

MECHANISMS OF VASCULAR DISEASE:

A REFERENCE BOOK FOR VASCULAR SPECIALISTS



EDITED BY ROBERT FITRIDGE AND MATTHEW THOMPSON
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Mechanisms of Vascular Disease

Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

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Table of Contents

Contributors vii

Detailed Contents xi

1. Endothelium 1
Paul Kerr, Raymond Tam, Frances Plane (Calgary, Canada)
2. Vascular smooth muscle structure and function 13
David Wilson (Adelaide, Australia)
3. Atherosclerosis 25
Gillian Cockerill, Qingbo Xu (London, UK)
4. Mechanisms of plaque rupture 43
Ian Loftus (London, UK)
5. Current and emerging therapies in atheroprotection 79
Stephen Nicholls, Rishi Puri (Cleveland, USA)
6. Molecular approaches to revascularisation in peripheral vascular disease 103
Greg McMahon, Mark McCarthy (Leicester, UK)
7. Biology of restenosis and targets for intervention 115
Richard Kenagy (Seattle, USA)
8. Vascular arterial haemodynamics 153
Michael Lawrence-Brown, Kurt Liffman, James Semmens, Ilija Sutalo (Melbourne & Perth, Australia)
9. Physiological haemostasis 177
Simon McRae (Adelaide, Australia)
10. Hypercoagulable states 189
Simon McRae (Adelaide, Australia)
11. Platelets in the pathogenesis of vascular disease and their role as a therapeutic target 201
Sandeep Prabhu, Rahul Sharma, Karlheinz Peter (Melbourne, Australia)
12. Pathogenesis of aortic aneurysms 227
Jonathan Golledge, Guo-Ping Shi, Paul Norman (Townsville & Perth, Australia; Boston, USA)
13. Pharmacological treatment of aneurysms 247
Matthew Thompson, Janet Powell (London, UK)
14. Aortic dissection and connective tissue disorders 255
Mark Hamilton (Adelaide, Australia)
15. Biomarkers in vascular disease 277
Ian Nordon, Robert Hincliffe (London, UK)
16. Pathophysiology and principles of management of vasculitis and Raynaud's phenomenon 295
Martin Veller (Johannesburg, South Africa)
17. SIRS, sepsis and multiorgan failure 315
Vishwanath Biradar, John Moran (Adelaide, Australia)
18. Pathophysiology of reperfusion injury 331
Prue Cowled, Robert Fitridge (Adelaide, Australia)
19. Compartment syndrome 351
Edward Choke, Robert Sayers, Matthew Bown (Leicester, UK)
20. Pathophysiology of pain 375
Stephan Schug, Helen Daly, Kathryn Stannard (Perth, Australia)

21. Postamputation pain 389
Stephan Schug, Gail Gillespie
(Perth, Australia)
 22. Treatment of neuropathic pain 401
Stephan Schug, Kathryn Stannard
(Perth, Australia)
 23. Principles of wound healing 423
Gregory Schultz, Gloria Chin,
Lyle Moldauer, Robert Diegelmann
(Florida, USA)
 24. Pathophysiology and principles of
varicose veins 451
Andrew Bradbury (Birmingham, UK)
 25. Chronic venous insufficiency and leg
ulceration: Principles and vascular
biology 459
Michael Stacey (Perth, Australia)
 26. Pathophysiology and principles of
management of the diabetic foot 475
David Armstrong, Timothy Fisher,
Brian Lepow, Matthew White,
Joseph Mills (Tucson, USA)
 27. Lymphoedema – Principles, genetics
and pathophysiology 497
Matt Waltham (London, UK)
 28. Graft materials past and future 511
Mital Desai, George Hamilton
(London, UK)
 29. Pathophysiology of vascular graft
infections 537
Mauro Vicaretti (Sydney, Australia)
- Index 549

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Detailed Contents

CHAPTER 1 – ENDOTHELIUM

Paul Kerr, Raymond Tam, Frances Plane

- Introduction 1
- Endothelium-dependent regulation of vascular tone 2
- Angiogenesis 7
- Haemostasis 8
- Inflammation 9
- Conclusions 10
- References

