Eur J Vasc Endovasc Surg **32**, 447–452 (2006)
doi:10.1016/j.ejvs.2006.04.021, available online at http://www.sciencedirect.com on ScienceDirect

REVIEW

Valves in Small Veins and Venules

A. Caggiati,[1*] M. Phillips,[2] A. Lametschwandtner[3] and C. Allegra[4]

[1]*Department of Anatomy, University "La Sapienza", Rome, Italy,* [2]*Department of Anatomy & Structural Biology, and, Department of Surgery, University of Otago, New Zealand,* [3]*Department of Organismic Biology, Vascular and Muscle Research Unit, University of Salzburg, Salzburg, Austria, and* [4]*Department of Angiology, San Giovanni Hospital, Rome, Italy*

It is commonly believed that valves are absent in veins smaller than two millimetres in diameter. Consequently, current investigations on the pathophysiology of chronic venous disease (CVD) consider and evaluate only the valvular competence of large veins. The authors review literature from their own collections as well as from medical database searches to assess the functional relevance of these valves.

Microscopic venous valves (MVVs) were first described in 1934 in the human digits and have subsequently been demonstrated in other parts of the human body as well as in many tissues and organs of animals.

Their location and arrangement suggests that MVVs prevent blood reflux in small sized veins and restrict flow from postcapillary venules back into the capillary bed. This haemodynamic role of MVVs is strongly supported by the clinical finding that grafting skin rich in MVVs results in long-lasting healing leg ulcers attributable to CVD.

The huge body of knowledge available concerning MVVs urges us to correct textbooks of anatomy. Studies on the pathophysiology of CVI should acknowledge that the valvular "chain" is not limited to large veins, but extends down to the venular level where MVVs play an important role in venous haemodynamics.

Keywords: Venous valve; Microcirculation; Chronic venous insufficiency.

Historical Introduction

"…*Valves are absent in the very small veins.*…".[1] *This* popular statement is reported in all textbooks dealing with venous anatomy and histology.[1,2] As a result investigations of pathophysiology of chronic venous insufficiency (CVI) consider and evaluate only the role and efficiency of the macroscopic valves present in large veins.

In 1934, the Canadian pathologist Nicholas W. Popoff demonstrated in the human digit integuments that: "*… the collecting veins of the stratum reticulare and stratum subcutaneum are furnished with valves. Even very small peripheral digital vein shows the presence of valves …*".[3] Popoff also described the presence of microscopic venous valves (MVV) in the *venae efferentes* of arterio-venous anastomosis (AVA). The presence of MVV in the skin was confirmed in 1936 by Jager in the frog[4] and then by other prominent histologists.[5–9]

In 1950, the Italian anatomist Antonio Pirro described the presence of MVVs in the muscles of the human leg.[10] In 1958, Miani and Ruberti gave an exhaustive description of MVVs in venules larger than 40 microns in diameter and small veins with diameters up to 400 microns in the skin and subcutaneous tissue of the human foot sole.[11]

In 1981, Braverman and Keh-Yen demonstrated the existence of MVVs at the dermal-subcutaneous interface of the human anterior abdominal wall.[12] Two years later they published a detailed description of the ultrastructure of MVVs by transmission electron microscopy (TEM).[13] In the 1980s, MVVs were described in the muscles of the human legs by light microscopy (LM) and scanning electron microscopy (SEM)[14–17] (Figs. 1 and 2).

A milestone in the field of MVVs investigation was laid in 1971 when Murakami introduced a technique to obtain resin replicas of the microvascular bed and

*Corresponding author. Dr A. Caggiati, MD, Department of Anatomy, University "La Sapienza", Via Borelli 50, 00161 Rome, Italy.
E-mail address: alberto.caggiati@uniroma1.it

1078–5884/000447+06 $35.00/0

evaluated microvascular corrosion casts by Scanning Electron Microscopy (SEM).[18] In 1990, Lametschwandtner applied this technique to cast selected areas of the microvascular bed in human cadavers.[19,20] This technique allowed a less time-consuming, highly efficient investigation of the distribution and morphology of MVVs (Figs. 3 and 4).

