Failure of microvenous valves in small superficial veins is a key to the skin changes of venous insufficiency

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**Objective:** To determine the role of microvenous valves in the superficial venous system in the prevention of reflux and skin changes in the progression of venous insufficiency.

**Methods:** The venous anatomy of 15 amputated lower limbs, eight free from clinical venous disease and seven with varicose veins and ulcers, was examined using retrograde venography corrosion casting. Prior to amputation, all limbs were scanned by duplex ultrasound to confirm the presence or absence of reflux in the great (GSV) and small saphenous veins or their tributaries. The resulting resin casts were photographed and mapped to show the position, orientation, and competency of valves in the superficial venous network. Casts were also examined by scanning electron microscopy.

**Results:** Retrograde venous filling was demonstrated in the “normal” limbs despite a competent GSV. Microvalves were identified down to the sixth generation of tributaries from the GSV. Only in regions where incompetence existed in microvalves out to the third (i.e., the “boundary”) generation was the resin able to penetrate deeper into microvenous networks of the dermis. This was despite the presence of subsequent competent valves, which were able to be bypassed in the network. In limbs with varicose veins and venous ulcers, reflux into the small venous networks and capillary loops was more extensive with more dense networks and greater tortuosity.

**Conclusions:** This study demonstrates that valvular incompetence can occur independently in small superficial veins in the absence of reflux within the GSV and the major tributaries. We have shown that once there is incompetence of the third generation “boundary” microvalves, reflux can extend into the microvenous networks in the skin. These effects are markedly worse in the presence of GSV incompetence.

We propose that degenerative changes with valve incompetence are required in both the larger proximal vessels and the small superficial veins, in particular at the “boundary” valve level, for the severe skin changes in venous insufficiency to occur. (J Vasc Surg 2011;**54:**636–44)

**Clinical Relevance:** This study describes the presence of microvalves in the very small veins in the skin, which may be critical to whether skin changes occur in venous insufficiency. The concept may explain why some people with longstanding varicose veins do not develop venous ulcers. In addition, this article describes degenerative changes in the network of very small veins in the skin of the leg which may relate to appearances of reticular veins, corona phlebectatica, and venous flares. These degenerative changes occur without varicose veins but are much worse when they occur together.

Varicose veins are a common venous pathology of the lower limb, which are widely accepted to be the result of progressive valvular incompetence of the large superficial veins. However, opinion is divided as to whether valvular incompetence progresses in an ascending or descending manner in these larger veins. Until relatively recently, it was widely believed, and indeed published in anatomy textbooks, that valves do not exist in veins <2 mm in diameter. With this has been the presumption that, if present in these smaller-sized veins, reflux has an unimpeded effect on the microvascular bed of the skin. However, there have now been a number of studies providing robust evidence for the existence of valves in veins <2 mm diameter in human skin.1-5

Further investigation into these “microvenous valves” is warranted, as they may prove important to the development of the skin changes associated with venous insufficiency—including venous ulceration, reticular vein formation, and other manifestations. Studies to date have primarily investigated the diameter and density of these microvenous valves in normal skin.2,4 One study has compared the density of microvenous valves in areas of the lower limb at low risk of venous ulceration with the density of valves in areas at high risk, concluding that differences in valvular density alone were not enough to explain the differences in ulceration risk at different sites of the lower leg.5 While the variation in size and density of microvenous valves is noteworthy, it may be that the distribution of microvenous valves within the venous network is more pertinent to their normal role and their ability to prevent reflux. What happens to these microvalves in veins with superficial venous reflux and venous ulcer has not been described.
This study investigates microvenous valves in the skin of the lower leg without detectable venous disease and compares them with those in limbs with venous disease, including venous ulcers, using retrograde corrosion casting “venography.” From this, we describe a new concept in the hierarchy of venous networks, which may aid our understanding of the risk factors contributing to the formation of skin changes in chronic venous insufficiency (CVI).

METHODS

Corrosion casting is an established technique for investigating vascular structures. It is usually carried out using anterograde casting by injecting resin from the arterial side, through the capillary beds and into the veins. With anterograde filling, venous valves do not impede resin flow and, as a consequence, it is not possible to distinguish between the competent and incompetent venous territories. Retrograde resin infusion, from the venous aspect, allows this distinction to be made and is akin to retrograde phlebography, as used in the clinical demonstration of deep venous and perforator valvular incompetence. As this study aimed to look at both the position of valves and their integrity in the venous networks draining into the great saphenous vein (GSV), a retrograde technique has been used. This is the first description of this technique in fresh human material.

