treatment compared with the smaller leg telangiectasias (<0.5 mm; 4% clearance); however, the reverse held true with additional treatment sessions. By the fifth session clearance of the smallest telangiectasias reached 80.8% and was only 11% for the largest vessels (1.5–3 mm).

SMARTEPIL LS

A comparative study of the long-pulsed 1064-nm Nd:YAG laser with sclerotherapy was performed on 14 patients with leg telangiectasias 0.5 to 2 mm in diameter.[120] The Nd:YAG laser was used at 100 to 125 J/cm^2 through a 2.5-mm diameter spot and a 10-ms pulse without cooling. Sclerotherapy was performed with POL 0.5% without posttreatment compression. An evaluation of combinations of laser and sclerotherapy was also performed. There was no statistical difference in efficacy between the four different treatment modalities. However, the sclerotherapy-treated veins had better resolution.

XEO

A randomized controlled clinical trial comparing the efficacy of conventional sclerotherapy (75% glucose solution) to Nd:YAG laser (Xeo, Cutera) treatment was performed on 30 women (age 25–65, skin phototype I–VI). Enrolled participants had lower extremity telangiectasias 0.5 to 1.5 mm in diameter with no evidence of chronic venous insufficiency. Participants' lower extremities were randomly assigned laser (spot size of 3 mm, fluence 100–120 J/cm^2, pulse width 15 or 30 ms depending on vessel size) vs. sclerotherapy (75% glucose solution low-flow injections, total volume 1–2 mL) and treated in three sessions at monthly intervals. Subjects were not required to use compression posttreatment. Side effects between groups were similar and included one case of transient postinflammatory hyperpigmentation in both groups and a scar on the laser treated area. While clearing scores assessed using photographic analysis statistically favored the laser treated group; mean ± SD laser: 7.9 ± 1.0 vs. 7.0 ± 1.0 in the sclerotherapy group, patient pain assessment was significantly greater in the laser treated group (very painful 66.66%; slightly painful 22.33% compared with the sclerotherapy group: very painful 13.34%, slightly painful 86.66%, $P < 0.001$), and overall patient satisfaction favored sclerotherapy ($P = 0.04$). These results indicate that despite objectively noted improvement in outcomes in the laser treated group, procedural pain likely influences patient satisfaction and overall impression of final results. The authors concluded that although Nd:YAG 1064 laser treatment may achieve similar or perhaps even improved results to conventional sclerotherapy with glycerin, sclerotherapy is lower-cost, less painful, leads to likely faster clinical improvement and appears to be associated with improved patient satisfaction and a more positive overall impression of final results.[121]

QUANTEL MEDICAL MULTIPULSE MODE

A more recent development in long-pulse 1064-nm Nd:YAG technology has been the production of a nonuniform pulse sequence mode device with contact cooling to 5°C delivering a fluence of 300 to 360 J/cm^2 through a 2-mm diameter spot.[119] The rationale for multiple pulsing is to convert HbO_2 to metHb, which is better absorbed by 1064 nm. The pulse duration consists of a series of three 3.5-ms pulses each separated by 250 ms leading to a dissipation of energy from 60% in the first pulse, to 20% in each of the next two pulses. In an initial study of 11 patients with blue leg veins 1 to 2 mm in diameter treated up to 3 times at 6-week intervals, this methodology resulted in a 98% clearance and was associated with moderate procedural pain.

To summarize, we have found the 1064-nm, long-pulsed Nd:YAG lasers to be beneficial in the treatment of leg telangiectasias not responsive to sclerotherapy or other lasers. The benefit in using a 1064-nm laser is that its longer wavelength can penetrate more deeply, allowing effective thermosclerosis of vessels up to 3 to 4 mm in diameter. In addition, the 1064-nm wavelength permits treatment of patients of skin types I to VI with or without a tan because melanin absorption is minimal; however, the 1064-nm, long-pulse laser systems are not entirely without side effects. Cutaneous burns with resulting ulcerations, pigmentation and TM have been observed with each of these systems as parameters are being tested. The dynamically cooled 1064-nm Nd:YAG laser appears to produce the best clinical resolution with the least pain and adverse effects compared with other long-pulse 1064-nm lasers; however, sclerotherapy still provides better results in fewer treatments, is associated with less pain and has comparable adverse effects to lasers. Thus, the reader should evaluate the latest studies to ensure ideal results.

PROTECTION OF EPIDERMIS: EPIDERMAL COOLING

Protection of the epidermis is paramount to minimize treatment-associated adverse effects Epidermal cooling has been well studied in its ability to minimize epidermal damage through heat absorption, thus protecting pigment cells and keratinocytes, and can be applied in many different ways. The simplest method is continuous contact cooling with chilled water, which can be circulated in glass, sapphire or plastic housings. The laser impulse is given through the transparent housing, which should be constructed to ensure

that the laser's effective fluence is not diminished. The benefit of continuous contact cooling is its simplicity. The disadvantage is that the cooling effect continues throughout the time that the device-crystal is in contact on the skin. This results in a variable degree and depth of cooling determined by the length of time the cold housing is in contact with the skin. This nonselective and variable depth and temperature of cooling may necessitate additional treatment energy so that the cooled vessel will heat up sufficiently to thermocoagulate (Fig. 13.36).

Another method of cooling is contact precooling. In this approach, the cooling device contacts the epidermis adjacent to the laser aperture. The epidermis is precooled and then treated as the handpiece glides along the treatment area. Because the cooling surface is not in the beam path, no optical window is required and better thermal contact can be made between the cooling device and the epidermis. The drawback is the nonreproducibility of cooling levels and degrees that are based on the speed and pressure at which the surgeon uses the contact cooling device.

Yet another method for cooling the skin is to deliver a cold spray of refrigerant to the skin that is timed to precool the skin before laser penetration and also to postcool the skin to minimize thermal back-scattering from the laser-generated heat in the target vessel. The authors have termed this latter effect 'thermal quenching' (Fig. 13.37). This method reproducibly protects the epidermis and superficial nerve endings. In addition, it acts to decrease the perception of thermal-laser epidermal pain by providing another sensation (cold) to the sensory nerves. Finally, it allows an efficient use of laser energy because of the relative selectivity of the cooling spray that can be limited to the epidermis. The millisecond control of the cryogen spray prevents cooling of the deeper vascular targets and is given in varying

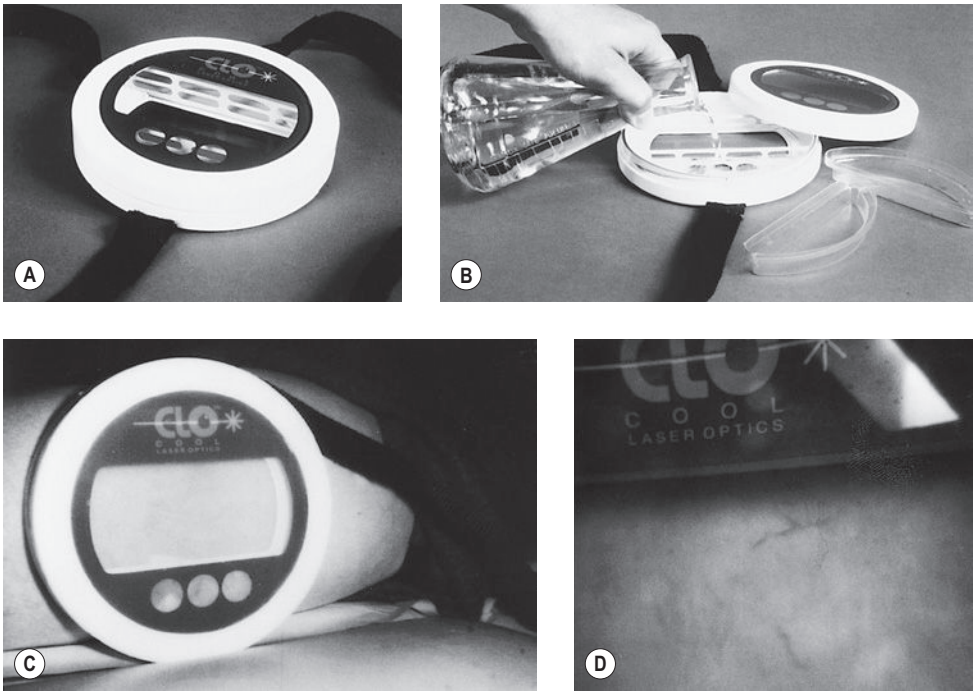


Figure 13.36 Cool laser optics (CLO) device. **A,** Appearance of device. **B,** Open unit being filled with ice water. Half-moon-shaped plastic forms to make ice blocks for lateral compartments of the unit. **C,** CLO unit attached with Velcro straps to the patient's left thigh over telangiectasias. **D,** Close-up of telangiectasias viewed through the CLO unit before treatment. (Courtesy Cyrus Chess, MD.)