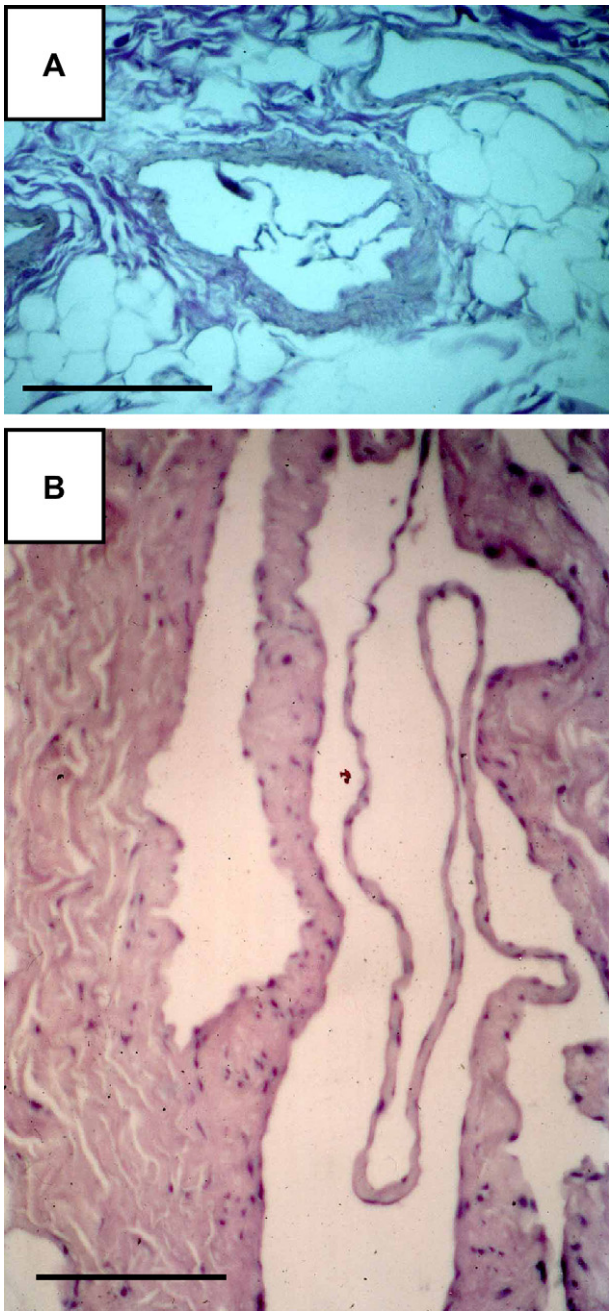

Fig. 1. Light Microscopy of human *vastus medialis*. A) Transverse section of a MVV located in a collecting venula (diameter: 80 micrometers). Scale bar: 50 microns. B) Longitudinal section of a MVV located in a small intramuscular vein (diameter 150 micrometers). Scale bar: 50 microns.

In the last decade, MVVs were investigated in the vascular pedicles of fascio-cutaneous flaps of major muscle groups used for grafting.[21–23] In 1994, Dunn *et al.*, evaluated the role of MVV in the skin of limbs afflicted with CVI.[21] More recently, this topic has been studied in greater depth in 2001 by Aharinejad *et al.*[22] and in 2004 by Phillips *et al.*[23] by vascular casting and SEM. Both groups independently identified MVVs in superficial veins as small as 20 μm in diameter (Figs. 5 and 6). Finally, SEMs of vascular corrosion casts demonstrated MVVs in many human or animal tissues and organs like the heart (Fig. 3), the tongue, the brain, the intestine (Fig. 4), and thyroid gland.[24–31]

Distribution of MVV in Humans

In humans, MVVs have been demonstrated in the integuments of the lower limb[11,22,23] (Figs. 5 and 6), the anterior and posterior walls of the trunk,[12,13,32,33] the face,[31] in the muscles of the leg and the thigh,[14–17] and in the tongue.[29] A thorough review of the literature revealed that MVV so far have not been described in other human organs or regions. Table 1 summarises the human organs and regions in which MVVs have been demonstrated (Table 1).

