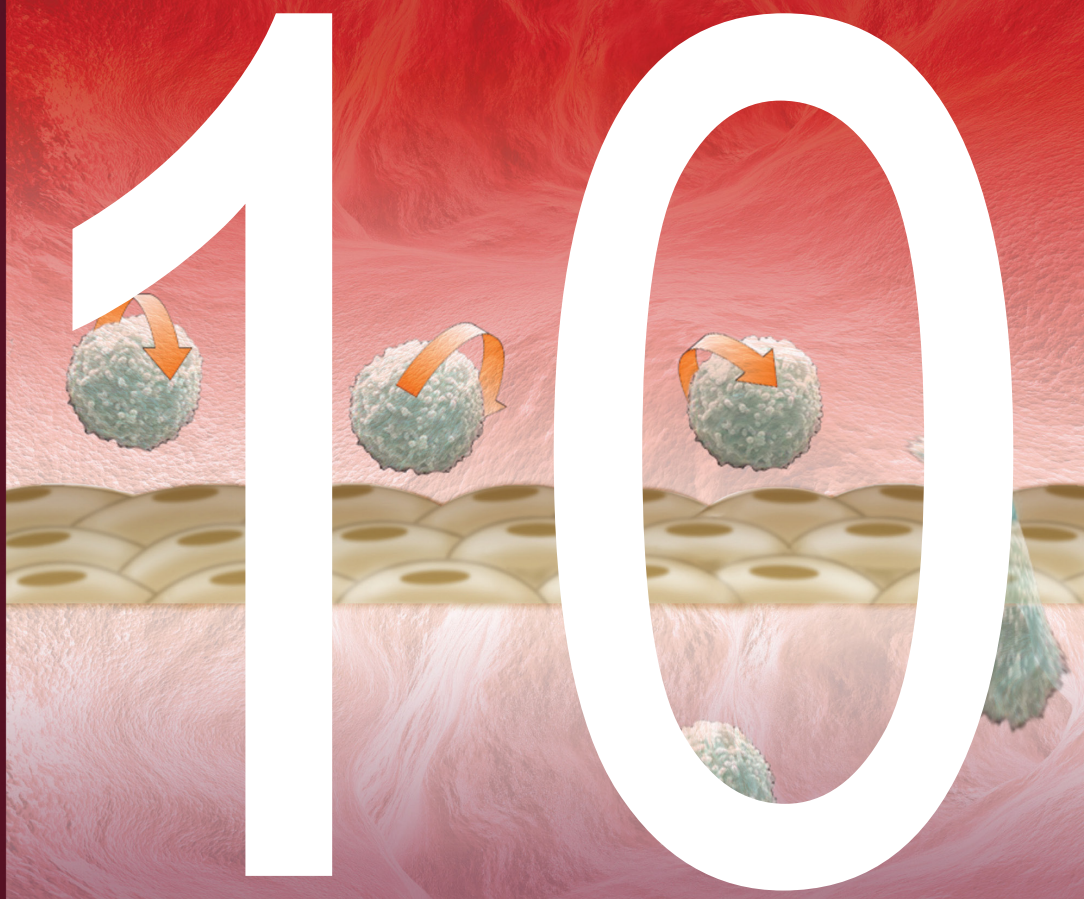
Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists



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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 Hinchliffe (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 Moldawer, 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 Ca^{2+}
Sources of cytosolic Ca^{2+} 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 immuntiy 34
Immune responses 36
MHC class II antigens and T cells
Oxidised LDL as a candidate antigen
HSP60 as a candidate antigen 37
B2-gylcoprotein Ib as a candidate antigen
Inflammation

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

CHAPTER 4 – MECHANSIMS 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 trigylcerides 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 deleopments 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
Multiorgan 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 (recuruitment)
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 behavious 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 insuffiency
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 arthopathy
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 lymphangiogensis 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	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

10 • Hypercoagulable States

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INTRODUCTION

Abnormal thrombus formation is central to the acute pathophysiology of both arterial and venous disease. Formation of thrombus superimposed upon the surface of ruptured atherosclerotic plaque, producing vessel occlusion and resulting tissue ischemia, is the common mechanism leading to acute symptoms and presentation in patients with arterial disease. Likewise deep vein thrombosis and pulmonary embolism, important community causes of morbidity and mortality, both result from abnormal thrombus formation in the venous circulation. An understanding of conditions that may predispose to abnormal thrombus formation, including a knowledge of how the presence of these conditions may or may not impact on patient management, is important for all clinicians involved in the management of vascular disease.