Subjects. Casts were constructed from amputated lower limbs donated for the purpose of research. Written informed consent was obtained for the study, which was approved by the Regional Ethics Committee. Prior to surgical amputation, each limb was scanned with duplex ultrasound by the same trained vascular technologist to confirm the absence or presence of reflux in the GSV and its major tributaries. For the normal limbs, amputations were for causes unrelated to venous disease, and the majority were below knee amputations. One additional normal limb was a cadaveric specimen shown to have intact thigh GSV valves. Subjects were between 49 and 88 years of age at the time of amputation or death. There were eight limbs (three male and five female), with no demonstrable deep or superficial reflux. Seven limbs with venous disease (CEAP clinical class 6) were cast; of these, five were amputated primarily for unrelated disease, and two limbs were amputated for severe recalcitrant venous ulcers.

Vascular corrosion casting. Within 1 hour of amputation, or 12 hours of death, the GSV of each limb was cannulated with a 20-gauge needle at the level of the medial malleolus and flushed with saline. Limbs were then injected with resin (Batson’s #17 resin; Polysciences Inc, War- rington, Pa). As the resin began to flow from vessels at the proximal end of the limb, these vessels were identified and ligated. With the outflow vessels closed, further resin was injected until significant resistance was noted. Limbs were left immersed in saline overnight to allow the resin to harden. Tissue was then removed by maceration in 15% sodium hydroxide at 60°C.7

Mapping. The superficial veins were identified on the casts and mapped using a dissecting microscope. Maps were constructed to show four features: (1) location of the valve impressions within the network of tributaries; (2) vessel diameter; (3) valve direction; and (4) valvular competence or incompetence. Valves were identified by their characteristic impression left in the resin by the valve leaflets (as imaged under transillumination), which also indicated valve direction. Vessel diameters along with other measures were approximated from photographs using ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, Md). Where resin was present in dense networks of vessels <300 μm in diameter, these regions were examined for the presence of valves; however, individual vessels were not mapped, and for clarity, these regions are referred to as small vessel networks (SVN).

Valvular competence was deemed to exist when flow was contrary to valve direction and resin was held up at the valve, but if resin passed through and was present on both sides of the valve, it was considered incompetent. If it was suspected that resin had filled in behind a valve from collateral pathways, valve morphology was used to make a determination about competency. Resin was also present on both sides of a valve when it had passed a valve in the direction of blood flow—again, valve morphology was used to make an assessment. By visually assessing the diameter of the vessel, the relative length of the leaflets, and their symmetry, it was usually clear if a valve was competent or not. In a small number of cases where doubt remained, the ratio of vessel diameter to valve sinus depth was used (Supplementary Fig 1, online only). Based on the observation of 35 clearly competent and a similar number of incompetent valves, a ratio greater than 1.3 was consistent with incompetence.

Location of the valves in the network of tributaries was also defined according to the generation of the tributaries. The valves in the GSV and its accessory tributaries were assigned to be generation 0. The valves in each subsequent tributary were assigned a consecutively numbered generation. Where vessels of different generations were interconnected, the connecting vessel and any valves it contained were assigned the lower generation.

Scanning electron microscopy (SEM). SEM of vascular casts was carried out on the limbs with varicose veins and ulcers. Tissue blocks of 2 cm × 2 cm were removed from regions of the medial gaiter and lower calf in each limb, in areas immediately adjacent to and including the ulcer, prior to maceration of the resin-infused limb. The macerated block cast specimens were attached to large stainless steel specimen stubs using carbon tape. The casts were then sputter-coated with gold/palladium for 120 seconds (Bio-Rad SEM Sputter Coating System, Hercules, Calif). The vascular casts were examined on a Cambridge S360 SEM (Cambridge Instruments, Cambridge, United Kingdom), at 10 kV and a working distance of 15 mm.

RESULTS

Normal limbs. Despite the known absence of GSV reflux in the “normal” limbs, there were clear indications of resin reflux and valvular incompetence in the small tributaries in all but one GSV studied. The degree to which resin
was able to reflux from the GSV varied widely from limb to limb, reflecting the varied valvular integrity of the tributaries of the GSV to the resin flow. The retrograde resin venogram outlined the intact GSV with no filling into the tributaries in only one limb. There was normal anterograde outflow through mid and proximal calf perforators to the deep system (Fig 1, A). Two limbs had resin reflux solely to a first generation tributary through a single incompetent valve (Fig 1, B) but was restricted by competent valves in the second generation. The remaining limbs displayed degrees of resin reflux beyond the second generation, with the most extensive refluxing beyond the sixth generation and into the SVN in the skin (Fig 1, C). The number and size of these SVNs, composed of resin filled vessels <300 μm in diameter, varied greatly and extended to an area corresponding to approximately 45 cm² of skin in one (Fig 1, D) or covering much of the medial lower leg in another (Fig 1, E).