CHAPTER 2 – VASCULAR SMOOTH MUSCLE STRUCTURE AND FUNCTION

David Wilson

- Introduction 13
- Smooth muscle (vascular) structure
- Cytoskeleton 14
- Contractile myofilament
- Functional regulation of vascular smooth muscle: Neuronal, hormonal, receptor mediated 15
- Smooth muscle function 17
- Myofilament basis of smooth muscle contraction and relaxation
- Smooth muscle contraction and relaxation 18
- Ion channels important in the regulation of smooth muscle function
- Regulation of cellular Ca²⁺
- Sources of cytosolic Ca²⁺ entry 19
- Potassium channels
- Endothelial regulation of smooth muscle vasodilatation 20

Smooth muscle proliferation and vascular remodeling 20

Summary 22

References

CHAPTER 3 – ATHEROSCLEROSIS

Gillian Cockerill, Qingbo Xu

Introduction 25

Atherosclerotic lesions 26

Fatty streaks

Plaque or atheroma

Hypercholesterolemia and oxidised-LDL 27

High-density lipoproteins role in atheroprotection 28

Hypertension and biomechanical stress 29

Biomechanical stress-induced cell death 30

Biomechanical stress and inflammation 31

Biomechanical stress-induced smooth muscle cell proliferation 32

Infections and heat shock proteins

Infections

Heat shock proteins 33

Infections and HSP expression

Infections, sHSP and innate immunity 34

Immune responses 36

MHC class II antigens and T cells

Oxidised LDL as a candidate antigen

HSP60 as a candidate antigen 37

B2-glycoprotein Ib as a candidate antigen

Inflammation

C-reactive protein	38
CD40/CD40L	
Summary and perspectives	39
References	

CHAPTER 4 – MECHANISMS OF PLAQUE RUPTURE

Ian Loftus

Introduction	43
Evidence for the ‘plaque rupture theory’	44
Coronary circulation	
Cerebral circulation	
The role of individual components of the arterial wall	
The endothelium	45
The lipid core	47
The cap of the plaque	49
Smooth muscle cells and collagen production	50
Macrophages and collagen degradation	51
The vessel lumen	56
The role of angiogenesis in plaque rupture	
The role of infectious agents in plaque rupture	57
Risk prediction of plaque instability	58
Imaging	
Blood markers	59
Therapy aimed at plaque stabilisation	
HMG Co-A reductase inhibitors	60
MMP inhibition	
Tissue inhibitors of metalloproteinases (TIMPs)	61
Synthetic MMP inhibitors	
Doxycycline	
ACE inhibitors	
Summary	62
References	63

CHAPTER 5 – CURRENT AND EMERGING THERAPIES IN ATHEROPROTECTION

Stephen Nicholls, Rishi Puri

Background	79
Pathology	
Risk factor modification	80
Statins, LDL lowering and C-reactive protein	
The complexity of HDL	84
The controversy of triglycerides	87
Hypertension	
Risk factor modification in the diabetic patient	89
Glycaemic control	
Global risk factor reduction in diabetics	91
The metabolic syndrome	92
Future targets	93
Conclusion	
References	94

CHAPTER 6 – MOLECULAR APPROACHES TO REVASCULARISATION IN PERIPHERAL VASCULAR DISEASE

Greg S McMahon, Mark J McCarthy

Introduction	103
Mechanisms of vascular growth	
Vasculogenesis	
Angiogenesis	104
Neovessel maturation	105
Microvascular network maturation	106
Arteriogenesis	
Therapeutic induction of vascular growth	107
Delivery of molecular activators of vascular growth	
Angiogenic activators	108
Arteriogenic activators	109
Clinical trials for angiogenic therapy of peripheral vascular disease	
Conclusions	110
References	