First used in 1937,[1] and then also in the first description of inherited antithrombin deficiency, the term 'thrombophilia' can be defined as an increased tendency to develop thrombosis, which may be either acquired or inherited.[3] Thrombophilic conditions vary both in prevalence and in the magnitude of the associated increase in risk of thrombosis. The discovery during the 1990's of the high prevalence factor V Leiden and prothrombin gene point mutations that predispose to thrombosis,[4,5] meant that an underlying thrombophilic condition could be found in approximately 50% of unselected patients with venous thrombosis.[6] This fact, along with the belief that the presence of such a condition may influence prognosis and may therefore help guide patient management, has led to a significant increase in laboratory testing for inherited thrombophilia.[7] Recent data has however suggested that testing for thrombophilia, particularly the more common inherited conditions, is unlikely to influence the management of the majority of patients in whom it is performed,[8] and guidelines as a result have recommended against widespread testing in unselected patients.[9]

This chapter will first describe individual inherited and acquired conditions that predipose to an increased risk of thrombosis. The potential clinical rationale will then be outlined, and finally current evidence and recommendations regarding the clinical utility of laboratory testing in specific clinical scenarios will be discussed.

CLASSIFICATION OF THROMBOPHILIA

Thrombophilic conditions can be broadly classified as being either inherited or acquired and will be described in these two broad categories.

Inherited Thrombophilia

In 2003 Crowther and colleagues proposed a further sub-classification of inherited thrombophilia into either type 1 conditions that involve a deficiency of one of the naturally occurring inhibitors of coagulation, and type 2 conditions that result in a gain of function or an increase in the level of one of the procoagulant proteins.[10] The distinction is of clinical relevance as the majority of patients with a type 1 condition will develop a symptomatic episode of venous thrombosis during their lifetime, whereas the majority of individuals with a type 2 condition will not. Similarly the presence of a type 1 thrombophilia clearly increases the risk of recurrent venous thrombosis and therefore influences decision making regarding the duration of anticoagulation, where again type 2 conditions in isolation do not strongly influence recurrence risk and their absence or presence should not be used in isolation to determine duration of treatment.[12]

Type 1 Conditions

Antithrombin Deficiency

Antithrombin (AT) is a single chain plasma glycoprotein belonging to the serine protease inhibitor superfamily (serpins).[3] It is a physiological inhibitor of thrombin and other activated coagulation factors (factors Xa, IXa, XIa). Heparin exerts is anticoagulant effect by binding to AT, resulting in a conformational change that increases the affinity of AT for thrombi more than 1000-fold. Familial AT deficiency, described in 1965, was the first identified inherited thrombophilia.[2,3] Individuals with AT deficiency typically have AT levels ranging between 40-80%, and estimates of the prevalence of the condition range from 0.02% to 0.15% of the general population.[13] Approximately 0.5-2% of unselected individuals with venous thromboembolism (VTE) will have AT deficiency.[14] Estimates of the increase in risk of VTE associated with AT deficiency vary from 5 to 20-fold.

Protein C and Protein S Deficiency

Protein C (PC) and protein S (PS) are both vitamin K dependent plasma glycoproteins synthesized in the liver.[3] When activated by thrombin, a process potentiated by the binding of thrombin to thrombomodulin, PC is converted to the active serine protease, activated protein C (APC).[15] In combination with its cofactor, PS, APC inactivates both factor Va and VIIIa, and plays a central role in controlling the procoagulant pathway. In plasma, PS circulates both free (40%) and bound to the C4b-binding protein (60%). It is the free form of PS that has cofactor activity.

