Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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Mechanisms of Vascular Disease

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A Reference Book for Vascular Specialists

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

25 • Chronic Venous Insufficiency and Leg Ulceration: Principles and Vascular Biology

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DEFINITIONS

Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is a term that is used to describe changes in the leg that include a variety of different clinical problems, which are caused by several types of abnormalities in the veins, and which may occur at a number of different locations in the leg.[1] For these reasons it has been difficult to make accurate comparisons of reports of chronic venous insufficiency from different institutions. As a result attempts have been made to formulate systems of classification that enable accurate comparisons to be made.

The most recent classification, referred to as the CEAP classification, was devised by an international panel and encompasses features of some of the earlier classifications.[2] This classification has four categories which include – Clinical (C), Etiology (E), Anatomy (A) and Pathophysiology (P). Within each category the different levels are each given a number or a letter or both. The clinical classification has seven levels from no visible or palpable signs of venous disease through to skin changes with active ulceration (Table 25.1). In addition the *Clinical* categories are further characterized according to the presence or absence of symptoms. The *Etiological* classification recognizes the roles of congenital (E_c), primary (E_p) and secondary (E_s) causes in venous dysfunction. The *Anatomical* classification can be represented as a simple or more detailed form. The simple form refers to the site at which the veins are involved as superficial (A_s), deep (A_d) or perforating (A_p). The more detailed form identifies the specific veins that are involved and has 18 segments that can be identified. The *Pathophysiologic* classification identifies the cause of venous dysfunction being either reflux (P_R) or obstruction (P_O), or both (P_{RO}). This classification can be used in part or in whole when describing the patients in a published report.

Leg Ulceration

Leg ulceration may occur as a result of many different aetiological factors (Table 25.2). For patients presenting with an ulcer on the leg it is imperative to determine the aetiology since the treatment may differ according to the cause. For ulcers on the leg, not including

TABLE 25.1: Clinical classification of chronic venous disease of the lower extremity. The presence or absence of symptoms is denoted by the addition of 's' for symptomatic, or 'a' for asymptomatic.

Class	Definition
0	No visible or palpable signs of venous disease
1	Telangiectases or reticular veins
2	Varicose veins
3	Oedema
4	Skin changes ascribed to venous disease (e.g. pigmentation, eczema, lipodermatosclerosis)
5	Skin changes as above in conjunction with healed ulceration
6	Skin changes as above in conjunction with active ulceration

TABLE 25.2: Commonest causes of leg ulceration.

Venous disease
Arterial disease
Rheumatoid arthritis
Diabetes
Vasculitis
Scleroderma
Pyoderma grangrenosum
Trauma
Infective
Ulcerating skin cancer

the foot, the commonest aetiology is chronic venous disease either alone or in common with another cause of impaired healing such as arterial disease, diabetes or rheumatoid arthritis. The venous abnormality that leads to venous leg ulceration may involve abnormalities at different locations in the venous system, of different extent and different aetiologies.

Assessment of Cause of Leg Ulceration

In order to determine the aetiology of a leg ulcer, a standardized assessment is strongly recommended.[3] That assessment should consist of the following

1) History – to determine the presence of other known diseases that might result in an impairment of the healing process. These include disease processes listed in Table 25.2.
2) Examination –
   a. General examination to assess for evidence of diseases in Table 25.2
   b. Examination of the lower limbs to assess for
      i. Venous disease
      ii. Arterial disease
      iii. Examination of the ulcer, specifically documenting
         1. Location
            a. Gaiter region – likely venous
            b. More proximal on the leg – consider other aetiologies
            c. Foot – not commonly venous aetiology
         2. Skin surrounding the ulcer
            a. Lipodermatosclerosis – venous disease
            b. Atrophie blanche – venous disease or vasculitis
            c. Atrophic skin changes – arterial

   d. Normal skin – consider other aetiologies
3. Ulcer edge
   a. Raised – neoplastic
   b. Punched out – arterial
   c. Undermined – infective
   d. Sloping – venous
   e. Dusky – vascilitis, pyoderma grangenosum
4. Ulcer base
   a. Necrotic tissue – arterial; large or small vessel disease
   b. Granulating – multiple aetiologies including venous
   c. Fibrotic slough – venous, multiple aetiologies

3) Investigations
   a. Ankle: brachial Doppler arterial pressure index
   b. Confirmation of venous disease
      i. Venous plethysmography
      ii. Venous duplex scan to assess for sites of venous reflux
      iii. Blood tests – anemia, renal failure, liver failure, diabetes, vasculitis
      iv. Ulcer biopsy – if suspicious appearance or if not responding to adequate compression therapy

Epidemiology

A number of epidemiological studies of leg ulceration have been conducted in different Western countries and have found a similar prevalence of leg ulceration ranging from 0.11% to 0.18% of the population.[4-8] These studies have confirmed that chronic venous disease is the commonest cause, representing approximately 65% of ulcers on the leg. These occur most commonly in elderly people with a mean age in excess of 65 years. There are nearly twice as many women as men with leg ulcers, however, when these are related to age, the prevalence for males and females is similar because there are more women than men in the older age groups.[4]

An Australian epidemiological study found that venous ulcers are associated with delayed healing (with a median duration of 26 weeks) and also tend to recur in over 70% of patients.[4]

Pathophysiology

Venous Abnormality

The basic underlying physiological abnormality in chronic venous disease is altered return of blood in the veins of the leg, which results in ambulatory venous hypertension in the superficial veins.[9] When venous pressures are measured in the surface veins in the foot or ankle, the pressure is normally highest (approximately 100mmHg) when standing immobile, and drops to 30 to 40mmHg when walking (Figure 25.1). This occurs because the 'calf muscle pump' assists the return of blood from the leg by compression of the deeper veins during muscle contraction. When the muscles relax, the emptied deeper veins have a lower pressure which allows more blood to flow into them from the surface veins, thereby reducing the pressure in those veins (Figure 25.2).