Location and Morphology of MVV in Humans

MVVs have been described in the microvascular bed (postcapillary venules and *venulae efferentes* of AVAs), in collecting venules and in small calibre veins (with diameters up to 800−1000 microns). In the lower limbs, MVVs are found in venules from 20 μm onwards.[22,23] In the wall of the trunk, they are in veins larger than 40 μm[13] and, in the face, in veins larger than 150 μm.[31]

Generally, MVVs are described as bicuspid. There are reports of monocuspid and tricuspid MVVs, but these are very rare. MVVs are arranged in series along a vein or are situated at the merging of two veins. The valves always point in the direction of the larger vessel as in collecting veins.[13] In smaller venules, MVV leaflets "*consist of delicate connective tissue membrane lined on both sides with endothelial cells*".[3] Two layers of endothelial cells surround a core of basement membrane material in which bundles of collagen fibrils are embedded.

In MVVs of larger veins, endothelial cells on the medial and lateral surfaces of the leaflets are oriented parallel and perpendicular, respectively, to the long axis of the vein.[22] This orientation is related to the need for flexibility, distensibility and strength of the valve leaflets.[26] TEM showed that valve leaflets have collagen

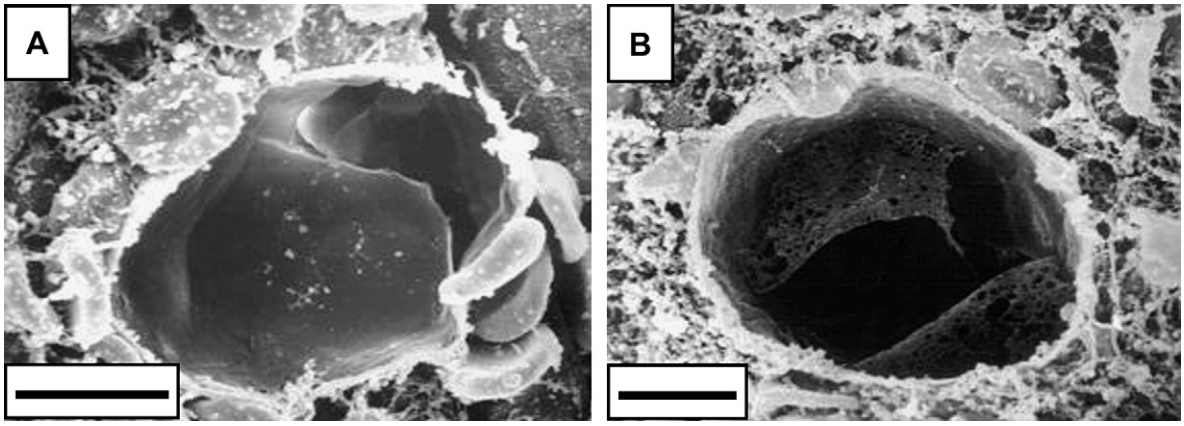

Fig. 2. SEM of KOH digested specimen from the human *vastus medialis*. A) A bicuspid MVV in a 25 microns venula. Scale bar: 5 microns. B) A bicuspid MVV in a 40 microns venula. Scale bar: 10 microns.

fibers that ascend towards the tip of the leaflet and that they are occasionally accompanied by elastic fibres.[13] Fibroblasts and myofibroblasts are present regularly only in the leaflets of valves of larger veins.[13]

Regional Differences in MVV Occurrence

In order to evaluate regional differences in MVV occurrence, Aharinejad *et al.* introduced two useful indices, namely the Venous Density Index (i.e., the total length of veins in a 1 mm^2 tissue area) and the Valvular Density Index (i.e.: the total number of MVVs in the same area).[22] Phillips *et al.* further refined these indices, by calculating valvular density for tissue volume (valves/cm^3), and the density of valves in relation to the density of vessels (valves/vessel intersect.[23]