Inherited PC deficiency was first described as a cause of venous thrombosis in 1981,[16] whereas PS deficiency was initially described as a cause of venous thrombosis in 1984.[17] PC and PS deficiency both have type I (quantitative deficiency) and type II (qualitative deficiency) subgroups, and in addition a type III PS deficiency state with normal total circulating but reduced free levels can occur. The estimated prevalence of heterozygous PC deficiency in the general population is between 0.2 and 0.4%,[18] and many of these individuals have no history of thrombosis. The community prevalence of PS deficiency is estimated at approximately 0.2%.[19] PC deficiency is found in 1–3%, and PS deficiency in 1–7% of unselected patients diagnosed with VTE. Estimates

from case-control and family cohort studies of the increase in risk of VTE associated with PC deficiency range from 5.0 to 10-fold, and 8.5 to 30-fold for PS deficiency.[8]

Type 2 Conditions

Factor V Leiden

In 1993, Dahlback and colleagues noted that plasma taken from a family with a strong history of venous thrombosis was resistant to the anticoagulant effect of APC.[20] This phenotype became known as APC Resistance. A point mutation in the factor V gene (G1691A) resulting in an amino acid change (Arg^{506} to Gly) at the cleavage site involved in the inactivation of factor Va by activated protein C was identified as the cause in more than 90% of individuals and became known as factor V Leiden (FVL).[4,21] The FVL mutation has a high community prevalence with 3 to 7% of Caucasians being heterozygous for the mutation, although a lower incidence is found in other ethnic groups.[22] It is the most commonly identified cause of inherited thrombophilia, being present in 12 to 20% of unselected patients with VTE,[23] and up to 50% of individuals from thrombophilic families presenting with venous thrombosis. The heterozygous state is a relatively low risk thrombophilia being associated with a 3 to 7 fold increase in risk of VTE,[8] with one study finding greater than 90% of individuals remaining event free by the age of 65.[24] Unlike individuals homozygous for natural anticoagulant deficiency states, homozygosity for FVL does not result in a catastrophic thrombotic state early in life, and it is estimated that 0.1% of the population are FVL homozygotes.[8] The risk of VTE, however, in homozygotes for FVL is greater than that in heterozygotes, with estimates of the magnitude of risk ranging form 25 to 80-fold that of the healthy controls.

The Prothrombin (G20210A) Gene Mutation

In 1996, Poort and colleagues described a common mutation (G20210) of the prothrombin gene, which has become known as the prothrombin gene mutation (PGM).[5] Located in the 3' untranslated region of the gene, the mutation is associated with increased mean plasma prothrombin levels due to increased efficiency of 3' end processing of the gene resulting in accumulation of the encoded mRNA.[26] The prevalence of the mutation in Caucasian populations is approximately 2%, and it is rare in Asian and African populations.[27] In unselected patients with venous thrombosis the mutation has been found in between 4.0 to 7.1% of individuals,[8] and 18% of individuals with a strong family history of VTE. The PGM is a relatively weak risk factor for VTE, being associated with a 2 to 5 fold increase in risk.[8]

FVL/PGM compound heterozygotes

Given the high community prevalence of both the FVL and PGM mutations it is not uncommon for individuals to be heterozygous for both conditions, with an expected prevalence of 1 per 1000 in Caucasian populations.[28] In a pooled analysis of case control studies, double heterozygotes were estimated to have a 20-fold increase in risk of VTE in comparison to healthy controls.[28]

Other inherited conditions

Homozygosity for the C667T mutation in the methylenetetrahydrofolate reductase (MTHFR), producing a thermolabile gene product with reduced function, is the commonest inherited cause of raised plasma homocysteine levels.[29] In prospective studies a 5µmol/L (micromolar) increase in total plasma homocysteine levels has been shown to be associated with an approximate 1.3-fold

increase in the risk of venous thrombosis,[30] and patients with peripheral vascular disease have been shown to have a slight elevation of homocysteine levels in comparison to controls.[31] Conversely homozygosity for the C667T MTHFR mutation has been shown to have no association with venous thrombosis in folate replete societies,[29] and to have only a weak association with arterial disease (OR 1.2, 95% CI 1.0-1.4).[32] Performing testing for this mutation is therefore not recommended outside the research setting.