In patients with chronic venous insufficiency the pressure in the surface veins drops only a small amount, hence the term 'ambulatory' venous hypertension (Figure 25.1). An increase in the pressure in the surface veins above that present on standing is very uncommon, and only occurs when there is extensive proximal venous occlusion. The failure to reduce superficial venous pressure on exercise occurs when there is reflux in either the deep veins or the surface veins. Reflux in the deep veins results in rapid refilling of the deep veins when the calf muscles relax (Figure 25.3). This results in only a small increase in the amount of blood that

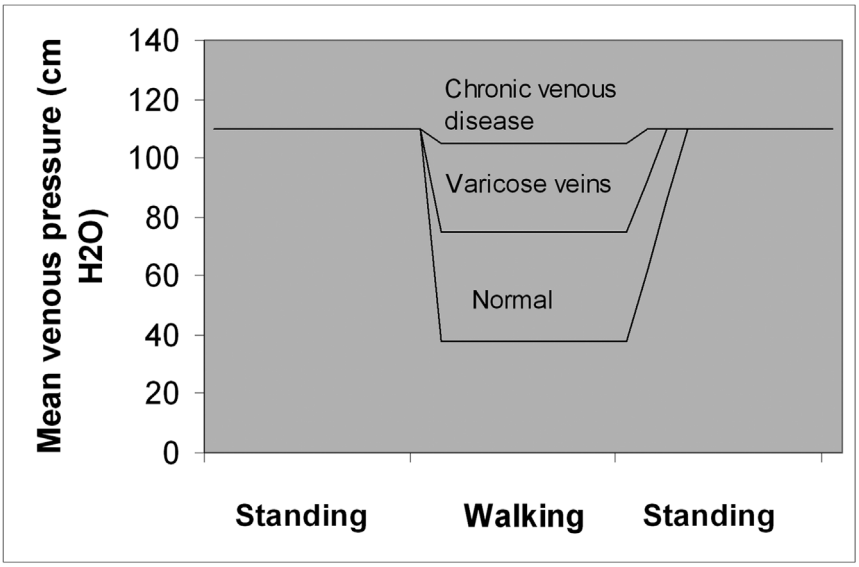

FIGURE 25.1: Superficial venous pressures in normal legs and legs with chronic venous disease.

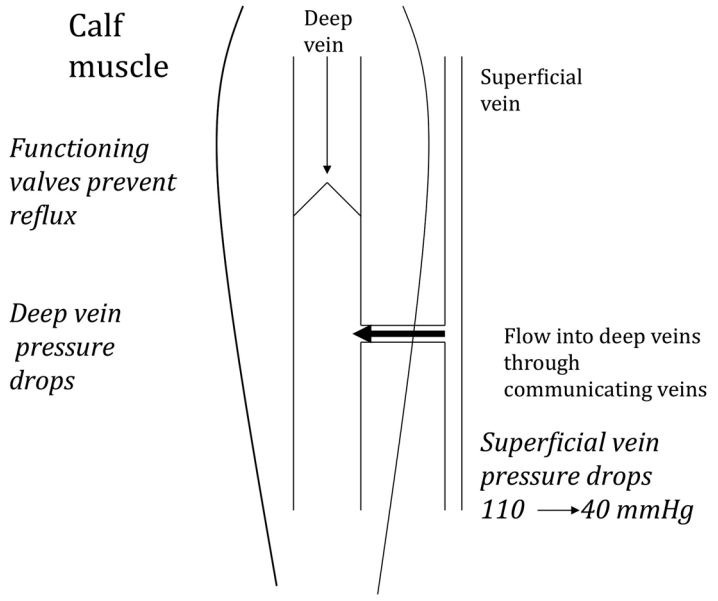

FIGURE 25.2: Pressure in the deep and superficial veins in a normal leg after calf muscle contraction.

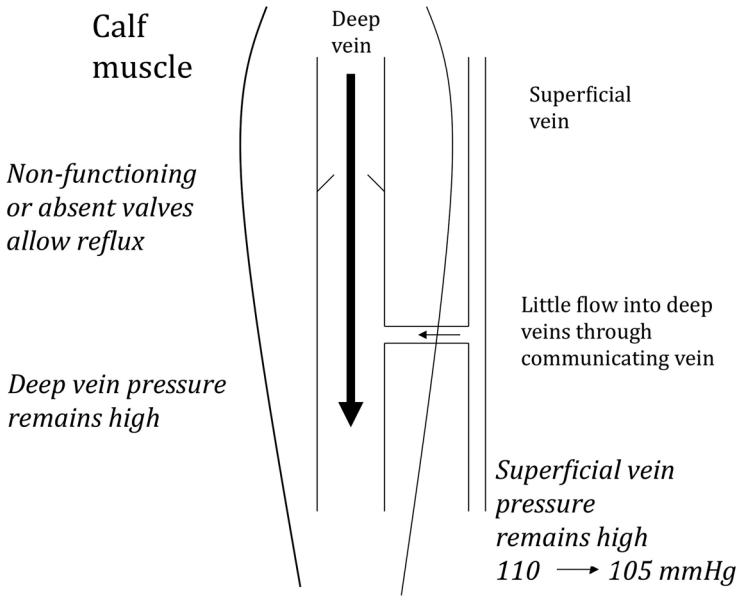

FIGURE 25.3: Pressure in the deep and superficial veins in a leg with chronic venous disease after contraction of the calf muscle.