As a result, Aharinejad could demonstrate that areas where venous ulcers usually develop have an higher concentration of MVVs.[21] He reported that MVVs were more frequently encountered in regions over hard structures such as bones and tendons, with a higher valve index in calf area. This distribution was significant different from the distribution of MVV in the venules of the skin regions over muscles, where MVVs were fewer.[21] The highest number of MVV was found in the big toe, where venous ulcers do not develop at all. The authors concluded that valvular density alone cannot explain for the preferential sites of venous ulcers in the gaiter region. The lower concentration of MVVs in the integuments overlying muscles could indicate that local drainage is

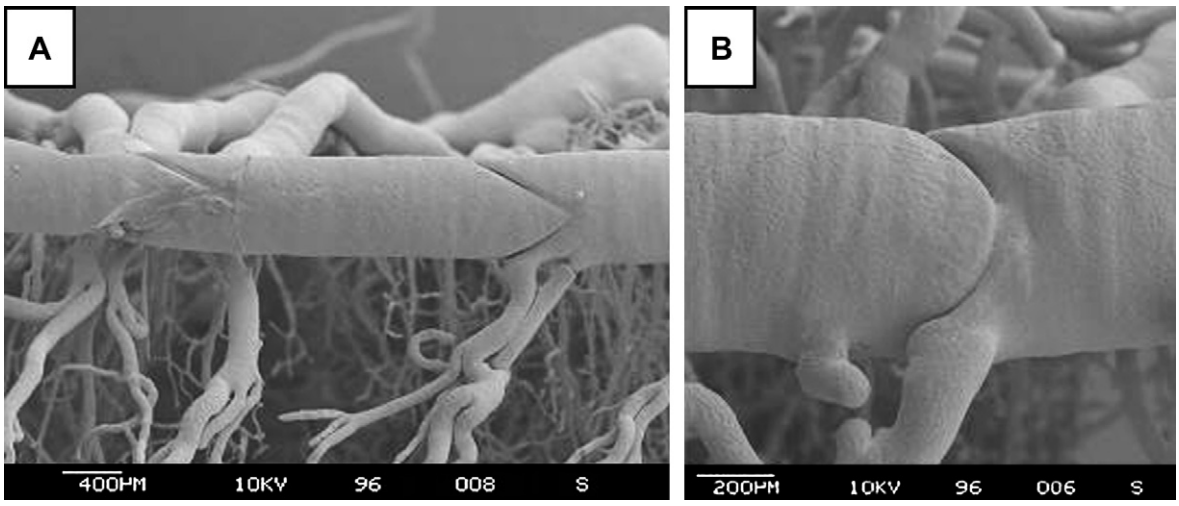

Fig. 3. SEM of the mouse coronary bed. A) Imprinting of MVV on a large venula (400 micrometers). B) The MVV is located in correspondence of the merging of a tributary vein.

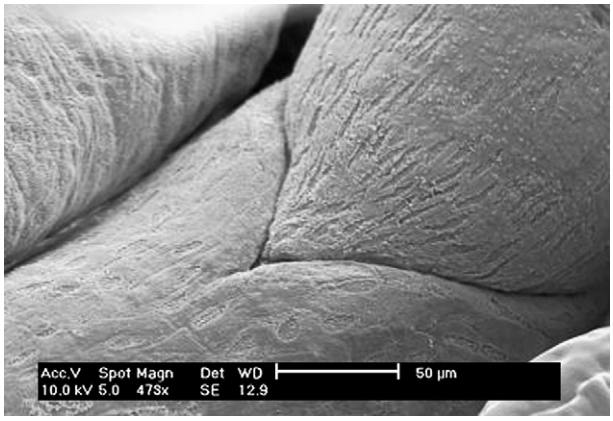

Fig. 4. SEM of corrosion cast of mouse stomach. Note the endothelial cell nuclei imprint patterns and the differences distal (elongated imprints) and proximal to the valve (roundish imprints).

facilitated by the activity of neighbouring muscles. Conversely, Phillips found a lower density of MVVs in the gaiter region of the lower limbs, the region most commonly affected by venous ulceration, as compared to the mid and upper calf regions.[34]

Functional Role of MVV

MVVs have been demonstrated only by histology so their functional role can only be deduced from their morphology. The following possible functional implications of MVVs have been theoretically hypothesized:

