Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

Edited by Robert Fitridge and Matthew Thompson

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A Reference Book for Vascular Specialists

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Table of Contents

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Detailed Contents

CHAPTER 20 – PATHOPHYSIOLOGY OF PAIN

Stephan Schug, Helen Daly, Kathryn Stannard

CHAPTER 21 – POST-AMPUTATION PAIN

Stephan Schug, Gail Gillespie

CHAPTER 26 – PATHOPHYSIOLOGY AND PRINCIPLES OF MANAGEMENT OF THE DIABETIC FOOT

David Armstrong, Timothy Fisher, Brian Lepow, Matthew White, Joseph Mills

CHAPTER 27 – LYMPHOEDEMA – PRINCIPLES, GENETICS AND PATHOPHYSIOLOGY

Matt Waltham

CHAPTER 28 – GRAFT MATERIALS PAST AND FUTURE

Mital Desai, George Hamilton

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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

24 • Pathophysiology and Principles of Management of Varicose Veins

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INTRODUCTION

The management of superficial and deep venous reflux and obstruction that leads to the development of varicose veins (VV)[1] and the post-thrombotic syndrome (PTS)[2] forms a large part of the workload for most vascular and endovascular specialists and is likely to increase as the population ages.[3] However, the epidemiology,[4,5] genetics[6] and pathophysiology of these conditions remains incompletely defined[7,8,9,10,11] and many clinicians lack a clear understanding of the underlying anatomy and vascular biology.[12] As a result, treatment outcomes are not infrequently sub-optimal.

ANATOMY

Venous blood from the lower limbs returns to the right heart against gravity through the superficial and deep venous systems. The superficial venous system comprises the great saphenous veins (GSV) and small saphenous veins (SSV) and their tributaries.[13] The GSV originates from the medial end of the dorsal venous arch, passes anterior to the medial malleolus, and continues up the medial aspect of the calf and then the thigh to enter the common femoral vein in the groin at the saphenofemoral junction (SFJ). The SSV originates from the lateral end of the dorsal venous arch, passes posterior to the lateral malleolus and then continues up the back of the calf between the heads of gastrocnemius to enter the popliteal fossa. It is joined variably by gastrocnemius veins and then usually enters the popliteal vein at the sapheno-popliteal junction (SPJ). The SPJ may be absent in which case the SSV continues up the postero-medial aspect of the thigh (Giacomini vein) and often joins the GSV. These two systems interconnect at many other (highly variable) points through an extensive network of tributaries. In the deep system, veins, which are often paired, accompany each named artery. The superficial and deep systems connect at numerous points at various non-junctional perforators in addition to the SFJ and SPJ. These systems and interconnections are interdependent, both anatomically and functionally in health and disease.

In health, the deep venous system transmits 90% of the venous return from the leg. The superficial system drains only the skin and subcutaneous tissues, with

most of that blood draining immediately into the deep system via perforators in the foot, calf and thigh. It also plays a role in thermoregulation.

HISTOLOGY

The vein wall comprises three layers but these are less well defined than in the arterial system. The intima is thin and surrounded by a fine elastic lamina. The media is made up of elastin and layers of muscular bundles that are arranged in different orientations. The relative amounts of muscle and elastin varies with the calibre and working pressure of the vein. Beyond this, the adventitia merges with the perivenous connective tissue, which contains nerve fibres and vasa vasorum and provides for vessel distension which is an important part of normal venous function. With increasing age, and particularly with the development of disease, abnormalities have been described in all three layers[14] and the structure of the vein wall becomes progressively more disorganised.[15] Typically, there is thickening of the intima with disorientation of the elastic fibres. The outer muscle layer of the media becomes hypertrophied with dystrophic elastic fibres and the adventitia is increasingly fibrous.

PHYSIOLOGY

Venous return against gravity is primarily dependent on muscle pumps located in the foot and the calf. Pressure on the sole of the foot, and muscular contraction (systole) in the fascial compartments of the calf compresses the sinusoidal intramuscular veins directing blood into the deep system and thence up the leg. Superficial veins collect blood from the superficial tissues, and during muscle relaxation (diastole) this blood enters the deep system through the perforating veins down a pressure gradient, filling the sinuses. Reverse flow (reflux) during muscle relaxation is prevented by the closure of valves. These are delicate but strong bicuspid leaflets at the base of a localized dilated sinus in the vein. In both superficial and deep systems the density of valves is greatest in the calf and reduces gradually up the lower limb, with the iliac and inferior vena cava (IVC) frequently lacking valves altogether. Valves are present in venules down to about 0.15mm diameter.