flows from the surface veins into the deep veins. If the reflux is primarily in the superficial veins, the superficial veins refill quickly and the ambulatory venous pressure remains elevated even though more blood may be flowing into the deep veins.[10]

Reflux in veins is caused either by destruction of the valves when a venous thrombosis recanalizes, or by primary incompetence of the valves. The relative proportions of the two causes in the deep veins remain a point of debate. Definite evidence of previous deep vein thrombosis has been reported in 40 –50% of patients with venous ulceration.[10,11] In chronic venous insufficiency the venous reflux may involve the deep veins or may involve only the surface and perforating veins. Involvement of the deep veins has also been variously reported at between 40 and 90%.[11,12] The major reason for this variation in reporting is the use of different techniques for assessing the deep veins. The rate of deep vein involvement was reported at higher rates when the standard method of assessing veins was venography.[11] Duplex scanning has now become the major method for assessing veins, and the quoted rates of deep vein involvement have dropped.[12] This possibly relates to the difficulty in visualizing the calf veins with duplex scanning.

Effect of Ambulatory Venous Hypertension on the Tissues in the Leg

The obvious clinical finding in CVI is the pigmentation and fibrosis that occurs in the skin in the gaiter region of the leg, referred to as lipodermatosclerosis (Figure 25.4). Histologically there is also an increase in the extent of the capillary bed in the skin, although there is some debate as to whether the capillaries are all perfused.[13,14] This is particularly the case in areas of atrophie blanche (white atrophy) in which there are tufts of capillaries interspersed within

relatively avascular skin (Figure 25.5). This condition is common in venous ulceration, but may also be present in other conditions such as vasculitis.[15]

A number of hypotheses have been proposed over the years to try and explain how ambulatory venous hypertension affects the tissues and thereby leads to impaired healing. It has generally been acknowledged that there must be some impairment to the nutrition to the skin cells either due to reduced nutrients or reduced oxygenation. To date such reduced skin nutrition has not been conclusively demonstrated. Many studies have shown reduced transcutaneous oxygen measurements,[14] however because of the change to the structure of the skin this may not be an accurate reflection of tissue oxygenation.

Theories that have been proposed to support the concept of reduced nutrition to the skin are arteriovenous shunting,[16] the

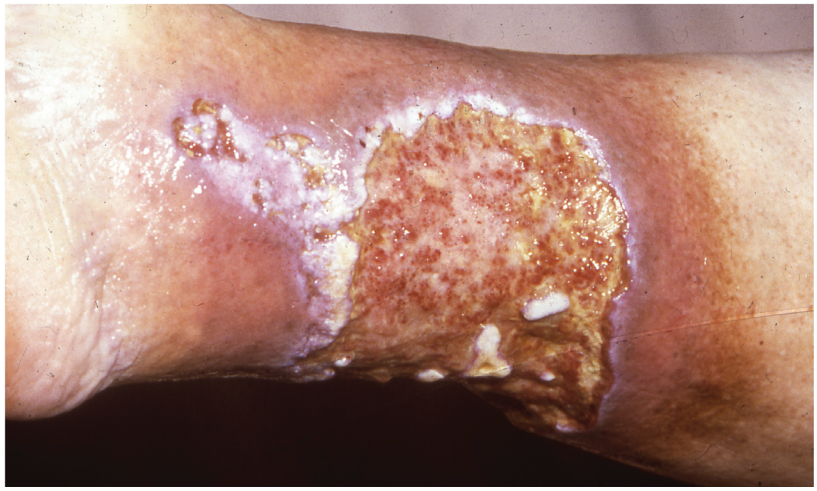

FIGURE 25.4: Lipodermatosclerosis and ulceration in a leg with chronic venous disease.

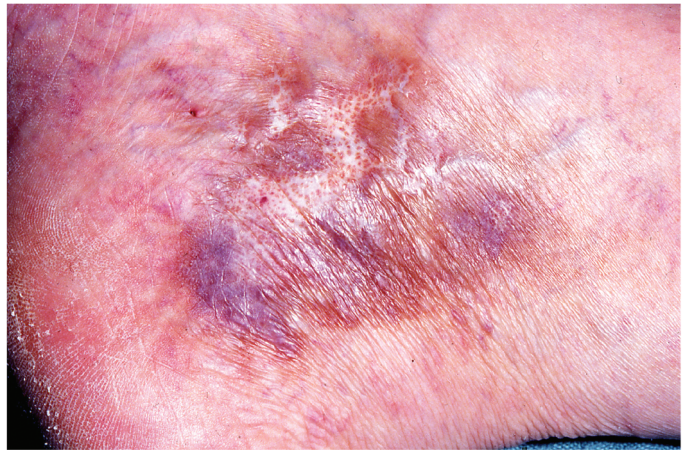

FIGURE 25.5: Atrophie blanche in a leg with chronic venous disease.

presence of a diffusion barrier to oxygen by fibrin and other proteins that deposit around skin capillaries,[17] and the occlusion of capillaries by activated white cells becoming 'trapped' in the capillary bed.[18] Other theories have hypothesized that growth factors are trapped in the pericapillary protein deposits which therefore impedes the healing process (Figure 25.6).[19] Localised reperfusion injury has also been hypothesized in association with intermittent periods of ambulatory venous hypertension and lower venous pressures.[20] Other hypotheses have focused on the presence of factors that directly damage the tissue by activation of white cells which subsequently release factors such as cytokines, proteases and oxygen free radicals that can impede healing.[21,22] To date there is no conclusive support for any given hypothesis, although the presence of an excessive inflammatory response has been repeatedly demonstrated in venous ulcers.