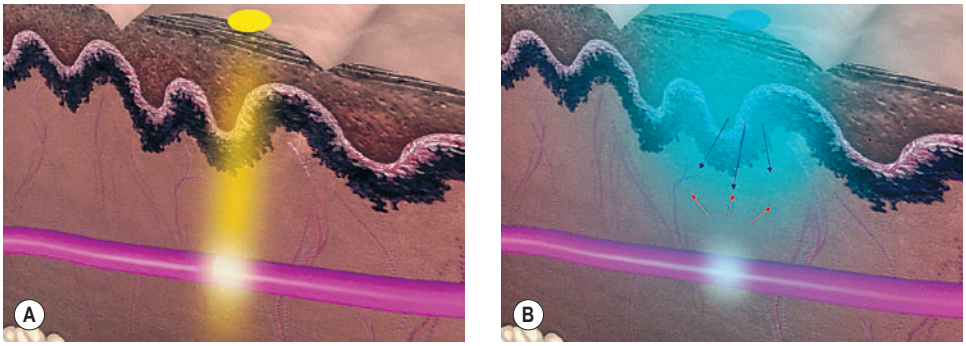


Figure 13.37 Thermal quenching through the application of dynamic cooling. **A,** Laser pulse penetrates through the epidermis and dermis to be absorbed by the vascular target. **B,** After absorption by the blood vessel, a pulse of cooling selectively protects the epidermis and quenches the heat rising from the thermocoagulated vessel. (Courtesy New Star lasers.)

amounts so that epidermal absorption of heat is counteracted by exposure to cryogen.

PERCUTANEOUS LASER TREATMENT: ND:YAG

Iannini et al[122] more recently published on the use of an Nd:YAG 1064-nm laser (EVLASER, Elettronica Valseriana, Casnigo, Italy) using a minimally invasive percutaneous approach to the treatment of lower leg telangiectasias without clinical venous insufficiency. Twenty women (24 to 47 years old) received a maximum of 3 sessions (mean 2.5 ± 0.11 sessions) targeting a total number of 35 ± 8 vessels (range of diameter 0.3–5 mm) using a 200-μm optical fiber. Sixteen of 20 patients obtained a good or excellent result ($P < 0.01$) and were 'very satisfied'. Recanalization was seen in 2 patients and dyschromia (hypo/hyperpigmentation) in 2 patients, and was nearly absent at 6 months.

COMBINED TREATMENT APPROACHES

COMBINED LASER–SCLEROTHERAPY TREATMENT OF LEG TELANGIECTASIAS

Goldman et al[54] hypothesized that the combination of sclerotherapy with laser thermocoagulation may be effective in the treatment of leg veins as early as 1990. Theoretically, combining administration of a laser with an injected sclerosant to treat leg telangiectasias could decrease the amount of each therapy necessary to yield optimal results, thus mitigating the individual side effect profiles of each. In the earliest of studies evaluating this combined approach, 27 patients, with either bilaterally symmetrical telangiectatic patches or a large 'sunburst' telangiectatic flare that could be divided into two separate treatment sites, were evaluated.[55] Patients were treated at one site with the 0.45-ms, 585-nm PDL alone, and at the other site with laser fluences 1 to 2 J/cm^2 less than those used with PDL alone immediately before injection of the telangiectasias with POL 0.25%, 0.5% or 0.75%, with a volume of 0.1 to 0.25 mL per injection site (Fig. 13.38). Forty-four percent of combination treated areas completely resolved (Table 13.3, Fig. 13.39). There appeared to be little difference in efficacy and adverse sequelae with concentrations of POL between 0.25% and 0.75%; however, there did appear to be an increased efficacy of treatment with laser energies of 7.5 to 7.75 J/cm^2. As with the PDL alone, treatment site did not appear to significantly affect outcome except for an increased incidence of complications in the ankle and knee areas.

In this study, the most significant difference between the PDL alone and combination treatment was the incidence of complications. With combination treatment, posttreatment ulceration and TM occurred in 11% of treated areas, compared with no adverse sequelae with PDL alone. Six of 23 nonulcerated treatment sites developed persistent pigmentation beyond 1 year. Two of 27 sites developed TM that lasted over 1 year, and four of 27 treatment sites developed superficial ulceration. In these ulcerated patients, laser fluences were equal to or greater than 6.5 J/cm^2 and POL concentration was equal to or greater than 0.5% (Table 13.4, Figs 13.40 and 13.41).

More recently, Moreno-Moraga et al[123,124] reported on two RCTs evaluating the combination of Nd:YAG and polidocanol (POL) micro-foam in class I (red vessels of less than 0.5 mm) and II (red–blue venulectasias of 0.5–1.5 mm) as well as class I, II and III (blue reticular veins measuring between 1.5 and 4 mm) with more promising results.

In 2013, they reported on a trial of 3 groups of 30 patients (age 19–46 years), skin type IV with vessels measuring less than 1.5 mm and no evidence of venous insufficiency. Patients were treated in two sessions 8 weeks apart with either (A) POL micro-foam alone; (B) Nd:YAG alone or (C) Nd:YAG following POL micro-foam injections. POL concentration of 0.3% was obtained by placing 2 mL of the sclerosant in a syringe with 8 mL of CO_2. A 1064-nm Nd:YAG laser (Synchron HP Laser Deka, Florence, Italy) was used with a 2-mm spot, 150 J/cm^2 fluence, programmed for emission of 8 Hz pulses with a pulse duration of 35 ms with 15

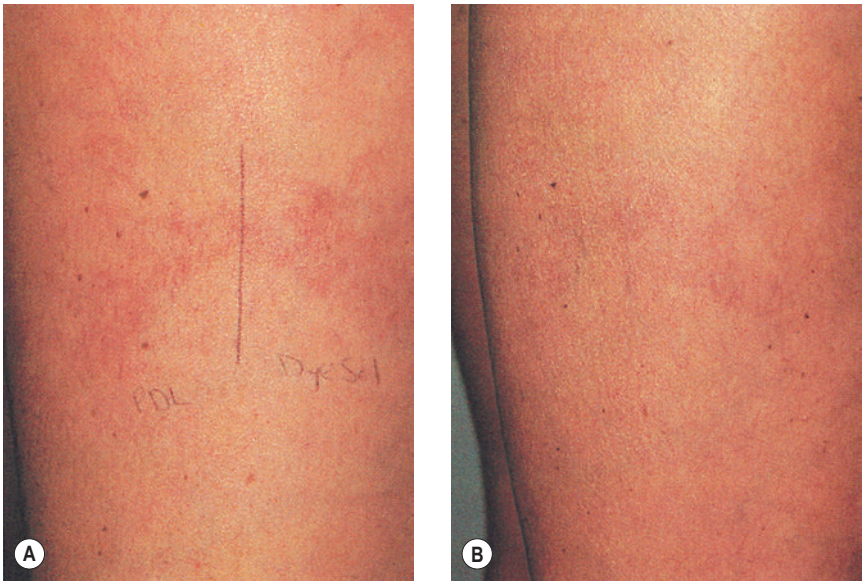


Figure 13.38 Telangiectatic flare on lateral thigh divided into two treatment sites. Anterior aspect treated with flashlamp-pumped pulsed dye laser (PDL) at 6 J/cm^2, 50 pulses, immediately before sclerotherapy with polidocanol 0.25%, 2 mL. Posterior aspect treated with PDL at 7 J/cm^2, 34 pulses. **A,** Immediately before treatment. **B,** Three months after treatment. Note complete resolution of vessels treated with each modality.