The mapping of venous tributaries and valves is illustrated in Fig 2. In total, 298 valves were identified in six specimens. The two most extensively refluxed specimens were not mapped, as the vessel density was so high that it was not possible to accurately follow any single channel. Using light microscopy, valves were found from the GSV and its accessories through to the sixth generation tributaries (Fig 3). The greatest number of valves (30%) was found in the third generation tributaries. While valves competent to the resin flow were found through all six generations, the vast majority of resin incompetent valves were observed in generations one to three (Figs 3 and 4). All valves, regardless of the vein size, were bicuspid.

Vessels also existed that had no valves at all. These vessels often provided collateral pathways by which resin was able to bypass competent valves to fill a more distal territory. These non-valved collateral pathways were rare in generations one and two, but became more common from the third generation onwards. This created a situation where, although valves were present in considerable numbers in these generations, they were of themselves not adequate to prevent resin reflux to more distal territories.

Fig 1. Varying patterns of retrograde resin casting in normal limbs (CEAP 0 or 1). All limbs had competent great saphenous veins (GSVs) as determined by ultrasound. A, No incompetent valves or reflux from the GSV, and normal drainage into the deep system through perforators (lower leg resin cast from an 81-year-old male). B, Filling of accessory veins, but none smaller than 300 μm (49-year-old female). C, Small vein network filling (arrowhead) with some varicosities (arrow), from a 73-year-old female. D, Multiple territories of small vein network filling and dilated tortuous (arrow) veins (63-year-old female). Of note, the GSV was intact with numerous competent valves and tributaries (arrowhead). E, Extensive filling of the superficial venous network (81-year-old female). Notice the straight course of the GSV (between the two arrows) and presence of competent GSV valves (arrowhead). Note the high degree of variability in small vessel filling in these limbs with no major, ultrasound-detected, superficial reflux. In all cases, the proximal end of the cast is to the right-hand side.
For the retrograde resin venogram to show reflux from the GSV to the small vessel networks, the resin had to pass a minimum of one and a maximum of three generations of incompetent valves (mean, 1.65; SD, 0.71; median, 2), as illustrated in Fig 5. The last valve generation before resin refluxed into an SVN was designated as the “boundary valve” (Fig 4). The majority (65%) of these boundary valves were in the third generation of the draining venous network (Fig 6). The boundary valves were assumed to be the limiting point preventing resin reflux into the SVN.

Of the five “normal” limb casts that showed reflux from the GSV to the small vessel networks, the resin had to pass a minimum of one and a maximum of three generations of incompetent valves (mean, 1.65; SD, 0.71; median, 2), as illustrated in Fig 5. The last valve generation before resin refluxed into an SVN was designated as the “boundary valve” (Fig 4). The majority (65%) of these boundary valves were in the third generation of the draining venous network (Fig 6). The boundary valves were assumed to be the limiting point preventing resin reflux into the SVN.

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**DISCUSSION**

This study, based on retrograde resin venography, reveals a number of observations pertinent to furthering our understanding of the function of the small veins and their microvalves in the skin of the lower leg, and their role in venous disease. Several observations were evident: (1) valvular incompetence in the small veins of the skin can exist independently of valvular competence in the GSV and its accessory tributaries; (2) areas of reflux occur in the small veins of the skin and often show the tortuosity and distension of varicosities despite a normally functioning GSV; (3) valves in the third generation of tributaries from the GSV are most often the last “boundary” valves, able to prevent reflux to the skin; (4) there are degenerative changes in the distal venous system that occur in the absence of duplex detectable reflux and clinical varicose veins; and (5) when GSV reflux is present, the competence of these small vessel (micro) valves may play a critical role in the progression of the skin changes of venous insufficiency.