Influence of Venous Disease on the Wound Healing Process

The cause of impaired healing in venous ulceration remains uncertain. This is in spite of the clinical observation that non-healing venous ulcers begin to heal once patients are admitted to hospital for bed rest. Efforts are continuing to try and determine what is occurring at a cellular and molecular level to impede the healing process. These have demonstrated a highly inflammatory environment with high levels of inflammatory cytokines, proteases and large numbers of immune cells.[22-24] The proteases that are elevated in venous ulcers compared to acute wounds include matrix metalloprotease-2 and -9 (MMP-2 and 9) (Figure 25.7) and collagenases (Figure 25.8). It is possible that this highly inflammatory environment may result in destruction of factors that are important in the normal healing process. These factors may include growth factors, cell surface receptors, the matrix in the base of the wound and cellular adhesion molecules.

Bacteria that colonise open wounds may contribute to the increased inflammatory wound environment. No clear link has been shown between the presence of bacteria and healing ability in venous ulcers.[25,26] Bacteria are known to form biofilms which consist of a matrix that is secreted by the

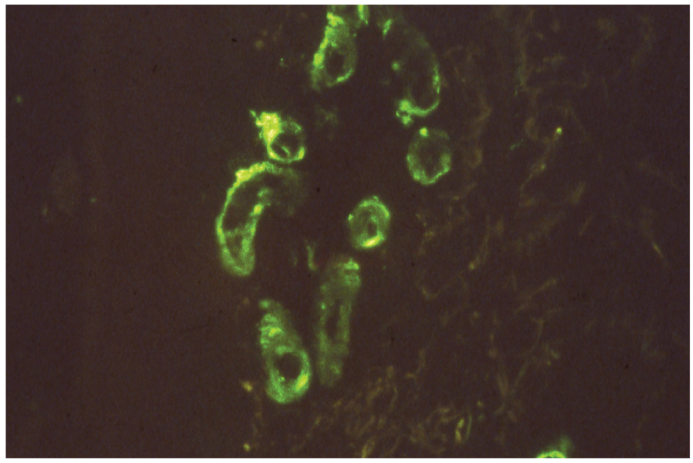

FIGURE 25.6: Pericapillary deposit of protein – fibrinogen.

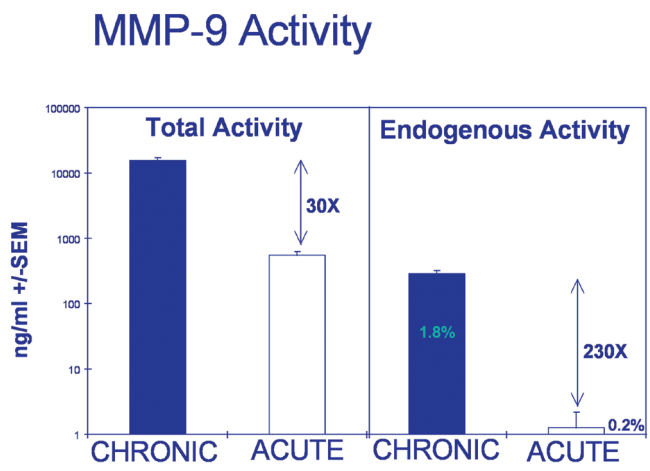

FIGURE 25.7: Matrix metalloprotease levels in wound fluid from acute and chronic wounds.

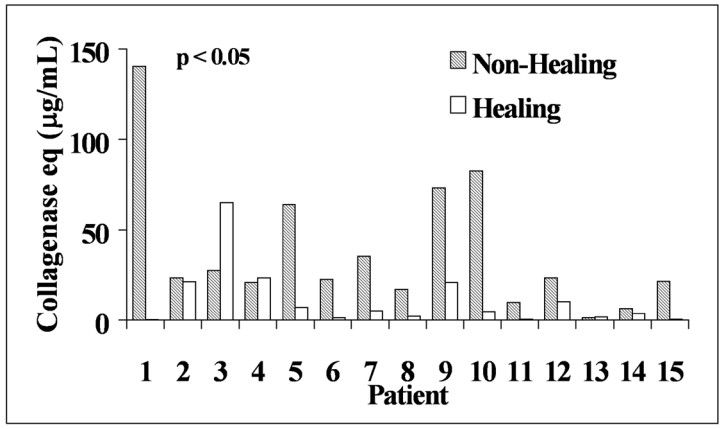

FIGURE 25.8: Collagenase levels in wound fluid from chronic venous ulcers.

bacteria which enables the bacteria to persist in an environment in which they are protected from the body's defense mechanisms.

The underlying causes of venous ulceration may affect both the ability to develop ulcers and the ability to heal ulcers; however, it is likely that additional factors will contribute to the impaired healing process once an ulcer has occurred. Further understanding of the factors that impede the healing process may lead to better treatments to improve ulcer healing.

Genetic Associations with Venous Ulceration

A number of research groups have now demonstrated that genetic polymorphisms are associated with the development of venous ulceration. Working independently, groups have demonstrated that the following polymorphisms to be associated with venous ulceration – tumour necrosis factor alpha 308 (a regulatory polymorphism),[27] fibroblast growth factor receptor type 2,[28] oestrogen receptor beta[29] and haemochromatosis

factor.[30] There is also a suggestion that a polymorphism in coagulation factor XIII may be associated with delayed healing of venous ulceration following venous surgery.[31] All of these studies have been performed on relatively small samples sizes and do require further confirmation in larger samples sizes. It is likely that a number of genetic factors will ultimately be shown to be associated with the ability to heal wounds.