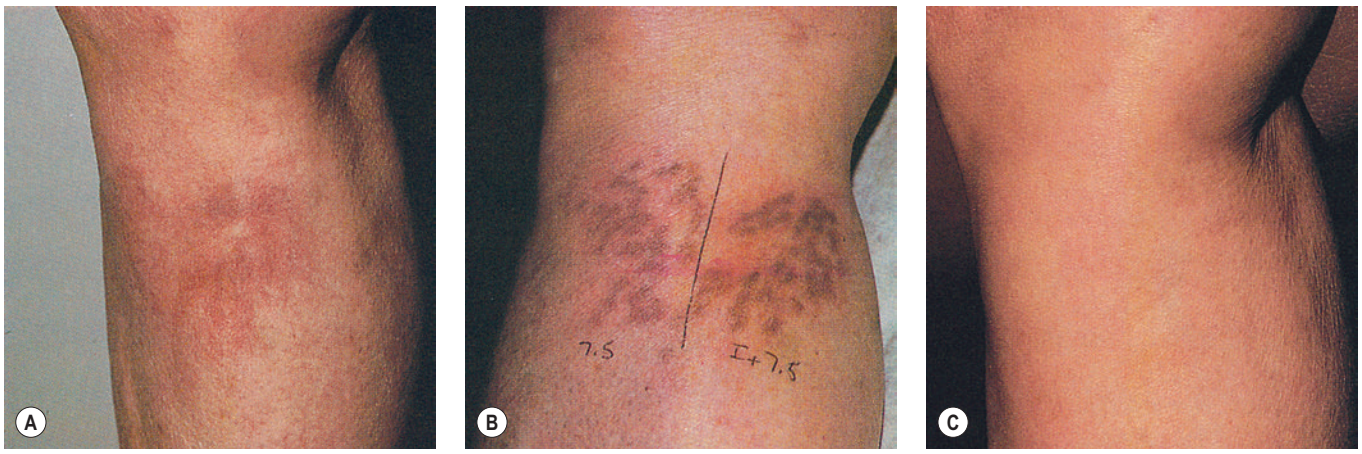


Figure 13.39 Telangiectatic matting on medial knee and calf 6 months after sclerotherapy. **A,** Immediately before treatment. **B,** Immediately after treatment with flashlamp-pumped pulsed dye laser (PDL) to anterior aspect at 7.5 J/cm^2, 51 pulses; posterior aspect treated with PDL at 7.5 J/cm^2, 41 pulses, followed by sclerotherapy with polidocanol 0.5%, 1 mL. **C,** 11 months after treatment.

Table 13.3 Results of PDL/SCL Treatment of Leg Telangiectasias (All POL Concentrations)

Laser Energy (J/cm^2)	No. of Sites Treated	No Change (%)	<90% Faded (%)	Total Fade (%)	Ulceration/ Matting (%)
5.5	3	—	100	—	—
6.0	10	20	30	40	10
7.0	4	—	25	25	50
7.25	2	—	50	50	—
7.5	7	14	14	72	—
7.75	1	—	—	100	—
Total	27	11	33	44	11

Modified from Goldman MP, Fitzpatrick RE: J Dermatol Surg Oncol 1990;16:338.
PDL, pulsed dye laser; POL, polidocanol; SCL, sclerotherapy.

Table 13.4 Results of PDL/SCL Treatment with PDL and POL 0.25% and 0.5%

Laser Energy (J/cm^2)	No. of Sites Treated	No Change (%)	<90% Faded (%)	Total Fade (%)	Ulceration/ Matting (%)
POL 0.25%					
5.5	1	—	100	—	—
6.0	6	17	33	33	17
7.0	1	—	—	100	—
POL 0.5%					
5.5	2	—	100	—	—
6.0	2	50	—	50	—
7.0	2	50	—	50	—
7.25	2	—	50	—	50
7.5	6	17	—	83	—
7.75	1	—	—	100	—

Modified from Goldman MP, Fitzpatrick RE: J Dermatol Surg Oncol 1990;16:338.
PDL, pulsed dye laser; POL, polidocanol; SCL, sclerotherapy.

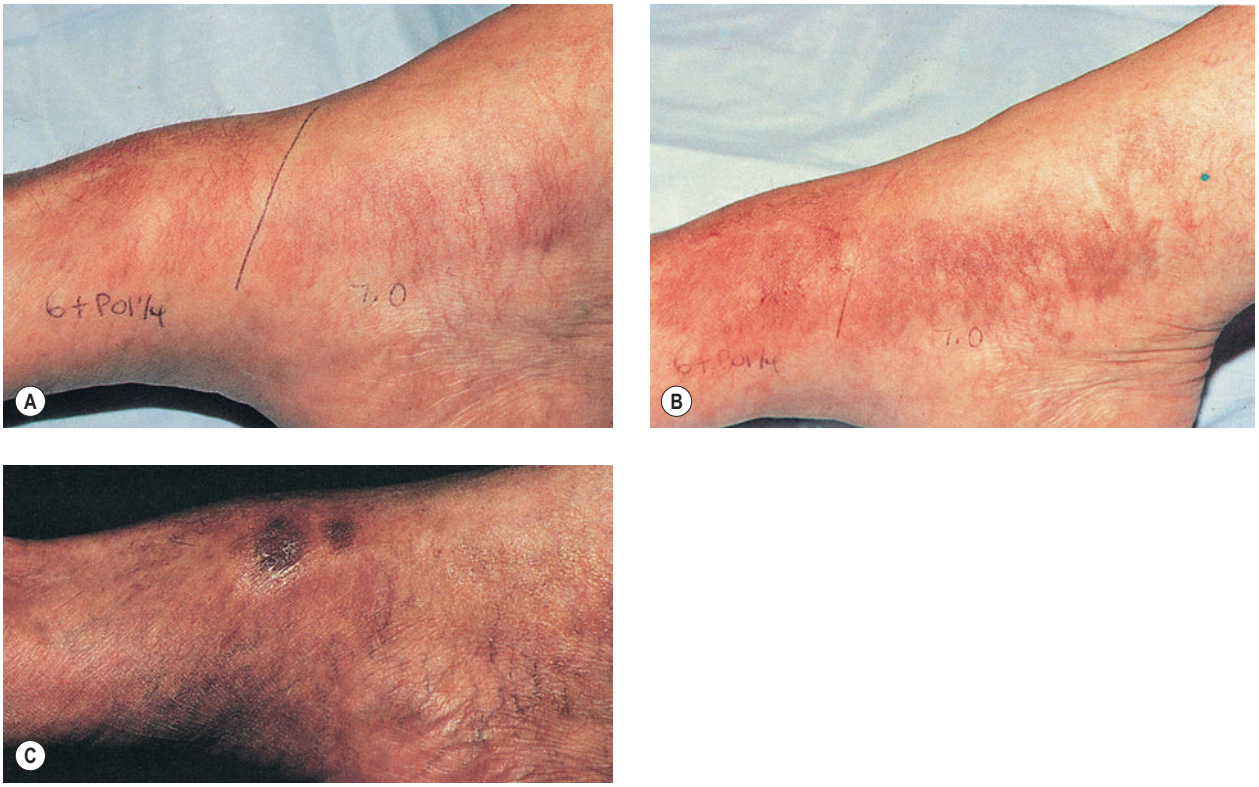


Figure 13.40 Essential telangiectasias on the feet. Distal aspect treated with flashlamp-pumped pulsed dye laser (PDL) at 6 J/cm^2, 114 pulses, immediately followed by sclerotherapy (SCL) with polidocanol 0.25%, 1 mL. Proximal aspect treated with PDL at 7 J/cm^2, 100 pulses. **A,** Immediately before treatment. **B,** Immediately after treatment. **C,** Four months after treatment. Note superficial ulceration at the PDL/SCL-treated site.