CHAPTER 7 – BIOLOGY OF RESTENOSIS AND TARGETS FOR INTERVENTION

Richard Kenagy

Introduction 115

Mechanisms of restenosis

Thrombosis 116

Remodelling

Intimal hyperplasia 123

Sequence of events after injury

Origin of intimal cells 125

Inflammation 126

Role of ECM production 127

The contribution of specific factors to restenosis

Growth factors/cytokines

Inhibitors 128

Coagulation and fibrinolytic factors 129

Matrix metalloproteinases

Extracellular matrix/receptors

Targets for intervention 130

Intracellular signalling molecules

mTOR and microtubules

Transcription factors

miRNA 131

Inflammation targets

Brachytherapy

Extracellular targets and cell-based therapies

Angiotensin pathway

Cell-based therapies 132

Differential effects on endothelium and SMCs

Delivery devices

Prevention versus reversal of restenosis

Conclusions 133

References 134

CHAPTER 8 – VASCULAR ARTERIAL HAEMODYNAMICS

Michael Lawrence Brown, Kurt Liffman, James Semmens, Ilija Sutalo

Introduction 153

Laplace's law of wall of tension 154

Newtonian fluid 155

Non-Newtonian fluid

Poiseuille flow 158

Bernoulli's equation

Young's modulus and pulsatile flow 159

Mass conversion 161

Reynold's number

Arterial dissection, collateral circulation and competing flows 163

Shear stress and pressure 164

Forces on graft systems 165

Case 1 – The cylindrical graft 168

Case 2 – The windsock graft

Case 3 – The curved graft 169

Case 4 – The symmetric bifurcated graft

Computational modelling 170

Recent development and future directions 171

Conclusions 172

References 173

CHAPTER 9 – PHYSIOLOGICAL HAEMOSTASIS

Simon McRae

Introduction 177

Primary haemostasis

Platelets

Platelet adhesion

Platelet activation and shape change 179

Platelet aggregation 180

Interactions between primary and secondary haemostasis 181

Secondary haemostasis

The coagulation cascade 182

Initiation 183

Amplification

Propagation 184

Normal inhibitors of coagulation

Fibrinolysis 185

Conclusions 186

References

CHAPTER 10 – HYPERCOAGULABLE STATES

Simon McRae

Introduction 189

Classification of thrombophilia

Inherited thrombophilia 190

Type 1 conditions

Antithrombin deficiency

Protein C and Protein S deficiency

Type 2 conditions 191

Factor V Leiden

The prothrombin (G20210A) gene mutation

FVL/PGM compound heterozygotes

Other inherited conditions

Acquired thrombophilia 192

Antiphospholipid antibodies

Heparin induced thrombocytopenia

Myeloproliferative disorders 193

Potential reasons for performing thrombophilia testing

Patients with venous thrombosis and their relatives

Providing an understanding of the aetiology of a thrombotic event

Determining risk of recurrence and therefore optimal duration of anticoagulation 194

Determining the need for primary prophylaxis in asymptomatic family members 195

Making decisions regarding the use of the oral contraceptive pill 196

Determining the need for thromboprophylaxis during pregnancy

Patients with arterial thrombosis

Potential detrimental effects of thrombophilia testing 197

Conclusion

References

CHAPTER 11 – PLATELETS IN THE PATHOGENESIS OF

VASCULAR DISEASE AND THEIR ROLE AS A THERAPEUTIC TARGET

*Sandeep Prabhu, Rahul Sharma,
Karlheinz Peter*

Introduction 201

Platelet function – Adhesion and activation

Platelet adhesion 202

Platelet activation 203

Mediators of platelet activation and ‘outside in’ signalling

Thrombin and collagen 204

Adenosine diphosphate (ADP)

Thromboxane A2 (TXA2)

Adrenaline 206

Second messenger systems 207

Physiological consequences of platelet activation

The GP IIb/IIIa receptor and ‘inside-out’ signalling

Granule exocytosis 208

Activation-induced conformational change of platelets

Platelets and atherosclerosis 209

Role of platelets in the initiation of the atherosclerosis

Role of the platelets in the progression of the atherosclerosis

Role of platelets in vulnerable plaques and plaque rupture

Current and future anti-platelet agents 210

Aspirin (salicylic acid)