ASSESSMENT OF VENOUS FUNCTION

In patients with venous ulceration, the history and clinical signs on the leg will give a strong indication of the presence of venous disease. When surgical treatment is to be considered it is imperative to have a clear outline of the veins with reflux and the presence of venous obstruction. If the deep veins are involved, the benefits of operating on surface and or perforating veins are limited and appear to be dependent on the extent of the venous reflux.[32,33] The commonest current method that is used to assess for sites of incompetence is Duplex scanning. Venography and imaging with contrast CT scan or MR venography are used infrequently and usually only when there is uncertainty about the information from the Duplex scan. Other methods of diagnosing venous disease such as plethysmography and hand held Doppler do not give a good indication of the sites of venous incompetence.[34,35] When performing a Duplex scan for chronic venous disease, the deep veins, superficial veins, and the communicating veins should all be evaluated.

TREATMENT OF VENOUS ULCERATION

The objective of the treatment of venous ulceration is to improve the physiological abnormality of ambulatory venous hypertension. The two methods available are compression therapy applied to the leg or direct treatment of the veins by surgery or other ablative techniques such as sclerotherapy, laser or radiofrequency ablation.[36] There are also ongoing studies to identify topical and systemic therapies that will have a direct influence on improve the healing process in the ulcers. The only such therapy that has been used in clinical practice in some parts of the world is topical platelet derived growth factor.[37]

Compression Therapy

Compression applied to the leg improves the venous return in the leg, primarily by reducing venous reflux into the leg and also by reducing the leg volume.[38] Compression bandages have also been shown to significantly improve the time taken to heal venous ulcers.[39] This reduces oedema in the leg that is considered to impede the healing process. The compression is applied to the leg below the knee from the base of the toes to just below the knee, and the level of compression that is recommended is to achieve a pressure of between 25 and 45mmHg at the ankle with a graduated reduction in pressure up the leg. The compression may be applied by either bandages or by compression stockings. In patients with an open ulcer, bandages are normally preferred because the exudate damages the stockings and shortens their lifespan.

There are many different types of bandage systems that have been employed for venous ulcers. Most benefit has been shown to occur with systems that are multilayered.[39,40]

The first layer consists of orthopaedic wool or similar padding that is placed beneath a plaster cast. This is to help protect the skin overlying bony prominences from excessive pressure. The next one or preferably two layers are the compression bandages that may be elastic or inelastic or a combination of the two. The top layer is one to help prevent slippage of the bandage. This may be a bandage that adheres to itself or a tubular stockingette. To date no difference has been shown in the efficacy of inelastic (short stretch) or elastic bandages (long stretch), as long as these are used as part of a multilayered system.

If a compression stocking is used this should be either class 2 (25–35mmHg at the ankle) or class 3 (35–45mmHg), and should aim to provide graduated compression. These come in a variety of sizes and should be fitted to the individual's leg. They come with and without zippers on one side that help with applying and removing the stocking. Patients with small or very large legs may need to have stockings custom made to fit their legs. Stockings can be difficult to both apply and to remove, particularly in patients with arthritis or in frail patients. To assist with application there are frames onto which the stockings can be placed and into which the patient then places their foot. Stockings are often useful in younger patients who have active jobs and for whom wearing bulky bandages is difficult.

Dressings

The dressing applied to the ulcer may be chosen from any that are available. No dressing, including those dressings containing silver and other topical antibacterial agents, have been shown to have a direct effect on improving the healing process.[41] Dressings are chosen according the needs of the patient and their wound. Different dressings may be chosen to absorb exudate, reduce pain, help liquefy slough, reduce bacterial contamination, reduce odour from the wound, or to protect the surrounding skin from maceration. The cost of the dressing also needs to be considered when making a selection. For patients who are using stockings a dressing that adheres to the skin is preferable as this aids with applying the stocking over it.

The dressings and compression may be left on the leg and for up to one week and even longer in cooler climates. Commonly however, the bandages and dressings may be changed anything from daily to weekly. The main determinants of the duration of application are the amount of exudate, the state of the wound and odour from the bandages.

Surgery

Surgery to the veins in the lower leg may include procedures on the superficial varicose veins, incompetent communicating veins or the deep veins in the leg. Surgery to the superficial veins includes surgery to the long and/or short saphenous vein by ligation and stripping, together with avulsion of varicosities.[33,42] Incompetent communicating veins can be accurately located by Duplex scanning and may be approached directly by a small incision over the site and subfascial ligation. In order to avoid making incisions through areas of lipodermatosclerosis or ulceration, the perforators in the lower leg may be treated by subfascial endoscopic perforator surgery (SEPS) (Figure 25.9).[43] The deep veins may be treated by direct repair of intact but incompetent valves. The repair may be directly by suture[44,45] or may involve applying a cuff around the valve to reduce the diameter of the vein and to restore competence.[46] Veins that have had previous venous thrombosis and which have recanalised with destruction of the valve can