ms delay. Treatment was applied moving the hand piece over a 3-cm vein segment with a maximum of five laser passes with 1 second used per pass. Improvement at 16 weeks per patient report was 'very good' or 'good' in 30% of POL-only patients, 23.33% of laser-only patients and 96.66% of combined POL and laser treatment patients. Results of objective assessment at 16 weeks correlated well with subjective impression of patients and were highly statistically significant for the combined treatment group ($P < 0.0001$). Complications were mild and not statistically significant between groups but included in group A: 2 cases of postinflammatory hyperpigmentation; group B: 2 cases of mild burning without subsequent postinflammatory hyperpigmentation and group C: 2 cases of mild burn without subsequent postinflammatory hyperpigmentation and 1 case of discreet matting in a treated area.[123]

The same group subsequently published a larger randomized polidocanol-controlled trial comparing 79 legs treated with POL and 517 legs treated with POL + Nd:YAG laser with a 3- year follow up. A total of 320 patients aged 19 to 72 (Fitzpatrick II–IV) with more than 20% of leg surface area covered with varicosities and no evidence of venous insufficiency were treated in in full (both legs from groin to ankle) in two treatment sessions at 3-week intervals. Efficacy was assessed at 3 months, 2 years and 3 years posttreatment. POL micro-foam was prepared similarly to their previous trial using a sclerosant concentration of 0.3% (maximum of 20 mL) in both legs used overall (generally less than 10 mL in each leg). The combination treatment group was subsequently treated with the Nd:YAG 1064 laser (Laserscope Lyra 'I', Laserscope, San Jose, CA, USA) with a spot size 2–5 mm (energy per pulse for 2 mm spot: 9.42 J, and 5 mm spot: 11.77 J/pulse), pulse width 30 ms for class I and II veins and 50 ms for class III veins with a pulse repetition rate of 5 Hz for class I and II and 2 Hz for class III. Pulses were applied along the length of the entire vessel. Results in the combined POL + laser treatment group were more than 5 SD greater than the POL-alone treatment group (Cohen's *d*-values 7.56, 4.72 and 4.87 for class I, II and III veins, respectively) at 3 months which further improved to exceed eight SDs at 3-year follow up (Cohen's *d*-values 8.22, 11.03, 12.65 for class I, II and III veins, respectively). The authors found in the POL-only group a clearance rate of less than 20% in class I veins and a maximum clearance of 43% in class III veins at the third month with effects largely disappearing within 2 to 3 years for all types of veins treated. In contrast, they found a 90% or above clearance rate in the POL + laser group, which improved to 89%, 94% and 95% for class I, II and II veins, respectively at 3 years. In the POL-only group, hyperpigmentation was noted in 6.3% of cases and TM in 2.5%, all of which had resolved by the second and third year at time of follow up. A total of 7.73% of patients in the combination POL + laser treatment groups were noted to have hyperpigmentation, hypopigmentation, blisters and matting, all of which had resolved with the exception of four cases of hypopigmentation (0.7%), which persisted into the third year. Patient-reported procedural pain was greater in the combination treatment group; light (8.6%), moderate

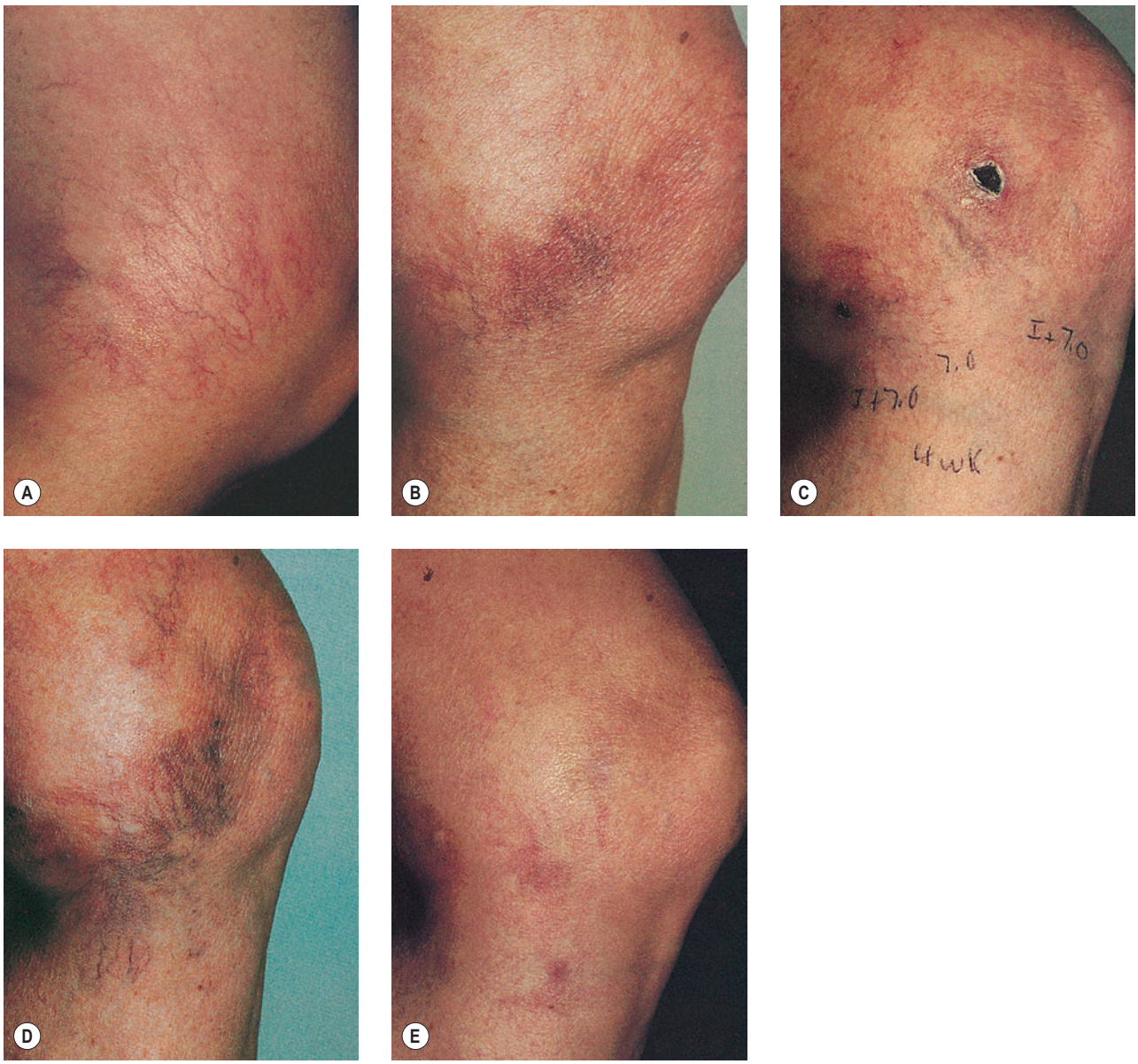


Figure 13.41 Treatment of telangiectatic matting (TM) 7 months after sclerotherapy (SCL) treatment of telangiectasias on the medial knee. **A,** Immediately before initial SCL treatment. **B,** Development of persistent TM 7 months after initial treatment. **C,** Three months after flashlamp-pumped pulsed dye laser (PDL) and PDL/SCL treatment, showing the development of a persistent superficial ulceration in the two PDL/SCL treatment sites. Anterior site treated with PDL at 7 J/cm^2, 31 pulses, before SCL with polidocanol (POL) 0.5%, 1 mL; medial site treated with PDL alone at 7 J/cm^2, 27 pulses; posterior site treated with PDL at 7 J/cm^2, 31 pulses, before SCL with POL 0.75, 1 mL. **D,** Seven months after initial PDL and PDL/SCL treatment, showing persistent TM and healing of the ulceration. **E,** Six months after treatment with chromated glycerin solution (diluted 1:1 with lidocaine 1%), 2 mL. Resolution of the TM has occurred.

(26.5%), severe (50.4%), very severe (14.5%), compared with the POL-only group: light (39.5%), moderate (34.2%), severe (20.9%) or very severe (5.4%).[124]

The authors hypothesized that observed outcomes in these combination treatment trials which would be related to otherwise sub therapeutic dosages of POL or laser alone may be caused by a synergistic mechanism of action between the POL micro-foam and laser light, including improved light scattering and light/heat contact with the vein wall as well as improved irritant reaction of POL caused by more efficient endothelial damage produced by the laser. This low energy laser pulse and POL combination therapy appears to be effective and safe in patients with darker skin color; however, given the comparison with relatively low dose POL, the efficacy of this combined treatment compared with a more standard dose sclerosant is unknown.