Thienopyridines 211

Clopidogrel

Prasugrel 213

Ticlopidine

Ticagrelor

GPIIb/IIIa Antagonists

Other anti-platelet agents and promising new developments 214

Platelet function testing 215

Light-transmission aggregometry

Whole blood aggregometry 217
 VerifyNow® Assay
 Flow cytometry 218

References

CHAPTER 12 – PATHOGENESIS OF AORTIC ANEURYSMS

*Jonathan Golledge, Guo-Ping Shi,
 Paul E Norman*

Introduction 227

Differences between thoracic and abdominal aortic aneurysms 228

Summary of current theories and stages of AAA evolution

Atherosclerosis and AAA

Immune mechanisms in AAA 229

Extracellular matrix dysfunction 232

Infection 233

Biomechanical forces

Angiogenesis

Intra-luminal thrombus

Extracellular matrix proteolysis 234

Genetics 236

AAA rupture 237

Biomechanical factors in aneurysms rupture

The role of enzymes in AAA rupture

Role of intraluminal thrombus in aneurysm rupture 238

Future research

References

CHAPTER 13 – PHARMACOLOGICAL TREATMENT OF ANEURYSMS

Matthew Thompson, Janet T Powell

Background 247

Screening programmes

Pathophysiology 248

Therapeutic strategies

Beta blockade

Modification of the inflammatory

response 249

Non-steroidal anti-inflammatories

Matrix metalloproteinase (MMP)

inhibition

Anti-chlamydial therapy 250

Drugs acting on the renin/angiotensin axis

HMG Co-A reductase inhibitors 251

The future – Data from recent

experimental studies

References

CHAPTER 14 – PATHOPHYSIOLOGY OF AORTIC DISSECTION AND CONNECTIVE TISSUE DISORDERS

Mark Hamilton

Introduction 255

Embryology of thoracic aorta and arch vessels

Haemodynamics of thoracic compared to abdominal aorta 257

Sizes of normal aorta

Classification of aortic syndromes

Acute/Chronic

DeBakey classification of class 1 dissection – Type 1, 2, and 3

Stanford classification 258

European task force

Pathogenesis of thoracic aortic dissection

Classical thoracic aortic dissection (class 1 dissection) 260

Intramural haematoma (class 2 aortic dissection) 261

Penetrating aortic ulcer (class 4 aortic dissection) 262

Complications of acute aortic syndromes 263

Visceral ischaemia /malperfusion syndromes

Fate of the false lumen

Aneurysmal degeneration and rupture 264

Connective tissue disorders and acute aortic syndromes

Marfan syndrome	
Fibrillin and Marfan syndrome	265
The role of transforming growth factor beta in development of the vascular system in health and disease	266
Ehlers-Danlos syndrome	267
Diagnosis of Ehlers-Danlos syndrome	268
Loeys-Deitz syndrome	270
Familial thoracic aortic aneurysm disease	271
Bicuspid aortic valve	273
Turners Syndrome	
Summary	274
Reference list	

CHAPTER 15 – BIOMARKERS IN VASCULAR DISEASE

Ian M Nordon, Robert J Hinchliffe

Introduction	277
What is a biomarker?	
Types of biomarkers	
A classical clinical example	278
Potential value of biomarkers in vascular disease	279
Biomarker discovery steps	280
AAA biomarkers	
Circulating extracellular matrix markers	281
Matrix-degrading enzymes	283
Proteins associated with thrombosis	
Markers of inflammation	284
Biomarkers of AAA rupture	285
Biomarkers following endovascular repair	
Inflammation	287
Lipid accumulation	
Apoptosis	
Thrombosis	
Proteolysis	288
Challenges in biomarkers discovery	
Future work	
Conclusion	289
References	

CHAPTER 16 – PATHOPHYSIOLOGY AND PRINCIPLES OF MANAGEMENT OF VASCULITIS AND RAYNAUD'S PHENOMENON

Martin Veller

Vasculitides	295
Introduction	
Classification of vasculitides	296
Clinical presentation of vasculitides	
Investigations of vasculitides	
Principles of treatment of vasculitides	297
The vasculitides of specific interest to vascular surgeons	298
Giant cell arteritis	
Takayasu's arteritis	299
Thromboangitis obliterans (Buerger's disease)	300
Behcet's disease	301
Polyarteritis nodosa	302
Vasculitides secondary to connective tissue diseases	303
Systemic lupus erythematosus (SLE)	
Antiphospholipid antibody syndrome (APS)	304
Rheumatoid arthritis	305
Scleroderma	
Infective vasculitides	306
Human immunodeficiency virus (HIV)	
Pathophysiology and principles of Raynaud's phenomenon	307
Prevalence of Raynaud's phenomenon	308
Clinical findings in Raynaud's phenomenon	309
Diagnosis of Raynaud's phenomenon	
Prognosis	310
Treatment	
Recommendations	311
References	312