During systole, blood is prevented from re-entering the superficial system through the closure of junctional (SFJ, SPJ) and non-junctional perforators (NJP). This was originally thought to occur solely through the closure of valves but several studies have failed to demonstrate such valves in NJP. Instead, external pressure from the fascia and muscle through which the perforators pass is thought to be responsible for limiting outward blood flow; somewhat akin to the 'pinch-cock' mechanism that prevents reflux at the gastro-oesophageal junction. Importantly, this also protects the superficial veins, subcutaneous tissues and skin from the extremely high deep venous pressures (up to 250mmHg) generated by the calf muscle pump in systole.

When standing motionless, with venous valves in the neutral position, the pressure in the foot veins gradually increases as blood continues to enter the veins from the arterial side. As soon as the pressure in one venous segment exceeds that in the segment just above, the valve opens. Eventually the hydrostatic pressure in the veins of the foot is that developed by an unbroken column from the foot to the right atrium – perhaps 90mmHg in a person of average height. With active movement, deep veins and sinuses are compressed raising venous pressure and moving blood cranially and, initially, caudally (Figure 24.1A). However, valve closure

normally prevents retrograde flow within 0.5-1.0 seconds. At this point, these closed valves divide the high-pressure, single column of venous blood described above into a large number of low-pressure, shorter columns (Figure 24.1B). As a result, the pressure in the foot veins falls in health to less than 25mmHg on walking; the normal ambulatory venous pressure (AVP) (Figure 24.2). This reduces venous pooling and lowers capillary hydrostatic pressure, reducing the tendency for accumulation of interstitial fluid (oedema) in the feet.[16] Patients with muscle pump and/or venous valve failure and/or venous outflow obstruction, demonstrate raised AVP. It is this raised AVP that underlies all the symptoms and signs of chronic venous insufficiency (CVI).

VARICOSE VEINS

Varicose veins (VV) are dilated, tortuous subcutaneous veins that permit reverse flow. They are most commonly found in the lower limb and may be primary, or secondary to deep venous pathology. The GSV system is most frequently affected with the SSV being involved in about 20% of cases. The aetiology of VV at a microscopic level is still disputed but the essential defect macroscopically is generally agreed to be the failure of venous valve closure resulting in the superficial veins becoming dilated, elongated and tortuous.[17,18] The main factor contributing to the development and progression of varicose veins is sustained venous hypertension that increases the diameter of the superficial veins resulting in further valve incompetence.

VALVULAR ABNORMALITIES

Failure of valve closure leading to valve incompetence and reflux may affect the deep and/or superficial venous systems and may be primary or secondary. Primary valvular incompetence (PVI) is believed to be due to loss of mural elastin and collagen, which

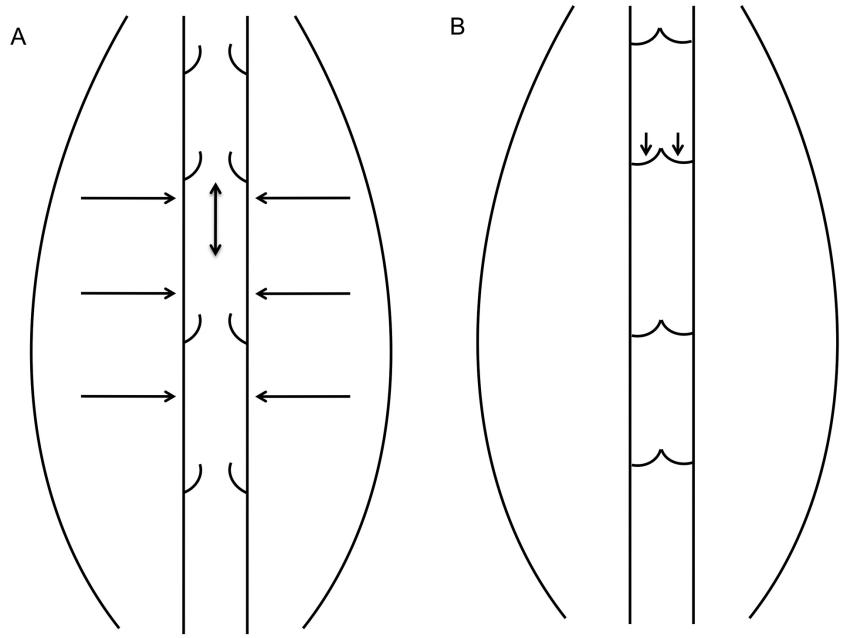

FIGURE 24.1: Influence of calf muscle pump and valves in venous return.