COMBINED LASER ND:YAG/PDL TREATMENT OF LEG TELANGIECTASIAS

Trelles et al[125] studied the response of lower extremity telangiectasias using a unique coupled 585-nm and 1064-nm pulse (Cynosure, Inc. 5, Carlisle, Westford, MA). Sixty female patients (aged 24–62, skin types II–IV) were treated with LPDL (585 nm) and 1064 nm delivered sequentially. Pulses were placed along the entire length of the targeted

vessels using a beam diameter of 7 mm, pulse of 10 ms and fluence of 9 J/cm^2 for LPDL and pulses of 30 ms with 80 J/cm^2 for the Nd:YAG with time delays between sequential pulses of 125, 250 and 500 ms for veins of 4, 3 and 2 mm diameter, respectively. At 2 months, 34 of 60 patients reported good or very good results and did not require additional treatment. Twenty-six patients were treated a second time. At 6 months, 18, 22, 14, 6 and 0 patients rated their results as very good, good, fair, poor and worse, respectively. This is compared with computer analysis, which rated results more favorably as 25, 24, 9, 2 and 0 using the same index. TM was seen in 7 patients. There was no incidence of hyper- or hypopigmentation or additional serious side effects. Of note larger (>1 mm) vessels responded better to treatment.

FUTURE DIRECTIONS

Alternative approaches to the treatment and recovery of venous function are actively underway. Rather than ablate or destroy faulty vessels, Frulini et al[126] described a possible new method of vein treatment aimed at recovering the original vein diameter in an attempt to restore valve function via photochemical-induced collagen cross-linking (CCL) on human GSV specimens. In this method, riboflavin (vitamin B2) was used as a cross-linking agent and a blue light–emitting diode (wavelength 450–480 nm) as the activator of photopolymerization. In this reaction, an oxygen singlet is produced with oxidative deamination forming new covalent bonds between collagen fibrils and water. Using this methodology, the authors were able to demonstrate rapid and significant venous shrinking with histological evidence of massive thickening of the venous wall up to triplication of the subendothelial connective tissue and the tunica media without endothelial damage. Such approaches to 'vein restoration' may in time be an important therapeutic addition to currently available treatment options for vein disease.

CONCLUSIONS

Overall, evidence suggesting consistent superiority of laser therapy in the treatment of lower extremity telangiectasias compared with conventional sclerotherapy is lacking. Given the relative cost-savings and reduced procedural pain of sclerotherapy compared with laser or IPL, sclerotherapy remains our preferred treatment modality for lower extremity telangiectasias. However, laser treatment either alone or in combination with conventional sclerotherapy may be preferred in some circumstances, including in patients who are needle-phobic or prone to TM as well as in vessels resistant to sclerotherapy. Vessels below the ankle are particularly appropriate to treat with lasers and light, because sclerotherapy has a relatively high incidence of ulceration in this area owing to the higher distribution of arteriovenous anastomosis (see Chapter 8). Finally, patients who have vessels that are resistant to sclerotherapy are excellent candidates, as efficacy of 75% clearance with two to three IPL treatments has been reported in sclerotherapy-resistant vessels.[127] In a similar 'vein', enhanced efficacy of treatment may occur by combining sclerotherapy with lasers or IPL. This technique is not new and was even reported approximately 30 years ago by the Italian vascular surgeon Leonardo Corcos, who used the argon laser to spot-weld telangiectasias so the sclerosing solution could have prolonged contact with the vessel wall.[25] Combination therapy (laser + sclerotherapy vs. laser therapy augmented with additional dyes) may allow decreased amounts of each therapy necessary to yield optimal results; however, given apparently synergistic effects between treatment modalities, additional research and great caution is needed to mitigate potential adverse effects.

In general, the single most important concept in the treatment of all lower extremity veins is that feeding reticular veins must be treated completely before treating the telangiectasias. This relieves the associated hydrostatic pressure from the 'feeding' venous system, minimizes adverse sequelae and enhances therapeutic results. At this time, the treatment of slightly larger 'feeding' vessels appears to be best achieved by use of micro-foam sclerotherapy or a longer wavelength, deeper penetrating laser (e.g. Nd:YAG) with a moderately long pulse duration and the smallest effective fluence and spot size to achieve immediate stenosis. Smaller, more superficial vessels, telangiectatic matting and essential telangiectasias may in turn be most effectively targeted by lasers with shorter wavelengths and more superficial penetration such as PDL, LPPDL and KTP as well as with broad spectrum IPL therapy.

So, is there a single laser that can adequately treat leg veins? The answer is yes and no. Yes, lasers are now available with pulse durations optimized to treat blood vessels of various sizes. As long as the pulse duration matches the diameter of the vessel, an appropriate fluence is selected and the epidermis is protected from nonspecific thermal effects, one can select virtually any wavelength from 532 nm through 1064 nm, as well as a broad spectrum IPL in the treatment of lower extremity telangiectasias.

However, the answer is also no, as presently available lasers still require skillful use for safe and effective treatment. The laser of the future was detailed in a September 2001 publication.[128] This ideal laser will have a built-in thermal sensor to detect both epidermal and vascular heating, thus enabling it to automatically regulate the fluence so that the vessel is completely thermocoagulated, while cooling the epidermis to maintain its temperature below a damaging threshold. Even better would be an infrared sensor that would determine the location of feeding dermal vessels so that they too can be treated along with the visible telangiectasias. One could imagine in the future, the patient placing the leg into a laser machine that would map the visible veins to be thermocoagulated and automatically treat the entire superficial venous network. At this time, the only barrier preventing the development of such a laser is money and the willingness of a company to produce a machine of this type.

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14 Venoactive Drugs

Albert-Adrien Ramelet

INTRODUCTION

Venoactive drugs (VAD) are a heterogeneous group of medicinal products, of plant or synthetic origin, which have effects on edema (C_3) or on symptoms related to chronic venous disease (CVD) (classes C_{0s}–C_{6s} according to the CEAP [clinical, etiology, anatomy and pathophysiology] classification).[1,2] A specific 'painkiller' effect has been suggested, as VAD are active on venous pain, which does not respond to anti-inflammatory drugs.[1–4]

In Germany approximatively 7% of the general population regularly use VAD, usually combined with compression stockings (70%). VAD appear to be taken mainly by female, preobese and obese patients in stages C_2 and C_3.[5]

VAD have no demonstrated clinical effect on varicose veins or in varicose vein prevention.

Many names have been used to describe VAD: edema-protective agents, phlebotonics, venotonics, vasoprotectors, phlebotropics and venotropics. These names should be discarded, as a standardization of appellations is highly desirable.

The following are the main mechanisms of action of VAD[1–3,6–12]:

- Increasing venous tone (this results in restoration of normal blood flow, dispersion of red cell aggregates and better oxygenation).
- Improving capillary hyperpermeability and lymph flow (thus protecting the microcirculation and decreasing the risk of edema).
- Inhibiting the leukocyte adhesion to endothelial cells and the transmigration of leukocytes into the venous wall.
- Improving fibrinolysis and blood rheology.

In the majority of published studies, major bias may be present; potential or evident conflicts of interest are not always mentioned (including in recent guidelines). It must be emphasized that at least one group has been accused of fraudulent behavior. As their studies have already been published, they are, unfortunately, still available in reviews and meta-analyses.