CHAPTER 17 – SIRS, SEPSIS AND

MULTIORGAN FAILURE*Vishwanath Biradar, John Moran***Epidemiology 315****Historical perspectives and definition 316****Risk factors for sepsis 317**

Causative agents

Pathophysiology of sepsis

innate immunity and toll-like receptors (TLRs) 319

Proinflammatory response

Coagulation cascade

Multorgan dysfunction syndrome (MODS) 320

Epithelial and endothelial dysfunction

Immune suppression and apoptosis

Sepsis, circulatory failure and organ dysfunction

Management 322

Steroids 323

Recombinant human activated protein C (rhAPC) 324

Glucose control 325

Renal replacement therapy

3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (HMG-CoA) 326

Other adjuvant therapies in sepsis

Cytokines and anticytokine therapies

Pooled immunoglobulin (IVIG)

Acute respiratory distress syndrome (ARDS) 327

References**CHAPTER 18 –
PATHOPHYSIOLOGY OF
REPERFUSION INJURY***Prue Cowled, Rob Fitridge***Introduction 331****Ischaemia**

ATP and mitochondrial function

Gene expression during ischaemia 332

Reperfusion 333

Reactive oxygen species

Eicosanoids 334

Nitric Oxide 335

Endothelin 336

Cytokines

Neutrophil and endothelial interactions 338

Complement activation 340

Tissue destruction 341

Proteases and metalloproteinases

Apoptotic cell death during ischaemia-reperfusion injury

No-reflow phenomenon 342

Therapeutic approaches to IRI

Ischaemic preconditioning

Ischaemic post-conditioning 343

Conditioning effects of volatile anaesthetics

Pharmacological treatments 344

Summary 345**References****CHAPTER 19 – COMPARTMENT
SYNDROME***Edward Choke, Robert Sayers, Matthew Bown***Definition 351****Acute limb compartment syndrome**

Incidence

Anatomy/physiology 352

Aetiology/pathophysiology

Clinical presentation 354

Investigation 355

Treatment 357

Complication of LCS 359

Outcome 360

Acute abdominal compartment syndrome

Incidence 361

Aetiology

Pathological effects of raised intra-abdominal pressure 362

Clinical presentation 363

Investigation

Treatment 364

Complications of surgical decompression

Outcome 367

References 368

CHAPTER 20 – PATHOPHYSIOLOGY OF PAIN

Stephan Schug, Helen Daly, Kathryn Stannard

Introduction 375

Peripheral mechanisms

Nociception/transduction

Conduction 376

Spinal cord mechanisms

Ascending systems 377

Descending control

Pain modulation 378

Peripheral sensation

Central sensitisation in the dorsal horn

Neuropathic pain 379

Mechanisms of neuropathic pain

Peripheral mechanisms

Spontaneous ectopic discharge

Altered gene expression

Spared sensory neurons

Involvement of the sympathetic nervous system 380

Collateral sprouting

Effects of bradykinin

Central mechanisms

Wind up

Central sensitization 381

Central disinhibition

Expansion in receptive field size (recruitment)

Immediate early gene expression

Anatomical re-organisation of the spinal cord

Contribution of glial cells to pain conditions 382

Symptoms of neuropathic pain

Stimulus-dependent pain

Stimulus-independent pain 383

Sympathetically maintained pain (SMP)

Neuropathic pain syndromes

Peripheral neuropathies

Central neuropathies 385

References

CHAPTER 21 – POST-AMPUTATION PAIN

Stephan Schug, Gail Gillespie

Introduction 389

Classification and incidence of post-amputation pain syndromes

Stump pain

Phantom sensation 390

Phantom limb pain

Pathophysiology of post-amputation pain syndromes

Peripheral factors

Spinal factors 391

Supraspinal factors

Current pathophysiological model of post-amputation pain syndromes 392

Prevention of post-amputation pain

Perioperative lumbar epidural blockade

Peripheral nerve blockade 393

NMDA antagonists

Evaluation of the patient with post-amputation pain syndromes

Examination

Therapy of post-amputation pain syndromes 394

Calcitonin

Ketamine

Analgesic and Co-analgesic compounds

Opioids 395

Gabapentin

Clonazepam

Lidocaine

Carbamazepine

Tricyclic antidepressants (TCA)