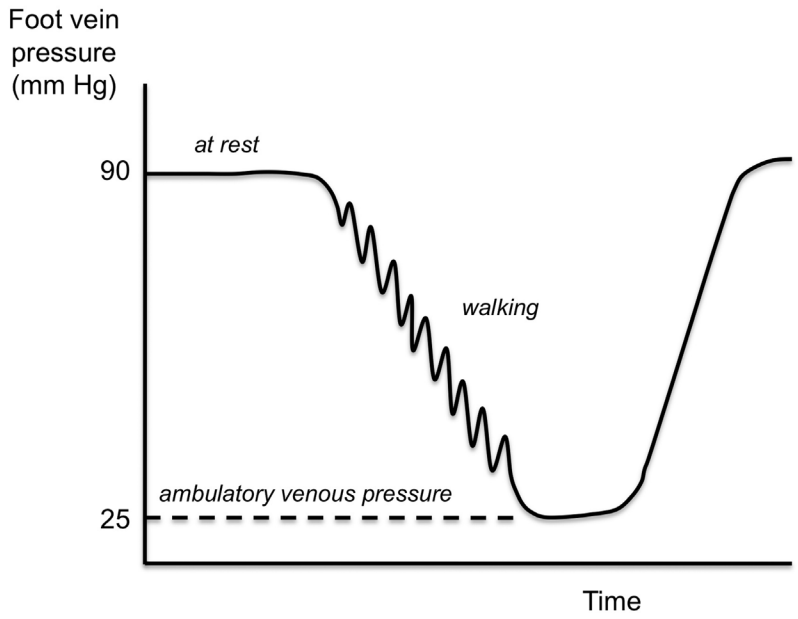

FIGURE 24.2: Resting and ambulatory venous pressure at the ankle in health.

leads to dilatation and separation of the valve leaflets. The commonest clinical consequence of this process is the development of VV. As an investing fascia often supports the main GSV trunk, it is often the tributaries that become varicose. PVI may also affect the deep venous system although because other tissues support the deep veins, the clinical consequences of PVI are less obvious and certain.

Secondary valvular incompetence may be due to a developmental weakness in the vein wall leading to secondary widening of the valve commissures, resulting in valvular incompetence and clinically, primary VV. It also follows thrombosis, most commonly in the deep venous system; deep venous thrombosis (DVT). Blood flowing within the lumen of the vein provides the vascular endothelium with its oxygen and nutrition. DVT prevents this, therefore leading to endothelial destruction and inflammation within and around the affected veins. Although most venous segments occluded by DVT recanalise over the subsequent 6–12 months the vein is often scarred and narrowed and, because the valves have been destroyed, incompetent. If recanalisation does not occur, blood is forced to find an alternative drainage route. For example, blood may be forced out of the deep venous system via the SFJ, SPJ and NJP leading to dilatation of the superficial veins (secondary VV). Obstruction of the iliac veins may lead to the development of groin and pelvic collaterals. Venous reflux and obstruction secondary to DVT leads to PTS which represents the most severe form of chronic venous insufficiency (CVI). The superficial venous system may also be affected by thrombosis, either in isolation or in combination with DVT, leading to superficial thrombophlebitis (SVT).

Rarely, VV and CVI may be due to congenital valve hypoplasia or agenesis, or due to arterio-venous malformations. In Klippel-Trenaunay syndrome, for example, there is deep venous hypoplasia and a laterally placed venous complex that acts as

the main venous outflow of the limb. All the symptoms and signs of chronic venous insufficiency are due to ambulatory venous hypertension resulting from these various pathological processes acting upon the microvasculature of the skin and subcutaneous tissues.

MUSCLE PUMP FAILURE

Any cause of chronic debility or immobility is associated with calf muscle pump dysfunction; for example, old age, stroke, neuromuscular conditions, arthritis and trauma. Injuries that limit or prevent ankle movement have a particularly adverse effect upon the calf muscle pump.

VENOUS RECIRCULATION

In patients with VV there is often a recirculation of venous blood within the leg. During calf relaxation abnormally large volumes of blood enter the muscle pump from the superficial varices (increased preload). During exercise the muscle pump expels blood from the leg only for it to re-enter the lower leg by refluxing down GSV and/or SSV VV (akin to an increase in afterload due to aortic regurgitation). This blood then re-enters the muscle pump through the perforating veins in the lower calf and so on. The effect is that the same blood can re-circulate up and down the leg several times before eventually finding its way up the iliac veins to the heart.

Patients with mild superficial reflux and/or an efficient calf pump are able to compensate for this by increasing their calf muscle pump 'stroke volume' and output. This allows them to still reduce their AVP to (near) normal levels on walking. However severe reflux and/or a weak muscle pump may overwhelm the deep system and lead to the development of sustained venous hypertension and skin changes of CVI. This accounts for two important clinical observations:

- CVI & ulceration can develop without primary deep venous pathology
- In a proportion of patients with VV and deep venous reflux the latter disappears following eradication of superficial disease.