**Limbs with venous insufficiency and venous ulcers.**

In the limbs in which there was venous insufficiency with venous ulcer, the retrograde resin venogram showed extensive valvular incompetence to resin flow. The extent of SVN was greater and more dense and tortuous (Fig 7). There was resin reflux into the venules of the papillary plexus and reaching up into the capillary loops of the skin (Supplementary Fig 3, online only) as best observed with SEM (Fig 8). The microvalves in these specimens were observed down to approximately 100 μm and were also significantly stretched, and the vessels distended and tortuous. The majority of valves occurred at branch points and, despite the appearance of competence, were freely bypassed by the resin in the microvascular network.

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fashion, recent discussion has broached the possibility of the distal origin and development of incompetence and reflux with a subsequent ascending progression of venous incompetence. In this study, none of the normal limbs had varicose veins or valvular incompetence in the larger vessels of the superficial system. Yet five of the eight subjects showed resin reflux to the small veins of the skin due to incompetent valves. This clearly shows that valvular incompetence can exist in the small superficial veins of the leg independently of incompetence in the GSV or its accessories. This gives some additional support to the argument for ascending incompetence.

The concept of “boundary” valves is new and clearly evident. Where a valve is positioned in the tributary order determines its ability to prevent reflux. In all cases but one, once resin had reached the third generation, it was able to penetrate to the small vessels of the skin regardless of any further competent valves. The smallest valves...
observed in this study by light microscopy were approximately 140 \mu m in diameter and down to just under 100 \mu m within the SVN using SEM. This is consistent with the findings of Braverman and Keh-Yen,1 Miyake et al,3 and Zhang and Stringer.11 However, both Philips et al2 and Aharinejad et al6 claim to have identified valves with smaller diameters. Regardless of how small these microvalves are, this study suggests that beyond the ‘boundary’ valves, the interconnected nature of the small vessels precludes valves preventing reflux. Presumably, therefore, these microvalves serve other functions for optimizing flow within the networks.

In the series of casts from the limbs with normal GSV, there was a progression of severity of microreflux, with more extensive SVN involvement as more of the critical microvalves became incompetent. However, the changes seen also included varying degrees of distal venule tortuosity and varicosity and, remarkably, extension into the papillary dermis of the skin. Whether it is microvalve incompetence that precedes or follows the venule wall changes is not apparent. Nevertheless, these same appearances are consistently seen in all the resin casts of the skin of the limbs with severe venous insufficiency, with a greater severity particularly in the gaiter area. We would suggest that when proximal vein incompetence and reflux is present and spills into the SVN, with the loss of boundary valve function, then the stage is set for more severe changes in a descending fashion right out to the capillary loops. It is possible that it is the boundary valves that determine whether varicose veins progress to the more severe manifestations seen in the skin and set the stage for venous ulceration. Our suggestion is that degenerative changes with valve incompetence in both the larger vessel network and the microvenous networks are necessary for skin changes to occur. While reflux and wall changes may occur independently in each of these networks, with modest physiological and clinical consequence, it is only when the networks connect with the breaching of the boundary microvalves and free reflux back into the SVN that there is a significant impact in the skin. These changes may come about not only from an ascending deterioration but equally well from descending influences, as has been suggested for the larger veins of the superficial venous system.10
These observations may shed some light on several clinical questions. For example, the phenomena seen in some patients who have very long standing gross varicosities without skin changes may be explained by the resistance of microvalves, and in particular, the boundary valves, to increased hydrostatic pressure effects and to degenerative vascular matrix changes in the small venules and the SVN beyond. Another clinical question is the increased prevalence of venous skin changes seen with increasing age in patients with varicose veins. This may be a consequence of decreased dermal thickness and stromal support for the SVN and small veins, with resulting increased boundary valve failure. Our observations may also be consistent with venous flares, corona phlebectatica, and reticular veins being overt manifestations of the degenerative changes in the SVN. The appearances of the resin casts are very suggestive of this, as the reflux extends into areas where reticular veins, corona phlebectatica, and venous flares occur. Also, our unpublished duplex studies, tracking foam injected into reticular veins, demonstrate appearances consistent with the reticular vein being part of an underlying dilated SVN. The changes seen with capillaroscopy in the skin affected by venous insufficiency with dilated capillary loops also fit well with what we have described.

Retrograde resin venography has its limitations, not the least being that it is done in amputated limbs and is non-physiological, bearing no relation to the hemodynamic subtleties of valve closure, blood flows, and pressure differ-

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![Fig 7](image-url)  
**Fig 7.** Tissue excised from venous ulcers (4 cm² regions). A, Gross, resin filled, ulcer specimen and B, matching macerated specimen. **C** and **D**, Extensive venous filling in separate ulcer specimens showing the superficial (**C**) and deep (**D**) surfaces of the casts. All ulcer casts showed extensive filling of the venous network, particularly at the ulcer margins. Scales in mm.