MVVs are identical in structure, location and orientation to the valves of larger veins of the leg. The shape of MVVs clearly demonstrates that they may close due to inertial fluid stress, as happens in larger veins. On the other hand, MVVs located in the microcirculatory bed supposedly have a similar mechanism to that present in collecting lymphatics,[35] and they "… *would use viscous fluid stress to close* …".[22] Closure of MVVs probably prevents venous reflux in small sized veins. At the microcirculatory level, they may also prevent reflux from post-capillary venules into the capillary bed and into AVAs. Two arguments are in favour of this hypothesis: Firstly, the lack of MVVs in regions with a favourable venous return, secondly the abundance of MVVs in regions where gravitational back flow occurs and where blood flow is irregular or is altered by muscle contraction.[21,36]

In the lower limb, in the trunk walls, and in the maxillary region of the face in humans, fragmentation of the hydrostatic column would extend down to microcirculatory level. In the event of valvular incompetence in macroscopic veins, the column of refluxing blood would be not free to flow towards the microvascular bed of the regions furnished with effective MVV.

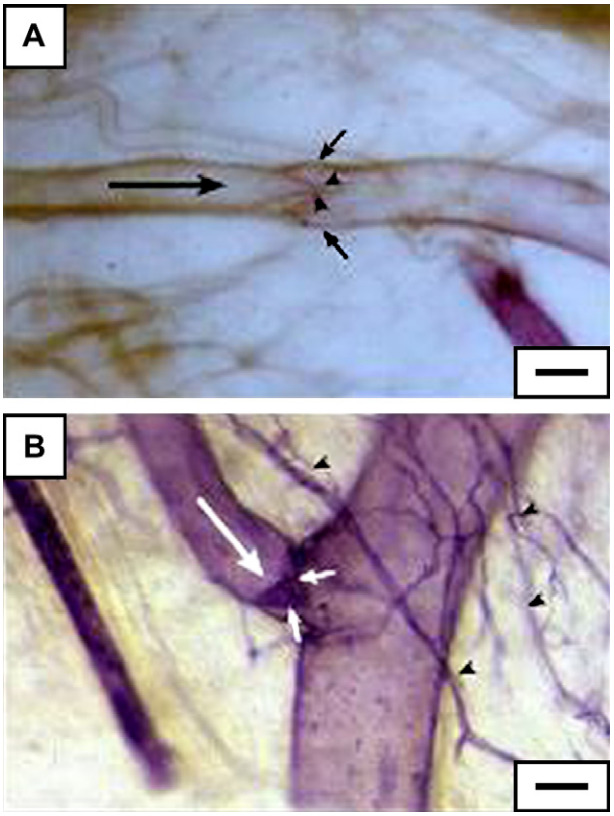

Fig. 5. Plastinated superficial tissue from the skin of the human leg. A) A longitudinal section through a venous valve in a vein 100 µm in diameter, from Valve cusps (arrowheads) and the valve sinuses (small arrows). The direction of blood flow is indicated by the arrow). Scale bar = 100 µm. B) A venous valve located within the orifice of a tributary (140 µm in diameter). This valve appears as two semi-circular cusps (small arrows). Overlying the larger vein is a number of capillaries (arrowheads). The presumed direction of blood flow is indicated (large arrow). Scale bar = 100 µm.

In 1958, Miani and Ruberti proposed an active participation of MVVs in contributing to the progression of the blood micro-column.[11] This hypothesis was based upon the presence of vascular smooth muscle cells inside the leaflets of larger MVVs and upon the muscular thickening of the wall at the site of valve insertion. Once passively distended, the muscle cells could contract and thus enhance blood flow at the MVVs level.