RECURRENT VARICOSE VEINS

Recurrent VV after conventional surgical or endovenous intervention may be classified into three groups: new, persistent and true recurrent.

New varicose veins

This is the development of new VV, often in a second saphenous system, since the original operation.[19] This may be due to:

1) Inadequate assessment at the time of the initial treatment; however, now that most patients undergo full duplex ultrasound mapping prior to intervention for their VV this should be less common
2) Reflux developing at a site that was previously demonstrated to be competent; in other words, true disease progression

Persistent varicose veins

This is due to inadequate treatment of VV at the time of the original intervention. Again, with proper use of duplex ultrasound and modern techniques this should be a relatively uncommon scenario in current phlebological practice. The risk is perhaps greater with catheter based techniques such as radiofrequency ablation (RFA) and Laser ablation (EVLA) which, while being highly successful in eradicating truncal reflux,

do not deal with the varices themselves. A proportion of patients undergoing RFA and EVLA will, therefore, need further treatment, either with foam sclerotherapy or local anaesthetic phlebectomies.

True recurrent varicose veins

This is where further VV develop in the same, previously treated saphenous system. When surgery was the main treatment modality most were the result of failure to properly perform a 'flush' SFJ (SPJ) ligation and/or to 'strip' the GSV or SSV.

Neovascularisation (NV), defined as the 'development of new vessels connecting previously ligated superficial veins to the deep venous system', and the role it might play in the development of recurrent VV after surgery has received a lot of attention over the years. There is no doubt that in a proportion of patients with recurrent GSV (SSV) VV, duplex ultrasound clearly shows the presence of small venous channels within scar tissue apparently connecting the 'stump' of the GSV in the groin (SSV in the popliteal fossa) to recurrent VV in the thigh (calf). However, it seems unlikely that such small, therefore high resistance, veins will be capable of transmitting significant reflux and thus of constituting a significant cause of recurrence on their own. In an era where the vast majority of patients can have non-surgical treatment for their VV, the whole issue of NV becomes much less important. Going forward, most true recurrent VV are likely to be due to recanalisation of the trunk veins and/or their major tributaries that have previously been occluded by means of foam sclerotherapy, RFA or EVLA.[20,21] However, unlike redo surgery which is technically demanding and often associated with disappointing outcomes, such recanalisation can be successfully treated as an out-patient and so poses no real clinical difficulty.[19]

CELLULAR AND MOLECULAR BIOLOGY OF VARICOSE VEINS

The molecular biology of varicose veins has recently been reviewed. The aetiology of varicose veins is undoubtedly multifactorial. There are some genetic disorders and mutations that predispose to venous incompetence and development of varicosities (FOXC2, NOTCH3). However these diseases are rare whilst varicose veins are common.

In recent years there has been much research to define the structural and molecular events that accompany the formation of varicose veins, with an overall underlying hypothesis that varicose vein formation is most likely due to a structural, cellular or molecular abnormality within the vein wall. On a gross level, varicose veins exhibit intimal hyperplastic areas and underlying plaques with infiltration of leukocytes and mast cells. There is fragmentation of elastin fibres and the total content of elastin and Type III collagen is reduced. These extracellular matrix abnormalities may be regulated by disordered MMP and TIMP production.

Cell types within the varicose vein may show disordered function with endothelial activation leading to vasodilatation and a possible loss of venous tone. Many of the smooth muscle cells in the varicose vessel wall exhibit a synthetic rather than a contractile phenotype, and appear to have reduced rates of apoptosis. These cells may have a reduced capacity for contraction, which may exacerbate the vasodilatory tendency. The stimuli for the disordered function demonstrated by these intrinsic cells remains ill defined, but hypoxic stress and low shear stress may play a role.

There is certain to be further research in the next few years to further define the vascular biology of varicose veins. There has been some suggestion that this may lead to a medical therapy for varicose veins, although the practicality of this is not immediately apparent. Nevertheless research into the molecular aetiology of varicose veins will continue to define vascular pathways.[22]

CONCLUSION

Despite the very large numbers of patients affected by CVI and VV, research into venous disease is generally given low priority and so there are still significant gaps in our knowledge. Further work is needed if we are to improve our understanding of the aetiology of the disease and improve the results of treatment.

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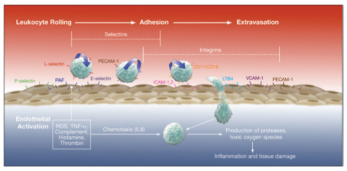

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