The effectiveness of VAD has been regularly discussed, mostly by pharmacologists. Some pharmacologists have a poor knowledge of phlebology and VAD; their assertions are debatable. Others are not aware of the difficulty of assessing the activity of VAD. Symptoms are subjective, although they can be correctly quantified. Clinical signs such as edema are not easy to measure, owing to significant daily variations in each individual. The efficacy of VAD on edema and venous symptoms may currently be considered as correctly established. However, there is a need for further randomized controlled clinical trials with greater attention paid to methodologic quality.[7,10,11]

CLASSIFICATION OF VAD

The various classes of VAD are shown in Table 14.1.[1–3]

In this chapter, we shall distinguish VAD as:

- Benzopyrones
- Saponins
- Other plant extracts
- Synthetic drugs
- Animal-derived extracts

BENZOPYRONES

This large group of medicines contains many substances, which are often closely related and endowed with multiple pharmacologic properties. Benzopyrones (α- and γ-pyrones) are obtained from many plants, often used in traditional medicine. They belong to the family of phytophenols, and are related to resveratrol, which is currently undergoing a wide range of studies to assess its possible preventative and therapeutic value in atherosclerosis.

α-BENZOPYRONES

Coumarin (1,2-benzopyrone; 5,6-benzo-α-pyrone) has been used either alone (mainly for the treatment of lymphedema) or in low doses in combination with oxerutin.

Esculetin (6,7-dihydroxycoumarin) and umbelliferone (7-hydroxycoumarin) are coumarin derivatives. Dicoumarols (dimers of 4-hydroxycoumarins) are powerful oral anticoagulants (acenocoumarol, phenprocoumon, warfarin). Their therapeutic properties thus differ fundamentally from those of VAD, despite their chemical similarities.

Coumarin is quickly absorbed and has a short half-life of 1 hour. Both it and its metabolites are excreted via the kidney.

Coumarin induces proteolysis of high-molecular-weight proteins present in lymphedema. Small-size protein fragments can then be more easily drained via the lymphatics. The oncotic pressure drops and edema lessens. However, effectiveness is debatable.[13] Although coumarin and its derivatives have an antiedematous effect, they do not modify the coagulation of blood, in contrast to dicoumarols. Alongside its therapeutic properties, the aromatic properties of coumarin are extensively used in spices for cooking, cosmetology (soap, perfumes) and the tobacco industry.

Table 14.1 Classification of the Main Venoactive Drugs

Group	Substance	Origin	Dosage (mg/Day)	Pregnancy	Breastfeeding	Number of Intakes/Day
Benzopyrones						
α-Benzopyrones	Coumarin	Melilot (*Melilotus officinalis* L.) Woodruff (*Asperula odorata* L.)	90 and troxerutin (540)	+	–	3
γ-Benzopyrones (flavonoids)	Diosmin	*Citrus* spp. *Sophora japonica* L.	300–600	+	–	1 or 2
	Micronized purified flavonoid fraction		1000	+	–	1 or 2
	Rutin and rutosides	*Sophora japonica* L. *Eucalyptus* spp. Buckwheat (*Fagopyrum esculentum* Moench)	1000	+	–	1 or 2
	O-(β-hydroxyethyl)-rutosides (troxerutin, HR)					
Saponins						
	Escin	Horse chestnut seed (*Aesculus hippocastanum* L.)	120, then 60	?	–	3
	Ruscus extract	Butcher's broom (*Ruscus aculeatus* L.)	2–3 tablets	+	–	2 to 3
Other Plant Extracts						
	Anthocyans (and flavonoids)	Bilberry (*Vaccinium myrtillus* L.)	116	?	–	2
		Red vine leaves (*Vitis vinifera* L.)	360–720	–	–	1 or 2
	Proanthocyanidines (oligomers)	Grape pips (*Vitis vinifera* L.)	100–300	+	–	1 to 3
		Maritime pine (*Pinus maritima* Lank) (Pycnogenol)	300–360	?	–	3
	Ginkgo biloba	*Ginkgo biloba* L.	2 ampules or capsules (extracts of Ginkgo, heptaminol and troxerutin)	–	–	2
Synthetic Products						
	Calcium dobesilate	Synthesis	1000–1500	–	–	2 to 3
	Benzarone	Synthesis	400–600	+	–	2 to 3
	Naftazone	Synthesis	30	+	–	1
Animal-Derived Extracts						
	Mesoglycan, Suledoxide	Polysaccharides from different animal tissues	250–500 ULS*	?	?	1 or 2

*May also be injected (intravenous or intramuscular).
+, The product has been administered during pregnancy; –, the manufacturer gives no indication, making the physician responsible for his or her decision; HR, hydroxyethylrutosides.

Several cases of drug-related hepatitis after taking high doses of coumarin or dicoumarols as an anticoagulant have been reported.[14] Coumarin has been withdrawn from the market for this reason, except in brands associating low doses of coumarin and troxerutin.[15] Poor cytochrome P450 (CYP)2A6 metabolizers may be concerned by this hepatotoxicity. Identifying such patients might avoid such side effects happening.[16]

γ-BENZOPYRONES (FLAVONOIDS)

These have been previously defined as 'vitamin P' or factor P (permeability), as flavonoid deficiency results in capillary fragility and increased vessel wall permeability in the animal. These appellations are obsolete.

Many plant pigments belong to this group. They are used in the form of plant extracts, in semisynthetic or synthetic preparations. The main distinction is between:

- Flavone and its derivatives, flavonols (kaempferol, diosmetin, diosmin, hidrosmin, quercetin, rutin [rutoside, oxerutin])
- Flavanes (or flavonones): hesperitin, hesperidin and its derivatives, Pycnogenol, procyanidolic oligomers, etc.

Substances mostly used therapeutically in CVD are described below. Each manufacturer has developed its own techniques to demonstrate some effects of its drug. Comparison between the various VAD is therefore quite difficult. One may, however, consider that many results may be extrapolated from one VAD to another.

DIOSMIN AND MICRONIZED PURIFIED FLAVONOID FRACTION

Diosmin (3′,5,7-trihydroxy-4′-methoxyflavone-7-rhamnoglucoside) is extracted from plants (from the family Rutaceae) or obtained by synthesis (as another bioflavonoid, hidrosmin).[17] The half-life of diosmin is 8–12 hours, with its elimination being renal (65%) and biliary (35%).

Micronization enables a decrease in particle size of the flavone fraction from 20 to 2 μM, thereby increasing the intestinal absorption and bioavailability of the substance.[18–23]

Diosmin and micronized purified flavonoid fraction (MPFF) act on venous tone (by inhibiting the breakdown of norepinephrine [noradrenaline] by catechol-*O*-methyltransferase. The degree of this effect varies in linear relation to the dose administered, lymphatic drainage (decrease in the diameter of lymphatic vessels and intralymphatic pressure, increased peristalsis) and the microcirculation (inhibition of adhesion of leukocytes, their intratissue migration, the release of inflammatory mediators).

MPFF is indicated in the treatment of edema and of symptoms related to venous insufficiency (edema, heavy legs, discomfort, pruritus, night cramps, pain, swelling). It may be indicated in pelvic congestion syndrome,[24] venous surgery (decrease in postoperative pain and more rapid recovery)[25] and lymphedema, including filarial.[26] Its other indications are gynecologic (tense, painful breasts, intrauterine device–related bleeding) and proctologic.

Double-blind clinical trials also demonstrate a significant improvement in the quality of life of patients with chronic venous insufficiency. However, the number of patients registered in these trials is small. One study did not demonstrate a beneficial effect of MPFF, except on night cramps.[21]

According to five clinical trials joined in a meta-analysis, MPFF may hasten the healing of leg ulcers.[23] However, relative efficacy was demonstrated only in a small subgroup of venous ulcers (ulcers between 5 and 10 cm^2 in area, and those present for 6–12 months), and the results need to be interpreted very cautiously. Moreover, the most rigorously conducted study (Zucarelli F, Rieger H, 2004) was not published and yielded negative results.[27] Therefore, this indication is not considered in the latest guidelines.[28]

RUTOSIDES AND OXERUTIN

A standard mixture of several flavonoid derivatives is obtained by hydroxyethylation of a natural substance, rutin (oxerutin, HR or hydroxyethylrutosides). Troxerutin is a fraction of oxerutine. Absorbed by the digestive tract, oxerutine has a half-life of 24 hours and is principally excreted in bile. A large number of pharmacologic and clinical studies[8,29–33] have provided evidence of its influence on disturbances of capillary permeability, effects on erythrocyte deformation and aggregation, antiedematous actions and inhibition of prostaglandin synthesis. Its diffusion and accumulation in the venous wall have been demonstrated.[31]

Rutosides are indicated as an antiedematous agent in venous disorders, in proctology (hemorrhoids) and in ophthalmology (retinopathy). Oxerutine is absorbed following topical application, and its action on cutaneous capillary fragility has been demonstrated.[34]

SAPONINS

ESCIN

Escin is a mixture extracted from horse chestnut seed (HCSE). It contains many compounds, such as protoescigenin, barringtogenol, α- and β-escin, cryptoescin and benzopyrones.