Selective serotonin reuptake inhibitors

Baclofen

Capsaicin

Symptomatic treatment of pain components 396

Neuropharmacological therapies

Invasive therapies
 Electroconvulsive therapy (ECT)
 Nerve blockade
 Spinal cord stimulation
 Implantable intrathecal delivery systems
 Dorsal root entry zone (DREZ) lesions
 Psychological therapy 397

Future aims

References

CHAPTER 22 – TREATMENT OF NEUROPATHIC PAIN

Stephan Schug, Kathryn Stannard

Introduction 401

Principles of treatment

Pharmacological treatment 402

Opioids

Recommendations for clinical use of opioids

Tramadol

Mechanism of action

Efficacy 403

Adverse effects

Recommendations for clinical use of tramadol in neuropathic pain

Antidepressants

Tricyclic antidepressants (TCAs)

Mechanism of action 404

Adverse effects

Selective serotonin re-uptake inhibitors (SSRIs)

Serotonin/Noradrenaline reuptake inhibitors (SNRIs) 405

Recommendations for clinical use of antidepressants as analgesics

Anticonvulsants

Mechanism of action 406

Individual medications

Clonazepam

Gabapentin

Pregabalin 407

Carbamazepine

Sodium valproate 408

Phenytoin

Lamotrigene

Recommendations for clinical use of anticonvulsants as analgesics

Local anaesthetics and antiarrhythmics 409

Mechanism of action

Lignocaine

Mexiletine

Recommendations for clinical use of lignocaine and mexiletine in neuropathic pain

N-methyl-D-aspartate-receptor antagonists (NMDA)

Ketamine 410

Other NMDA antagonists

Miscellaneous compounds for systemic use

Clonidine

Efficacy

Baclofen

Levodopa 411

Cannabinoids

Topical treatments

Lignocaine 5% medicated plaster

Capsaicin 412

Mechanism of action

Efficacy

Non-pharmacological therapy

Transcutaneous electrical nerve stimulation (TENS)

Spinal cord stimulation (SCS) 413

Sympathetic nerve blocks

Neurosurgical destructive techniques

Cognitive behaviour therapy

References 414

CHAPTER 23 – PRINCIPLES OF WOUND HEALING

Gregory Schultz, Gloria Chin, Lyle Moldawer, Robert Diegelmann

Introduction 423

Phases of acute wound healing

Haemostasis

- Inflammation 426
 - Neutrophils 427
 - Macrophages 428
- Proliferative phase 429
 - Fibroblast migration 430
 - Collagen and extracellular matrix production
 - Angiogenesis 431
 - Granulation 432
 - Epithelialization
 - Remodelling 433
- Summary of acute wound healing 435
- Comparison of acute and chronic wounds**
 - Normal and pathological responses to injury
 - Biochemical differences in the molecular environments of healing and chronic wounds 436
 - Biological differences in the response of chronic wound cells to growth factors 439
- From bench to bedside**
 - Role of endocrine hormones in the regulation of wound healing
 - Molecular basis of chronic non-healing wounds
 - Chronic venous stasis ulcers 441
 - Pressure ulcers
- Future concepts for the treatment of chronic wounds 442**
 - Bacterial biofilms in chronic wounds 443
- Conclusion 445**
- References**

CHAPTER 24 – PATHOPHYSIOLOGY AND PRINCIPLES OF MANAGEMENT OF VARICOSE VEINS

Andrew Bradbury

- Introduction 451**
- Anatomy**
- Histology 452**
- Physiology**

- Varicose veins 453**
- Valvular abnormalities**
- Muscle pump failure 455**
- Venous recirculation**
- Recurrent varicose veins**
 - New varicose veins
 - Persistent varicose veins
 - True recurrent varicose veins 456
- Cellular and molecular biology of varicose veins**
- Conclusion 457**
- References**