Elevated levels of the coagulation factors VIII, IX, XI and prothrombin (factor II) have all been shown to be associated with increased VTE risk. In the case of factor VIII, familial clustering of individuals with elevation of this factor has been demonstrated suggesting an underlying inherited cause, although a specific genetic defect is yet to be identified.[8] Other common mutations within coagulation proteins that have been documented to increase the risk of venous thrombosis include the Plasminogen Activator Inhibitor 4G/5G mutation (OR 1.62) and the alpha-fibrinogen Thr312Ala point mutation (OR 1.4). However there is no clear evidence that the presence of these mutations should alter patient management at present. [33]

Acquired Thrombophilia

There are a number of important acquired conditions that predispose to venous or arterial thrombosis that can be defined by laboratory testing. External or environmental acquired risk factors such as recent surgery or hospitalization, while often playing a central role in the causation particularly of venous thrombosis, will not be discussed further.

Antiphospholipid antibodies

The term antiphospholipid antibody syndrome (APLAS) was first used in the 1980's to describe a non-inflammatory autoimmune condition characterized by the presence of antibodies targeting a variety of phospholipid membrane associated proteins, and a history of either arterial or venous thrombosis or adverse pregnancy outcomes.[34] Laboratory confirmation of the presence of antiphospholipid antibodies requires the demonstration of the presence of a lupus anticoagulant, characterized by prolongation of phospholipid dependant coagulation assays such as the APTT, or a positive immunoassay for anti-cardiolipin or anti-beta2-glycoprotein1 antibodies. To classify a patient has having APLAS, antibody testing should be positive on at least two occasions 12 weeks apart.[35] The risk of an initial thrombotic event in patients with a positive test for antiphospholipid antibodies varies from no increase in blood donors in whom the often transient antibodies are an incidental finding, to annual risk of thrombosis of 2 to 4% in patients with SLE who are antibody positive.[34] As will be discussed, patients with the APLAS, particularly those with a positive test for a lupus anticoagulant, are at increased risk of recurrent thrombosis and therefore they will usually receive long-term anticoagulation after an initial event.

Heparin Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) is immune-mediated adverse drug reaction to heparin. It results from the formation of antibodies, in the majority of patients, directed against a complex of heparin and the positively charged molecule platelet factor 4 (PF4).[36] These antibodies then bind to the heparin-PF4 complex bound to the platelet surface, leading to platelet activation most likely due to signalling via the platelet Fc receptors. Platelet and probable concurrent endothelial activation result in activation of the coagulation cascade and

increased thrombin generation, manifesting clinically as increased risk of venous and arterial thrombosis. Without institution of alternative anticoagulation, patients with confirmed HIT have a daily incidence of new thrombotic complications of up to 6%, with the historical risk of death or amputation due to venous gangrene approaching 50%. Early recognition of HIT is therefore important and monitoring of platelet counts between day 2 and 14 of exposure should be performed in all patients receiving heparin. A fall in platelet count to less than 150×10^9/L or a fall in total platelet count by greater than 50% should prompt laboratory investigation for HIT antibodies. Patients testing positive for HIT antibodies should be started on a non-heparin alternative anticoagulant such as lepirudin or danaparoid.[36]

Myeloproliferative Disorders

The primary bone marrow disorders polycythaemia rubra vera (PRV), myelofibrosis and essential thrombocytosis (ET) make up the bcr-abl negative myeloproliferative disorders. In almost all patients with PRV, and a significant proportion with ET, a somatic acquired mutation known as the JAK2 V617F mutation will be detected.[37] Patients with PRV and ET in particular have been shown to be at an increased risk of both venous and arterial thrombosis. The annual incidence of thrombosis in patients with essential thrombocytosis has been shown to be 12 per 1000 per year, of which approximately 50% will be arterial and 50% venous.[37] This compares with a background incidence in the general population of approximately 1 per 1000. Full blood examination is therefore recommended in all patients with venous thrombosis. It has also been recently observed that a significant proportion of patients with unprovoked portal and mesenteric vein thrombosis will be found to have the JAK2 V617F mutation present, often without clear evidence of a myeloproliferative disease on the peripheral blood examination.[38] While the therapeutic implications of this finding are still being evaluated, testing for this mutation should be considered in this patient group.