Recently, Lurie *et al.* (2003), hypothesized that venous valves in large veins, in addition to maintaining antegrade blood flow, might accelerate it.[37] The authors claimed that the blood acceleration results from the decreasing luminal diameter at the site of valve leaflets, a similar situation as occurs within an

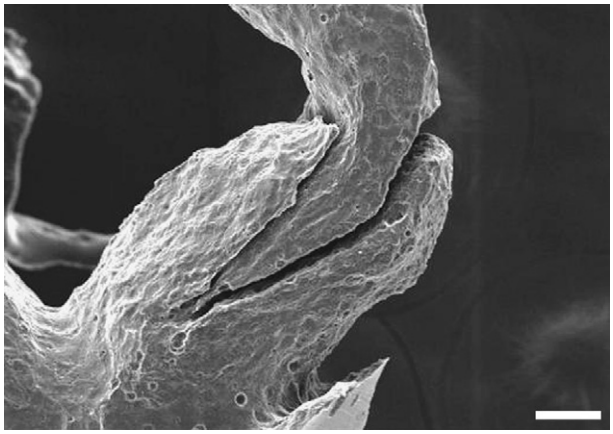

Fig. 6. SEM of corrosion cast from the skin of the human leg. The venula is approximately 224 microns in diameter. Scale bar: 50 microns.

arterial stenosis. The same mechanism could occur at the level of MVVs in small veins and venules.

Venular MVVs could also contribute to the fine regulation of flow-motion in the capillary bed and in the AVAs. In fact, it has been shown that blood flow in human skin capillaries is pulsatile in both the arteriolar limb (with 14–71 mmHg of pressure) and the venular limb (with 11–52 mmHg of pressure).[38] In the venular limb the pressure wave shows a dicrotic notch identical to that seen in the arteriolar limb.[34] Considering the magnitude of these pulsatile blood pressure variations, it is reasonable to assume that MVVs in venules ensure the forward motion of the blood flow. Moreover, the pressure increase at the venular side sometimes surpasses the colloid osmotic pressure and theoretically MVVs could prevent an imbalance of the transcapillary transport of fluids and molecules, leading to an augmented transcapillary fluid filtration. MVVs have to fulfil this function particularly where venous hypertension occurs with pressures in venules higher than in arterioles and with the AVAs open.[16]

Table 1. The human organs and regions in which MVVs have been demonstrated

Popoff, 1934	Digital skin
Pirro, 1950	Calf muscles
Miani and Ruberti, 1958	Foot sole skin
Braverman *et al.*, 1983	Abdominal wall
Curri *et al.*, 1987	*Vastus lateralis*, *Gastrocnemius*
Caggiati *et al.*, 1987	*Vastus lateralis*
Miyake *et al.*, 1996	Human maxilloface
Aharinejad *et al.*, 1997	Exocrine pancreas
Aharinejad *et al.*, 1997	Human dorsal thoracic fascia
Aharinejad *et al.*, 1998	Skin of the scapular area
Aharinejad *et al.*, 2001	Skin of the lower limb
Shangkuan *et al.*, 2001	Tongue
Phillips *et al.*, 2004	Skin of the lower limb

Pathophysiology of MVV

As it is impossible to study MVVs in vivo, their role in limbs afflicted with CVI is still a matter of discussion. Nevertheless, a possible role of MVVs was indirectly demonstrated in limbs afflicted with CVI by Photoplethysmography.[21,22] These studies evaluated the venous refilling time (VRT) in the periulcer skin of limbs with severe CVI (CEAP: C4-C6) and in the grafted skin of a free fasciocutaneous flap from cutaneous areas rich in MVV (about 90 valves per flap). Both studies reported an immediate significant increase in VRT as compared to preoperative values. The authors attributed the increase in VRT exclusively to the transfer of MVVs, because no treatment was performed to correct valvular incompetence in the proximal large veins. The improvement of the local venous haemodynamics was also confirmed by the clinical results with no recurrent ulceration and no recurrent tissue lipodermatosclerosis up to 9 years.

These data suggest that MVVs play a role in counteracting venous hypertension caused by valvular failure of larger veins. Therefore MVV incompetence could explain the occurrence of skin changes associated with CVI in limbs with competence of proximal valves and a short VRT[39] and in those without any relevant venous disease (obese patients, calf pump dysfunction, heart or respiratory failure).