![Fig 8](image-url)  
**Fig 8.** Scanning electron microscopy of extensive superficial venous network filling from a (mixed) ulcer in an 83-year-old male. **A**, Superficial surface view (scale bar 2 mm), equivalent to that shown in **Fig 7, C**. **B**, Lateral view (scale bar 1 mm). Note the extensive filling of the papillary loops (**arrowheads**).
ences that occur in vivo. In a retrograde resin cast, what lies behind competent valves is not seen, and unfortunately, the status of unfilled segments cannot be assumed with this technique. However, by using a resin with a viscosity similar to blood, that can readily penetrate the small vessel networks of the skin, this technique still provides revealing morphology. We suggest that the reflux of resin is likely to reflect the state of the venous microcirculation and microvalves of the limbs studied.

There are certainly unanswered questions that arise from this study, including: what is the role of microvenous valves in networks in which they can be bypassed; what causes these degenerative changes in the small veins, microvalves, and SVN — are they the same as those occurring in larger refluxing varicose veins and are the structural changes comparable? Are these changes flow-mediated remodeling, or primary changes in wall metabolism or composition of extracellular wall matrix, or due to loss of supporting structures? All of these questions deserve further exploration.

A concept which has been of some help in understanding the interrelationships of venous networks and their influence on venous disease and management has been described by Franceschi and Zamboni. They describe five networks from the deep veins (N-1) out to the microcirculation (N-5) contained in three anatomical compartments (deep AC-1 with N-1, saphenous AC-2 with N-2, and superficial AC-3 with N-3 and N-4). While N-5 is called the microcirculation network, it is also placed in the superficial compartment (AC-3), and receives relatively little attention. We propose that the concept of these different anatomical compartments be extended to a fourth anatomical compartment, AC-4. Our observations in this study suggest there is greater importance to N-5 than previously realized, with the “boundary valves” and the bypassing patterns of the SVN and likely different hemodynamics. It would give greater attention to the N-5 network to place it in its own compartment (AC-4), out of the subcutaneous layer and within the dermal layer of the skin. This compartment has its own supporting structures and characteristics. We believe this is a useful addition in the understanding of venous hemodynamics and disease.

In conclusion, this study has demonstrated that valvular incompetence can occur in small superficial veins in the absence of reflux within the GSV. We propose that degenerative changes with valve incompetence are required in both the larger proximal vessels and the small superficial veins, in particular at the third generation of vessels draining into the GSV, where “boundary” valves may act as the key regulators of reflux into the capillary networks of the skin.

The concept of “boundary” valves may have important implications for the management of cardiovascular disease (CVD). While not immediately suggesting a new therapy for CVD, it may help identify those with varicose veins most at risk of venous ulcer and in need of treatment. Further, it points to the potential risk of extensive, inadvertent retrograde filling of venous networks in the dermis from intentionally injecting sclerosant into these small vessels adjacent to an ulcer to enhance healing would seem unwise.

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AUTHOR CONTRIBUTIONS
Conception and design: GJ, VR
Analysis and interpretation: GJ, JV, VR
Data collection: GJ, JV, GH
Writing the article: GJ, JV, VR
Critical revision of the article: GJ, VR
Final approval of the article: VR
Statistical analysis: JV, GJ
Obtained funding: VR
Overall responsibility: VR

REFERENCES

Additional material for this article may be found online at www.jsvscsu.org.

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Supplementary Fig 1 (online only). Measuring valves to assess competency. Vessel diameter (ø) was measured at the point of attachment of the two valve leaflets. Sinus depth (s) was measured from the attachment of the valve leaflet at the vessel wall to the free edge. If the valve ratio (ø/s) was greater than 1.3, then a valve was considered incompetent. The typical appearance of “competent” straight segment (A) and tributary (B) valves, with ratios of 0.5 and 0.6 respectively, are shown. C, shows a straight segment valve that would be classified as incompetent (ratio 1.5).
Supplementary Fig 2 (online only). Varicosities seen in areas of reflux from casts of limbs with competent great saphenous veins (GSVs). Note the extent of resin penetration and the absence of valves.
Supplementary Fig 3 (online only). Venous ulcer from an 86-year-old male. A, Gross, resin-filled, ulcer margin specimen, (B) macerated specimen (4 cm²) of the skin neighboring the ulcer, and (C) light microscope image showing the tortuous microvessels within this specimen.