HCSE compounds are poorly absorbed in the digestive tract (12.5%). Maximum activity of the preparation occurs 16 hours after ingestion. Escin and its metabolites are eliminated via the kidney and gallbladder; its percutaneous absorption has also been demonstrated.

Escin increases venous wall tone and has a well-demonstrated antiedematous effect.[9,35–39] The HSCE extracts were evaluated in one Cochrane study, which curiously excluded other VAD.[9]

RUSCUS

Extracts of ruscus (butcher's broom) contain saponins and flavonoids. The precise composition of these extracts is poorly understood. Venotonic and antiedematous actions have been well demonstrated in open and randomized controlled trials (RCTs) and are associated with a reduction of symptoms and improvement in quality of life in patients with CVD.[40–49]

OTHER PLANT EXTRACTS

Extracts of *Ginkgo biloba*[50,51] contain terpenes and flavonoids. Antagonists of platelet-activating factor, they have an action on platelet aggregation, blood viscosity and edema. Extracts of *Centella asiatica*[10,52,53] are believed to enhance collagen synthesis in connective tissue.

Many other plants are used successfully in the treatment of symptoms of CVD. All of them contain flavonoids, among other active substances: procyanidolic oligomers (anthocyans in bilberry extracts; proanthocyanidols in white grape seeds, red vine leaves (*Vitis vinifera*),[54–63] and maritime pine [Pycnogenol]).[64–66]

PHYTOTHERAPY

Plant extracts used in phytotherapy are often poorly standardized and controlled. Their active substance content may vary according to plant genetics, as well as according to climatic factors, quality of the ground in which the plants were grown, the time of harvesting and the extraction methods used. Flavonoids may be at least partially responsible for their pharmacologic effects, but other glycosides might also be active.[67,68]

NUTRITIONAL SUPPLEMENTS

The use of nutritional supplements is a new trend. Some brands have been introduced in countries where VAD are

not available or as a new commercial over-the-counter channel. They contain vegetal derivatives, mostly polyphenols, and antioxidants to relieve the symptoms of CVD.

OTHER PREPARATIONS USED IN THE PAST

Dihydroergotamine and dihydroergocristine (rye ergot extract)[1] are no longer used in CVD treatment.

SYNTHETIC DRUGS

CALCIUM DOBESILATE

This synthetic substance (calcium 2,5 *dihydroxy benzenesulfonate*) is well absorbed after oral administration. Plasma levels are maximal 6 hours after ingestion. The half-life is short (5 hours).

The drug is eliminated principally in the urine, without being metabolized. It is absorbed following topical application.

Calcium dobesilate decreases capillary permeability and blood viscosity and improves lymphatic drainage.[69–76] The antiedematous effect persists for about 2 months after treatment is stopped. Its effectiveness is enhanced by concomitant administration of rutosides.[74]

Its other indications are ophthalmologic and proctologic.[77]

BENZARONE

Benzarone, or (2-ethyl-1-benzofuran-3-yl)-(4-hydroxyphenyl) methanone, is well absorbed following oral administration. Its half-life is about 10 hours. It is eliminated with its metabolites by the kidney. Benzarone has fibrinolytic properties and inhibits platelet aggregation.[1]

Several cases of severe hepatitis have been reported.[78] Photosensitization may occur during treatment. Therefore, this drug should no longer be used.

NAFTAZONE

β-Naphthoquinone monosemicarbazone, or naftazone, is rapidly absorbed from the digestive tract. Its half-life is short (1.5 hours), and its metabolites are eliminated in urine.[1,79,80]

A venoconstrictor effect and lowering of serum β-glucuronidase levels have been demonstrated following the administration of 30 mg/day of naftazone. This substance might act on vessel wall permeability and on abnormalities of endothelial cells seen in CVD.

TRIBENOSIDE

Ethyl-3,5,6-tri-*O*-benzyl-D-glucofuranoside or tribenoside is a glucose derivative.[1] It is well absorbed following oral administration and is believed to have a half-life of about 24 hours. Its metabolites are excreted in the urine. Tribenoside can also be used by topical application.

Tribenoside decreases capillary permeability and has anti-inflammatory and analgesic actions. The usefulness of this preparation is limited by the frequency of its adverse effects: digestive and, above all, cutaneous (up to 7.2%). It has currently been abandoned.

ANIMAL-DERIVED DRUGS

Developed more than 30 years ago in Italy, sulodexide is a highly purified mixture of extracts of porcine digestive mucosa, composed of two glycosaminoglycans: 80% of fast moving heparin and 20% dermatan sulfate.

Suledoxide has beneficial effects on blood viscosity, inflammation, fibrinolysis, platelet adhesion and inhibition of the secretion of matrix metalloproteinases, among others.[81–84] It may improve venous ulcer healing.[85,86]

However, recent RCTs are missing, and one may be astonished on finding several publications in a single issue of *International Angiology* (2014, volume 33, number 3).

PRINCIPAL MODE OF ACTION OF VAD

VAD have a demonstrated positive action on the following:

- Edema: decrease in capillary permeability, improved lymphatic drainage
- Venous tone, direct and indirect action
- Microcirculation: inhibition of leukocyte adhesion and migration, inhibition of the release of inflammatory mediators and the expression of certain leukocyte (L-selectin) and endothelial (intercellular adhesion molecule 1, vascular cell adhesion molecule 1) adhesion substances initiating the inflammatory events leading to raised microcirculatory venous pressure, inhibition of prostaglandin synthesis and antioxidant effects (anti–free radicals)
- Erythrocytes: inhibition of aggregation, decrease in erythrocytic deformation and decrease in blood viscosity

ADMINISTRATION, DOSAGE AND LIMITS

VAD are mainly administered orally. The drug substances of plant origin are frequently poorly absorbed. Absorption may be enhanced by various chemical modifications, as hydroxyethylation or micronization.[87]

The usual dosages prescribed are mentioned in Table 14.1. Low VAD doses should not be prescribed, as they are ineffective.[1,2]

The effectiveness of combinations of different preparations has not been established, except for rutosides and calcium dobesilate. This association is more effective than each drug administered separately.[74]

Few studies have included comparison of different VAD in clinical trials, some with major bias.[6,29,49,87–89]

One may consider that most VAD are almost equivalent in their effectiveness.

DURATION OF TREATMENT

A course of VAD treatment generally lasts 1 month. It is not appropriate to prescribe a VAD for more than 3 months, except in the event of re-emergence of the symptoms after treatment discontinuation.

PREMENSTRUAL SYNDROME

A particular dosage regimen (intake restricted to the last 2 weeks of the menstrual cycle) has been recommended for women presenting with premenstrual syndrome with pain and edema of the legs.[90–92]

PREGNANCY AND LACTATION

Some VAD have been used without any problems during the second and third trimesters of pregnancy to relieve edema and symptoms of CVD and have been effective.[93–95] They are indicated in Table 14.1. The pharmaceutical companies do not advise administration during pregnancy, however, and generally recommend that VAD should not be administered during breastfeeding.

TOPICAL APPLICATION

Topical VAD preparations are also available (rutosides, escin and calcium dobesilate, among others). Absorption of the active drug has been demonstrated to have a degree of efficacy in a few double-blind studies.[34,96]

ADVERSE EFFECTS

Safety is in general good. Adverse effects occur in about 5% of the patients treated (Table 14.2). The side effects are rarely severe and comprise:

- Dizziness, headache
- Minor gastrointestinal disorders: 'heavy' stomach, flatulence, rarely nausea and vomiting, constipation and diarrhea
- Rare skin rashes

However, the intake of benzarone has been associated with hepatitis, as high doses of coumarin are potentially hepatotoxic in poor CYP2A6 metabolizers.[16] Prescription of these drugs is debatable. Coumarin has been withdrawn from most western countries. Low doses of coumarin combined with rutosides, marketed in certain countries, do not appear to induce such complications.