CHAPTER 25 – CHRONIC VENOUS INSUFFICIENCY AND LEG ULCERATION: PRINCIPLES AND VASCULAR BIOLOGY

Michael Stacey

- Definitions 459**
 - Chronic venous insufficiency
 - Leg ulceration
 - Assessment of cause of leg ulceration 460
- Epidemiology 461
- Pathophysiology
 - Venous abnormality
 - Effect of ambulatory venous hypertension on the tissues in the leg 463
 - Influence of venous disease on the wound healing process 465
 - Genetic associations with venous ulceration 466
- Assessment of venous function 467**
- Treatment of venous ulceration**
 - Compression therapy
 - Dressings 468
 - Surgery
 - Prevention of venous ulcer recurrence 470
 - Sclerotherapy and other techniques to obliterate surface and perforating veins
 - Other therapies 471
- References**

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

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

- Introduction** 475
- Pathophysiology of the diabetic foot** 476
- Neuropathy
 - Structural abnormalities/gait abnormalities
 - Angiopathy 478
- Diagnosis**
- History and rapid visual screening
 - Neurological examination 479
 - Monofilament testing
 - Vibration testing
 - Dermatologic examination 480
 - Anatomy of occlusive disease – vascular examination
 - Prediction of wound healing: assessment of perfusion 481
 - Arterial imaging
 - Soft tissue imaging 482
- Classification systems** 483
- Diabetes mellitus foot risk classification
 - University of Texas wound classification system
- Clinical problems and principles of management** 484
- Ulceration
 - Epidemiology and risk factors
 - Offloading
 - Non-vascular surgical treatment 485
 - Class I – Elective 486
 - Class II – Prophylactic
 - Class III – Curative
 - Class IV – Emergency (urgent)
 - Post-operative management
 - Infections 487
 - Charcot arthropathy
- Prevention** 490
- Conclusion** 492
- References**

CHAPTER 27 – LYMPHOEDEMA
– PRINCIPLES, GENETICS AND
PATHOPHYSIOLOGY

Matt Waltham

- Introduction** 497
- Classification of lymphoedema**
- Classification of primary lymphoedema 498
- The genetics of lymphangiogenesis in primary lymphoedema** 500
- Milroy's disease
 - Lymphoedema – distichiasis syndrome 501
 - Hypotrichosis – lymphoedema – telangiectasia syndrome 502
 - Meige disease (primary non-syndromic lymphoedema)
 - Other primary lymphoedema disorders 503
- Structure and development of the lymphatic circulation**
- Clinical aspects of lymphoedema** 505
- Summary**
- References**

CHAPTER 28 – GRAFT
MATERIALS PAST AND FUTURE

Mital Desai, George Hamilton

- The pathophysiology of graft healing** 511
- The peri-anastomotic area
 - Healing of prosthetic grafts 512
 - The healing process of the anastomosis
 - Graft porosity and permeability
- Physical properties of prosthetic materials** 514
- Tubular compliance
 - Anastomotic compliance mismatch
 - The compliance hypothesis of graft failure
- Synthetic grafts** 515
- Newer developments of Dacron grafts
 - Modifications and newer developments of PTFE grafts 517
 - Polyurethane grafts

Newer developments of polyurethane vascular grafts	518
Biological vascular grafts	519
Newer developments of biological vascular grafts	520
Prosthetic graft modifications	
Modifications to reduce graft infection	
Modifications to improve patency	521
Nanocomposite grafts	
Endothelial cell seeding	522
Single stage seeding	
Two stage seeding	
Vascular tissue engineering	
Non-degradable polymer and cell seeding	523
Bioresorbable and biodegradable polymers	
Combined bioresorbable and tissue engineered grafts	524
Mechanical conditioning of seeded vascular cells	
Alternative scaffolds	
Tissue-engineered grafts	525
Graft materials for aortic endografts	526
The future	
References	527

CHAPTER 29 – PATHOPHYSIOLOGY OF VASCULAR GRAFT INFECTIONS

Mauro Vicaretti

Introduction	537
Natural history of prosthetic vascular graft infections	
Mechanism of graft contamination at operation	538
Pathogenesis of graft infections	
Bacteriology of vascular graft infections	
Investigations for detection of prosthetic graft infections	539
History and physical examination	
Laboratory investigations	
Diagnostic imaging	540
Management of prosthetic graft infections	
Prevention	
Reduction of prosthetic vascular graft infection with rifampicin bonded gelatin sealed Dacron	541
Established infection	
Antibiotic therapy	
Operative management	
Conclusion	542
References	