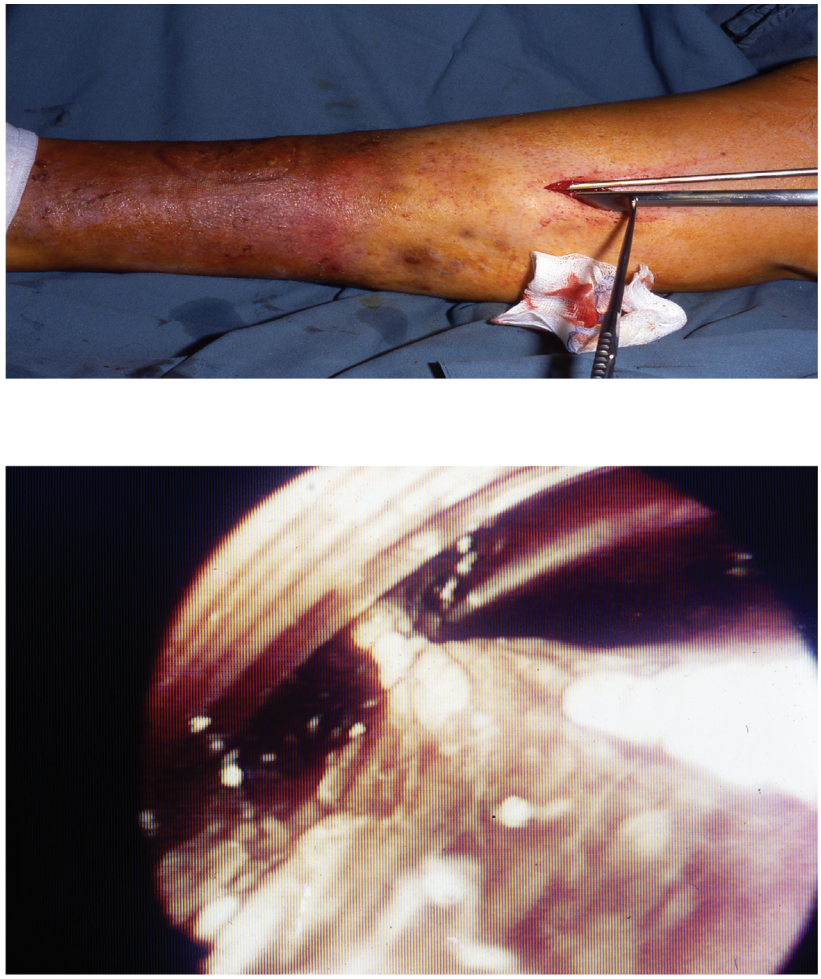

FIGURE 25.9: Subfascial endoscopic perforator surgery – instruments in position and clip on a perforator.

have a segment of vein containing competent valves taken from the arm and inserted to replace a segment of the femoral or popliteal vein.[47]

The roles of a number of these operations in patients with venous ulcers has in part been clarified by recent clinical trials and reviews of published data.[32,33] The benefits of surgery to the deep veins for patients with open or healed venous ulcers remain unproven and should be confined to studies assessing their efficacy rather than be used in routine clinical practice. Surgery to the superficial veins in combination with compression does not result in any improvement in venous ulcer healing compared to compression therapy alone.[32] However, surgery to the superficial veins in combination with compression does result in a significant reduction in venous ulcer recurrence. Individuals who are most likely to benefit from surgery to the superficial venous system are those with superficial venous incompetence and no deep incompetence or in patients with superficial incompetence and segmental deep incompetence. In both groups of patients there is a significant reduction in ulcer recurrence compared to compression

therapy alone. For patients with extensive deep vein incompetence, there was not a significant reduction in the rate of ulcer recurrence.[32,33,42]

The need to treat incompetent communicating veins at the same time as treating superficial veins remains uncertain.[42] Studies on patients with superficial venous incompetence and incompetent communicating veins, but without deep vein abnormalities, have indicated that in a majority of patients, the communicating veins cease to be incompetent after the superficial veins are ablated.[48,49] Another study has indicated that in the presence of deep vein reflux, ablation of superficial veins does not result in a return to competence in incompetent communicating veins.[50]

Anecdotal reports have suggested that operating on the superficial and perforating veins does improve the healing of venous ulcers. Randomised controlled trials have however, shown no improvement in venous ulcer healing when surgery is combined with compression bandaging compared to compression bandaging alone.[32,51] However, in patients who are not responding to optimal compression therapy and who have no or minimal reflux in the deep veins, the author's anecdotal experience is that surgery to the superficial and perforating veins does result in an active healing process. In addition, in patients with very painful ulcers, this surgery appears to reduce their level of pain. It is still important to continue the compression after the surgery.

Surgery to correct venous obstruction has included vein bypass, transposition of a vein to bypass an obstruction,[52] or balloon dilatation with stenting.[53] The efficacy of these procedures remains uncertain due to the infrequency with which they are performed, and the consequent anecdotal nature of reports.

Prevention of Venous Ulcer Recurrence

Once an ulcer has healed continued treatment should be implemented to help reduce the risk of ulcer recurrence. The simplest method is to use compression stockings.[54] These have been shown to significantly prolong the time before venous ulcers recur, however, they do not remove the risk completely. The stockings that are used are class 3, however, it is generally considered that class 2 stockings will have a similar benefit.

Surgery to the leg veins in patients with venous ulcers is most commonly used to reduce the risk of ulcer recurrence. This surgery is usually performed after ulcers have healed, to prevent the potential for wound contamination and infection from an open ulcer. As indicated above the only form of surgery that is used in routine practice is surgery to the surface and/or perforating veins. The benefits of this surgery are greatest in patients who have no evidence of post-thrombotic damage to the deep veins.

Sclerotherapy and Other Techniques to Obliterate Surface and Perforating Veins

Techniques other than surgery have been used to treat varicose veins and incompetent perforating veins. These include sclerotherapy,[55] ultrasound guided sclerotherapy to incompetent perforating veins and saphenous veins,[56] and laser or radiofrequency ablation of the long saphenous vein.[57] These techniques have not been specifically evaluated in the treatment of venous ulceration or the prevention of ulcer recurrence. It is likely that the benefit with these treatments would be commensurate with their efficacy in obliterating the appropriate veins compared to that achieved with the surgical techniques.