Several cases of agranulocytosis were associated, mostly in Spain, with calcium dobesilate (but with a possible causal relationship in only some cases).[69,97] Currently, to the best of our knowledge, the incidence of agranulocytosis with calcium dobesilate treatment is less than the spontaneous prevalence in the overall population.

SCIENTIFICALLY RECOGNIZED INDICATIONS

MAIN INDICATIONS FOR VAD

The following are the main indications for VAD:

- Edema
- Subjective symptoms related to varicose veins or attributed to CVD (heavy legs, 'heaviness', 'discomfort', pruritus, pain along varicose vein paths)

Table 14.2 Adverse Effects of VAD

Substance	Skin Rashes*	Gastrointestinal Disorders†	Other Adverse Effects
Coumarin and HR	+	+	Hepatitis‡ (high-dose coumarin only)
Oxerutin and rutosides (HR)	+	+	
Escin (horse chestnut)		+	Urticaria
Ruscus extracts		+	
Anthocyans		+	
Proanthocyanidines and Pycnogenol	+	+	
Ginkgo biloba	+	+	
Diosmin and micronized purified flavonoid fraction	+	+	
Calcium dobesilate	+	+	Fever Agranulocytosis§
Benzarone	+		Photosensitization Hepatitis‡
Naftazone		+	Headache Dizziness
Mesoglycan, sulodexide	+	+	

*Skin rashes: undefined.
†Gastrointestinal disorders (minor): inappetence, nausea, constipation, diarrhea.
‡Hepatitis: after intake of coumarin (high doses) and benzarone.
§Agranulocytosis: some cases reported; however, almost all of them in the same region. Less than expected ratio of agranulocytosis in the general population.
HR: Hydroxyethylrutosides (oxerutin).

- Minor specific but frequently associated symptoms (paresthesia, nighttime cramps or restless leg syndrome)

LEG ULCER

Currently, indication of VAD in the treatment of venous ulcers is debatable. Such patients usually have many other medications, and, in the absence of proof of effectiveness from evidence-based medicine, additional medication may not be beneficial.

MPFF and hydroxyethylrutosides (HR) might hasten the healing of leg ulcers, but only in a tiny subgroup of venous ulcers (ulcers between 5 and 10 cm^2 in area and those present for 6–12 months). As mentioned by Scallon and colleagues,[27] these results must be interpreted with caution because most of the trials had a risk of bias in randomization, allocation concealment, blinding and methods for addressing incomplete outcomes with a possibility of publication bias, and conflicts of interest. VAD may, however, be used for symptomatic venous ulcers.[98]

Long-term administration of rutosides did not prevent leg ulcer relapses in one study.[99]

OTHER INDICATIONS

Other indications include the following:

- Prophylaxis of edema following long flights[100]
- Premenstrual syndrome[91,92]
- Pelvic congestion syndrome[24]
- Prevention of pain after venous surgery[25]

However, the indications vary depending on the country. These studies need to be confirmed by new ones with better methodology. VADs may also have been registered for other indications, such as episodes of hemorrhoids or diabetic retinopathy.

COMBINATION WITH COMPRESSION

Elastic compression is considered as the first-line treatment of CVD. In this setting, VAD may:

- Accentuate the effect of compression[32,101,102]
- Be prescribed instead of compression when compression is contraindicated (arterial insufficiency, sensitive neuropathies) or poorly tolerated (individual reactions, summer heat)[3,36]

RESULTS

The evaluation of VAD is complex, for the following reasons:

- Edema is hard to quantify, with major daily variations.
- Attenuation of symptoms is difficult to assess and subject to criticism.
- The placebo effect is marked, even though the drug substance effect is statistically greater. Thus, the overall scores of the assessments range from 54% to 76% for the drug substance and from 18% to 46% for the placebo groups.
- Genetic variations in neurotransmitter pathways that mediate placebo effects ("placebome") can modify them. The possibility of interaction between placebo and drug molecular pathways warrants consideration in RCT evaluation, and this may be quite important in VAD studies.[103]
- Relevant articles have frequently been published in phlebologic journals that are not indexed.
- University departments have little interest in CVD and scarcely contribute to the international studies. Some pharmacologists reject VAD without being sufficiently aware of the dossiers on those drugs.
- Conflicts of interest and implication of the industry in submitting papers or organizing consensus conferences are a major negative concern.

DEMONSTRATED THERAPEUTIC EFFECT

More than 130 RCTs or meta-analyses have been published to validate the clinical effectiveness of VAD. These publications have been evaluated in Cochrane reviews,[9,10,13,27,33,104] in other reviews,[11,28,63] and in consensus meetings,[3] some of which are debatable and not mentioned here (no declaration of conflicts of interest, although well known; poor and wrong appreciation of the mentioned papers).

Recommendations according to three levels of evidence—A, B and C—may be suggested after a critical review of the different papers devoted to VAD (Table 14.3, from Ramelet and colleagues[3] and updated with more recent publications):

- Grade A: RCT with large sample sizes, valid meta-analyses
- Grade B: RCT with small sample size
- Grade C: other controlled trials, no RCTs

GUIDELINES

Scientific societies have published guidelines with the purpose of developing double-blind trials whose parameters are incontestable.[63,105]

CONCLUSIONS

Although not available in the United States, VAD are widely used elsewhere in the world in the interest of patients.

VAD have no demonstrable effect on varicose veins or in varicose vein prevention, but they are effective in treating edema (C_3) and symptoms related to CVD (C_{0s}–C_{6s}). A specific 'painkiller' effect has been suggested, as VAD are active on venous pain, which does not respond to anti-inflammatory drugs. A difference of activity between the main VAD is difficult to establish.

Successful treatment of venous symptoms is cost-effective. Renouncement of the use of VAD may induce an augmentation of health budgets in the midterm, as demonstrated by Allegra.[106] If patients do not present early for symptoms of CVD, the complications of venous disorders will increase, inducing higher expenses: nonsteroidal anti-inflammatory drugs may be prescribed for venous pain, with expensive side effects; days off work may increase, among other effects

Table 14.3 Levels of Evidence and Grades of Recommendations

Recommendation	Compounds	RCT	Meta-analyses
Grade A	Micronized purified flavonoid fraction	Gilly 1994 Guilhou 1997 Chassignolle 1999 Danielsson 2002 Das 2003 Veverkova 2005 Pokrovsky 2007 Simsek 2007	Coleridge-Smith 2005
	Oxerutin	Kranendonk 1993 Diebschlag 1994 Cloarec 1996 Unkauf 1996 Grossmann 1997	Poynard 1994
	Calcium dobesilate	Casley-Smith 1988 Widmer 1990 Labs 2004 Rabe 2006 Martinez 2008 Rabe 2011	Espinoza 2001 Ciapponi 2004
Grade B	Horse chestnut seed extracts (escin)	Diehm 1996 Siebert 2002	Pittler 2002
	Ruscus extracts	Vanscheidt 2002 Parrado 1999 Lascasas 2009	Boyle 2003
Grade C	Diosmin	Carpentier 1994	
	Troxerutin	Vin 1994 Rehn 1993	
	Troxerutin-coumarin	Vanscheidt 2002	
	Gingko biloba	Zuccarelli 1986 Natali 1989	
	Proanthocyanidines	Kiesewetter 2000 Petrassi 2000 Rabe 2011	
	Naftazone	Vayssairat 1997	

RCT, Randomized controlled trial; Grade A, RCT with large sample sizes, valid meta-analyses; Grade B, RCT with small sample size; Grade C, other controlled trials, no RCTs.

of insufficient and late treatment of CVD, including alteration to quality of life.

While it is not acceptable for ineffective medications to be sold, it is no more acceptable for drug substances that have long been in use, and whose efficacy has been demonstrated, to be sacrificed for political reasons.

Further clinical RCTs are desirable, with greater attention paid to methodologic quality and better evaluation of potential conflicts of interest, to establish more accurately the place of VAD in the treatment of CVD.

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