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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	Adrenocorticotrophic 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
β 2-GPI	β 2-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	Calcitonin 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-1 α	Interleukin-1 alpha
IL-1 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 <i>Staphylococcus aureus</i>
MRSE	Methicillin resistant <i>Staphylococcus epidermidis</i>
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
T α CE	TNF α 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} genetics⁶ 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 layers¹⁴ 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

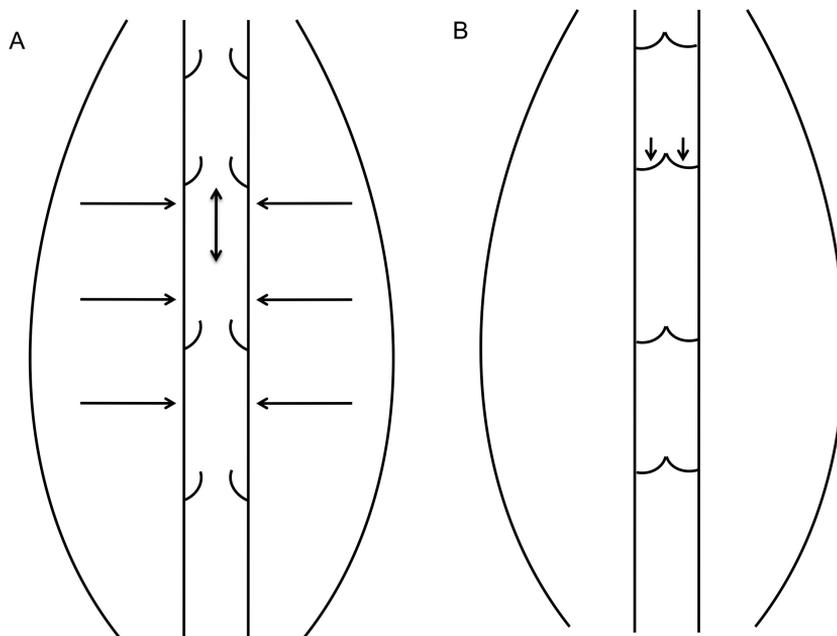


FIGURE 24.1: Influence of calf muscle pump and valves in venous return.

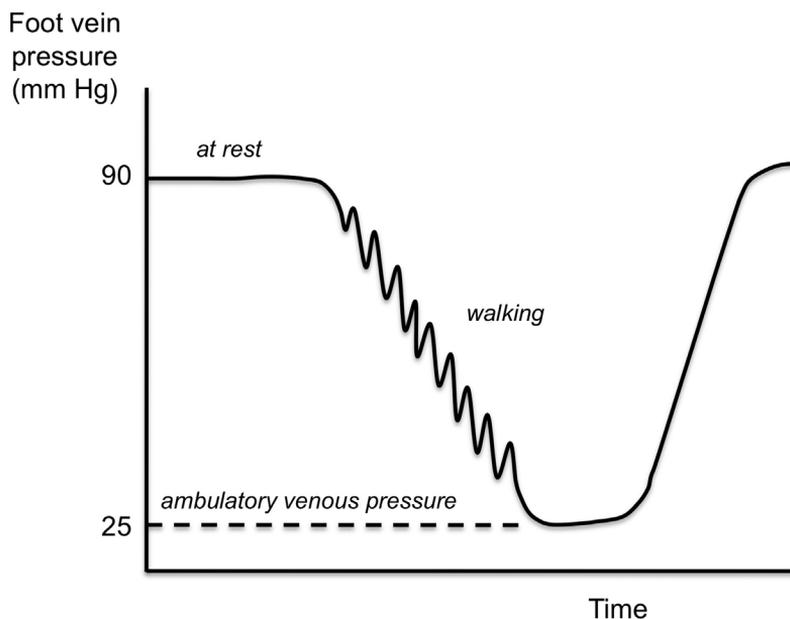


FIGURE 24.2: Resting and ambulatory venous pressure at the ankle in health.

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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MECHANISMS OF VASCULAR DISEASE

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