Other Therapies

The use of other systemic or topical therapies is an area in which there is ongoing research. Many different therapies have been evaluated; however, to date no single therapy has been shown to be of sufficient benefit to be used in routine clinical practice. Therapies that have or are being assessed include aspirin, oxpentifylline, platelet lysate or releasate, a number of different recombinant growth factors, growth factors derived from bovine whey, protease inhibitors, topical antibacterial preparations or dressings, systemic or topical antibacterials, and various vasoactive preparations.[58] There is some evidence that oxpentifylline does improve ulcer healing.[59] Other topical methods include ultrasound, magnetic therapy, ultraviolet light, electrical stimulation, and topical laser therapy.[60] To date there is no convincing evidence to support the efficacy of any of these therapies. Many therapies that have been proposed to aid venous ulcer healing have been selected on theoretical grounds rather than detailed knowledge of the cellular and molecular abnormalities that result in venous ulcers forming and that impede their healing. There is a need to better understand these processes so that this knowledge can be used to help identify improved methods for treating venous ulcers.

REFERENCES

1. Stacey MC. Investigation and treatment of chronic venous ulcer disease. *ANZ J Surg* 2001; **71**: 226–229
2. Eklof B, Rutherford RB, Bergen JJ, Carpenter PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: Consensus statement. *J Vasc Surg* 2004; **40**: 1248–52.
3. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic venous ulcers. A national clinical guideline. SIGN: Edinburgh, 2010.
4. Baker SR, Stacey MC, Jopp-McKay AG, et al. Epidemiology of chronic venous ulcers. *Br J Surg* 1991; **78**: 864–7.
5. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. *Br Med J* 1987; **294**: 1389–91.
6. Nelzen O, Bergqvist D, Lindhagen A, Halbook T. Chronic leg ulcers: an underestimated problem in primary health care among elderly patients. *J Epidemiol Commun Health* 1991; **45**: 184–7.
7. Cornwall JV, Dore CJ, Lewis JD. Leg ulcers: epidemiology and aetiology. *Br J Surg* 1986; **73**: 693–96.
8. Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F. Prevalence of leg ulceration in a London population. *QJ Med* 2004; **97**: 431–7.
9. Browse NL, Burnand KG, Lea-Thomas M. Diseases of the Veins. London: Edward Arnold, 1988.
10. Christopoulos D, Nicolaides AN, Cook A, Irvine A, Galloway JMD, Wilkinson A. Pathogenesis of venous ulceration in relation to the calf muscle pump function. *Surgery* 1989; **106**: 829–35.
11. Lea-Thomas M. Phlebography of the lower limb. Edinburgh: Churchill-Livingstone, 1982.
12. Van Rij AM, Solomon C, Christie R. Anatomic and physiologic characteristics of venous ulceration. *J Vasc Surg* 1994; **20**: 759–64.
13. Lascasas-Porto CL, Milhomens AL, Virgini-Magalhaes CE, Fernandes FF, Sicuro FL, Bouskela E. Use of

microcirculatory parameters to evaluate clinical treatments of chronic venous disorder (CVD). *Microvascular Research* 2008; **76**: 66–72.
14. Junger M, Steins A, Hahn M, Hafner H-M. Microcirculatory dysfunction in chronic venous insufficiency (CVI). *Microcirculation* 2000; **7**: S3–12.
15. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *Br Med J* 1982; **1**: 478–81.
16. Brewer AC. Varicose ulceration, arteriovenous shunts. *Br Med J* 1950; **2**: 269–70.
17. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **2**: 243–5.
18. Thomas P, Nash G, Dormandy D. White cell accumulation in dependent leg of patients with venous hypertension: a possible mechanism for trophic changes in the skin. *Br Med J* 1988; **296**: 1693–5.
19. Falanga V, Eaglstein W. The trap 'hypothesis' of venous ulceration. *Lancet* 1993; **341**: 1006–7.
20. Greenwood JE, Edwards AT, McCollum CN. The possible role of ischaemia-reperfusion in the pathogenesis of chronic venous ulceration. *Wounds* 1995; **7**: 211–9.
21. Bucalo B, Eaglstein W, Falanga V. Inhibition of cell proliferation by chronic wound fluid. *Wound Rep Reg* 1993; **1**: 181–6.
22. Trengove NJ, Bielefeldt-Ohmann H, Stacey MC. Mitogenic activity and cytokine levels in non-healing and healing chronic leg ulcers. *Wound Rep Reg* 2000; **8**: 13–25.
23. Trengove NJ, Stacey MC, MaCauley S, Bennett N, Gibson J, et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. *Wound Rep Reg* 1999; **7**: 442–52.
24. Stacey MC, Lainez S, Skender-Kalnenas T, Morrison B. Alterations in immune cells in human chronic leg ulcers. *Phlebology* 1995; Suppl **1**: 923–5.
25. Trengove NJ, Stacey MC, McGechie DF, Stingemore NF, Mata S. Qualitative bacteriology and leg ulcer healing. *J Wound Care* 1996; **5**: 277–80.
26. Moore K, Huddleston E, Stacey MC, Hardung KG. Venous leg ulcers – the search for a prognostic indicator. *International Wound Journal* 2007; **4**: 163–72.
27. Wallace HJ, Vandongen Y, Stacey MC. Tumour necrosis factor alpha gene polymorphism associated with increased susceptibility to venous leg ulceration. *Journal Invest Dermatol* 2006; **126**: 923–6.
28. Nagy N, Szolnoky G, Szabad G, Bata-Csorgo Z, Dobozy A, Kemeny L, et al. Single nucleotide polymorphisms of the fibroflast growth factor receptor 2 gene in patients with chronic venous insufficiency with leg ulcer. *Journal Invest Dermatol* 2005; **124**: 1085–8.
29. Ashworth JJ, Smyth JV, Pendleton N, Horan M, Payton A, Worthington J, et al. Polymorphisms spanning the on exon and promoter of the estrogen receptor-beta gene esr2 are associated with venous ulceration. *Clinical Genetics* 2008; **73**: 55–61.
30. Zamboni P, Tognazzo S, Izzo M, Pancaldi F, Scapoli GL, Liboni A, et al. Hemochromatosis c282y gene mutation increases the risk of venous leg ulceration. *J Vasc Surg* 2005; **42**: 309–14.