Conclusions

Anatomists, physiologists and clinicians consider the venous bed as "valveless" from the venular level up to 2 mm large veins. In fact, assiduous investigation[3–31] demonstrates that MVVs are present in vascular territories with unfavourable venous haemodynamics to play a functional role which must be still comprehensively evaluated. The increasing number of studies confirming the presence of MVVs in venules suggests that the errors contained in textbooks of anatomy concerning MVVs should be corrected. The available evidence suggests that MVV incompetence could explain clinical syndromes characterised by signs and symptoms of CVI in limbs with competent venous valves in large veins. Investigation of the pathophysiology of CVI must take into account the possible haemodynamic role of a valvular "chain" extending down to the venular level. In the future the authors suggests that the

functional role of MVV in CVI will be investigated by techniques such as capillaroscopy, high frequency ultrasound probes, Laser Doppler and micro fibre angioscopy.

References

1 *Gray's anatomy*. 38th ed. London: Churchill Publisher, 1995.
2 Fawcett DW. *Bloom & Fawcett – a textbook of histology*. New York: Chapman and Hill, 1994.
3 Popoff N. The digital vascular system. *Arch Pathol* 1934;**18**: 307–322.
4 Jager A. Die Venenklappen des Frosches. *Pflug Arch Ges Physiol* 1936;**237**:710–716.
5 Watzka M. Ueber gafssperren und arteriovenose anastomose. *Ztschr Mikr Anat Forschung* 1936;**39**:512.
6 Bucciante L. Anastomosi artero-venose e dispositivi regolatori del flusso sanguigno. *Monit Zool Ital* 1949;**17**:1–23.
7 Conti G. Sur la morphologie des anastomoses arterio-veineuses et des dispositifs regulateurs de courant sanguigne. *Ann Anat Pathol* 1958;**3**:32.
8 Rugani F, Bertelli L. Sulla circolazione venosa dell'arto inferiore. *Folia angiologica* 1955;**2**:286–295.
9 Clara M. *Die arterovenosen anastomosen*. Wien: Springer, 1956.
10 Pirro A. Dimostrazioni istologiche di anastomosi artero-venose e dispositivi di blocco nelle minute arterie dei muscoli articolari del ginocchio. *Bollettino Società Italiana Biologia Sperimentale* 1950;**26**:1.
11 Miani A, Ruberti U. Sulla morfologia degli apparati valvolari delle venule efferenti delle anastomosi arterovenose della pianta del piede. *Minerva Cardioangiol* 1958;**6**:541.
12 Braverman IM, Keh-Yen A. Ultrastructure of the human dermal microcirculation. III. The vessels in the mid- and lower dermis and subcutaneous fat. *J Invest Dermatol* 1981;**77**:297–304.
13 Braverman IM, Keh-Yen A. Ultrastructure of the human dermal microcirculation. IV. Valve-containing collecting veins at the dermal-subcutaneous junction. *J Invest Dermatol* 1983;**81**:438–442.
14 Dech C, Tischendorf F, Curri SB. Nouvelles acquisitions morpho-functionelles sur la microcirculation du muscle strié. *Arteres Veines* 1983;**2**:212–230.
15 Curri SB, Annoni F, Montorsi W. Microvalves in microveins. 9eme Congres Mondial de Phlebologie, 1986.
16 Caggiati A, Curri SB. Sulla morfologia strutturale ed ultrastrutturale degli apparati microvalvolari nel tessuto muscolare striato dell'uomo. 4th Congress of the Italian Society of Phlebology, Napoli, 1987.
17 Curri SB, Annoni F, Montorsi W. Les microvalvules dans les microveinules. *Phlebologie* 1987;**40**:795–801.
18 Murakami T, Miyoshi M, Fujita T. Glomerular vessels of the rat kidney with special reference to double efferent arterioles. A scanning electron microscope study of corrosion casts. *Arch Histol Jpn* 1971;**33**:179–198.
19 Lametschwandtner A, Staindl O. Angioarchitecture of keloids. A scanning electron microscopy study of a corrosion specimen. *HNO* 1990;**38**:202–207.