31. Gemmati D, Tognazzo S, Catozzi L, Federici F, De Palma M, Gianesini S, et al. Influence of gene polymorphisms in ulcer healing process after superficial venous surgery. *J Vasc Surg* 2006; **44**: 554–62.
32. Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ et al. Long term results of compression therapy alone versus compression therapy plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. *BMJ* 2007; **335**: 83–7.
33. Howard DPJ, Howard A, Kothari A, Wales L, Guest M, Davies AH. The role of superficial venous surgery in the management of venous ulcers; a systematic review. *Eur J Vasc Endovasc Surg* 2008; **36**: 458–65.
34. Hoare MC, Royle JP. Doppler ultrasound detection of saphenofemoral and saphenopopliteal incompetence and operative venography to ensure precise saphenopopliteal ligation. *ANZ J Surg* 1984; **54**: 49–52.
35. Abramowitz HB, Queral LA, Flinn WR, et al. The use of photoplethysmography in the assessment of venous insufficiency: A comparison to venous pressure measurement. *Surgery* 1979; **86**: 434–41.
36. Stirling M, Shortell CK. Endovascular treatment of varicose veins. *Semin Vasc Surg* 2006; **19**: 109–15.
37. Wieman TJ. Efficacy and safety of recombinant human platelet-derived growth factor-BB (Becalpermin) in patients with chronic venous ulcers: a pilot study. *Wounds* 2003; **15**: 8–12.
38. Yang D, Vandongen YK, Stacey MC. The influence of minimal-stretch and elasticated bandages on calf muscle pump in patients with chronic venous disease. *Phlebology* 1999; **14**: 3–8.
39. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000265. DOI: 10.1002/14651858.CD000265.pub2
40. Stacey M, Falanga V, Marston W, Moffatt C, Phillips T, et al. Compression therapy in the treatment of venous leg ulcers: a recommended management pathway. *EWMA J* 2002; **2**: 9–13.
41. Palfreyman SSJ, Nelson EA, Lochiel R, Michaels JA, Dressings for healing venous leg ulcers. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD001103. DOI: 10.1002/14651858.CD001103.pub2
42. O'Donnell TF. The present status of surgery of the superficial venous system in the management of venous ulcer and the evidence for the role of perforator interruption. *J Vasc Surg* 2008; **48**: 1044–52.
43. Jugenheimer M, Junginger T. Endoscopic subfascial sectioning of incompetent perforating veins in treatment of primary varicosis. *World J Surg* 1992; **16**: 971–95.
44. Kistner RL. Surgical repair of the incompetent femoral vein valve. *Arch Surg* 1975; **110**: 1336–41.
45. Raju S, Fredericks R. Valve reconstruction procedures for non-obstructive venous insufficiency: Rationale, technique and results in 107 procedures with two to eight year follow up. *J Vasc Surg* 1988; **7**: 301–9.
46. Jessup G, Lane RL. Repair of incompetent venous valves: A new technique. *J Vasc Surg* 1988; **8**: 569–75.
47. Nash TP. Venous ulceration: Factors influencing recurrence after standard surgical procedures. *Med J Aust* 1991; **154**: 48–50.

48. Sales CM, Bilof ML, Petrillo KA, Luka NL. Correction of lower extremity deep venous incompetence by ablation of superficial venous reflux. *Ann Vasc Surg* 1996; **10**: 186–9.
49. Walsh JC, Bergan JJ, Beeman S, Comer TP. Femoral venous reflux abolished by greater saphenous vein stripping. *Ann Vasc Surg* 1994; **8**: 566–70.
50. Stuart WP, Adam DJ, Allan PL, Ruckley CV, Bradbury AW. Saphenous surgery does not correct perforator incompetence in the presence of deep venous reflux. *J Vasc Surg* 1998; **28**: 834–8.
51. Guest M, Smith JJ, Tripuraneni G, Howard A, Madden P, et al. Randomised clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. *Phlebology* 2003; **19**: 130–6.
52. Husni EA. Reconstruction of veins: The need for objectivity. *J Cardiovasc Surg* 1983; **24**: 525–8.
53. Blattler W, Blattler IK. Relief of obstructive pelvic venous symptoms with endoluminal stenting. *J Vasc Surg* 1999; **29**: 484–8.
54. Vandongen YK, Stacey MC. Graduated compression elastic stockings reduce lipodermatosclerosis and ulcer recurrence. *Phlebology* 2000; **15**: 33–7.
55. Fegan WA. The treatment of varicose veins during pregnancy. *Pacif Med Surg* 1964; **72**: 274–9.
56. Kanter A, Thibault P. Saphenofemoral incompetence treated by ultrasound guided sclerotherapy. *Dermatol Surg* 1996; **22**: 668–72.
57. Fassiadis N, Kianifard B, Holdstock JM, Whiteley MS. A novel endoluminal technique for varicose vein management: the VNUS closure. *Phlebology* 2002; **16**: 145–8.
58. Robson MR, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the treatment of venous ulcers. *Wound Rep Reg* 2006; **14**: 649–62.
59. Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD001733. DOI: 10.1002/14651858.CD001733.pub2
60. Flemming K, Cullum NA. Laser therapy for venous leg ulcers. Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001182. DOI: 10.1002/14651828. CD001182.

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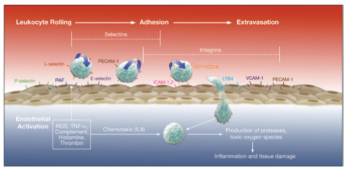

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