20 Lametschwandtner A, Lametschwandtner U, Weiger T. Scanning electron microscopy of vascular corrosion casts – technique and applications: updated review. *Scanning Microsc* 1990;**4**: 889–940.
21 Dunn RM, Fudem GM, Walton RL, Anderson Jr FA, Malhotra R. Free flap valvular transplantation for refractory venous ulceration. *J Vasc Surg* 1994;**19**:525–531.
22 Aharinejad S, Nedwed S, Michlits W, Dunn R, Abraham D, Vernadakis A *et al*. Valvular density alone cannot account for sites of chronic venous insufficiency and ulceration in the lower extremity. *Microcirculation* 2001;**8**:347–354.
23 Phillips MN, Jones GT, van Rij AM, Zhang M. Micro-venous valves in the superficial veins of the human lower limb. *Clin Anat* 2004;**17**:55–60.
24 Hossler FE. Anatomy of venous valves: studies on the duckling using corrosion casting, SEM and stereology. *Anat Rec* 1985; **214**:454.
25 Hossler FE, West RF. Venous valve anatomy and morphology: studies on the duckling using vascular corrosion casting. *Am J Anat* 1988;**18**:425–432.
26 Hossler FE, Olson KR. Microvasculature of the nasal salt gland of the duckling, *Anas platyrhynchos*: quantitative responses to osmotic adaptation and deadaptation studied with vascular corrosion casting. *J Exp Zoolog* 1990;**254**:237–247.
27 Rattanachaikunsopon P, Chunhabundit P, Bamroongwong S, Somana R. Microvasculature of the thyroid gland in the common tree shrew (*Tupaia glis*): microvascular corrosion cast/scanning electron microscopy study. *Acta Anat (Basel)* 1991;**142**:208–214.
28 Aharinejad SH, Lametschwandtner A. *Microvascular corrosion casting in scanning electron microscopy. Techniques and applications*. Wien-New York: Springer-Verlag, 1992:375.
29 Shangkuan H, Xinghai W, Shizhen Z, Zengxing W, Shiying J. A morphological study on human lingual venous valves. *Surg Radiol Anat* 1998;**20**:167–170.
30 Wungcharoen B, Pradidarcheep W, Santidhananon Y, Chongchet V. Pre-arterialisation of the arterialised venous flap: an experimental study in the rat. *Br J Plast Surg* 2001;**54**:621–630.
31 Miyake M, Ito M, Nagahata S, Takeuki Y, Fukui Y. Morphological study of the human maxillofacial venous vasculature: examination of venous valves using the corrosion cast technique. *Anat Rec* 1996;**244**:126–132.
32 Aharinejad S, Dunn RM, Fudem GM, Vernadakis A, Bock P, Firbas W *et al*. The microvenous valvular anatomy of the human dorsal thoracic fascia. *Plast Reconstr Surg* 1997;**99**:78–86.
33 Aharinejad S, Dunn RM, Nourani F, Vernadakis AJ, Marks Jr SC. Morphological and clinical aspects of scapular fasciocutaneous free flap transfer for treatment of venous insufficiency in the lower extremity. *Clin Anat* 1998;**11**:38–46.
34 Phillips MN. Anatomy of microvenous valves of normal and venous ulcerated lower limbs. PhD thesis, University of Otago, Dunedin (New Zealand), 2004.
35 Mazzoni MC, Skalak TC, Smid-Schombein GW. Structure of lymphatic valves in the spino-trapezius muscle of the rat. *Blood Vessels* 1987;**24**:304–312.
36 Franklin KJ. *A monograph on veins*. Springfield: CC Thomas, 1927.
37 Lurie F, Kistner RL, Eklof B, Kessler D. Mechanism of venous valve closure and role of the valve in circulation: a new concept. *J Vasc Surg* 2003;**38**:955–961.
38 Mahler F, Muheim MH, Intaglietta M, Bollinger A, Anliker M. Blood pressure fluctuations in human nailfold capillaries. *Am J Physiol* 1979;**236**:H888–H893.
39 Rutgers PH, Kitslaar PJ, Ermers EJ. Photoplethysmography in the diagnosis of superficial venous valvular incompetence. *Br J Surg* 1993;**80**:351–353.

Accepted 16 April 2006
Available online 9 June 2006