Potential Reasons for Performing Thrombophilia Testing

Clinical utility is an important concept when considering laboratory investigations for any condition. The clinical utility of any investigation can be defined as the degree to which the clinical outcome of an individual patient is improved by the performance of that test. Potential ways in which testing for an underlying thrombophilic condition may improve patient outcome are discussed below.

Patients With Venous Thrombosis and Their Relatives

a) Providing an understanding of the aetiology of a thrombotic event

As discussed above, a number of conditions have been shown to be clearly associated with an increased risk of a first episode of venous thrombosis (Table 10.1).[8,9] Patients with venous thrombosis are often keen to have an understanding as to why an event occurred, and therefore thrombophilia testing may help provide some explanation as to the aetiology of an event. It however should be emphasized that venous thrombosis is a multifactorial disease with many risk factors present at the time of an event, and therefore care should be taken in attributing an event entirely to an underlying thrombophilic condition.

The cost-effectiveness of performing thrombophilia testing solely to understand the aetiology is questionable. As discussed below, it is also important that both the patient and clinician understand that testing for the common genetic mutations, the FVL

TABLE 10.1: Increase in risk of initial and recurrent venous thrombosis with inherited thrombophilia.

	AT Deficiency	Protein C Deficiency	Protein S Deficiency	FVL mutation*	PGM mutation*
Increase in risk of first episode VTE	5 to 20-fold	5 to 10-fold	5 to 30-fold	3 to 7-fold	2 to 3-fold
Increase in risk of recurrent VTE	2.0-fold (pooled data)			1.2 to 1.6 fold	1.4 fold

*Refers to heterozygote state

and PGM mutations, is unlikely to change management, and that the results of a positive test for these conditions are not over-interpreted. Finally the potentially negative impact of testing including implications for insurance should be taken into account before testing is performed.

Determining risk of recurrence and therefore optimal duration of anticoagulation

Patients with venous thrombosis are at risk of recurrent events, with approximately 30% of affected individuals subsequently experiencing a recurrent event within 5 years of ceasing anticoagulation.[38] A potential role for thrombophilia testing is therefore to identify those patients at greatest risk of recurrent thrombosis, in whom exposure to the increased risk of haemorrhage with long-term anticoagulation may be justified. This is most relevant in patients with unprovoked venous thrombosis who have a substantially increased risk of recurrent thrombosis in comparison to patients in whom the event was associated with a definite provoking risk factor.

The high incidence inherited thrombophilic conditions, the FVL and PGM mutations, do not significantly increase the risk of recurrent thrombosis. A recent meta-analysis found that patients heterozygous for the FVL mutation compared to patients without the mutation had an approximate 1.6-fold increase in the risk of recurrent thrombosis.[39] When this analysis was restricted to patients with an unprovoked event this decreased to a 1.2-fold increase in risk that was no longer statistically increased. The same analysis found a borderline significant 1.4-fold increase in risk of recurrent venous thrombosis in patients heterozygous for the prothrombin gene mutation. This data suggests heterozygosity for the FVL or PGM should not be used by itself to determine duration of anticoagulation.

There is less data regarding the impact of antithrombin, protein C and protein S deficiency on the risk of recurrent venous thrombosis, and due to their lower incidence data tends to be pooled for all three conditions. Data from prospective cohort studies of unselected patients with venous thrombosis has suggested an approximate 2-fold increase in the risk of recurrence in patients with deficiencies of these proteins in comparison to patients with normal levels.[8] A retrospective study of thrombophilic families found that individuals with AT, PC and PS deficiency had a cumulative incidence of recurrent thrombosis of 55% by 10 years after ceasing anticoagulation, in comparison to a figure of 25% in patients with FVL, PGM or elevated FVIII levels.[40] These data suggest that patients with confirmed AT, PC or PS deficiency may benefit from long-term

anticoagulation. It is important to stress that the levels of these proteins may be spuriously low, for example in the case of recent extensive thrombosis, and, for protein C and S due to warfarin therapy. Therefore repeat testing in the absence of confounding factors should be performed to confirm the diagnosis prior to therapeutic decisions being made. While data is lacking on clinical factors that can be used to reliably identify patients with venous thrombosis that will have a deficiency of one of the natural inhibitors of coagulation, it would appear reasonable to focus testing on patients with unprovoked events, younger age (<50 yrs of age), unusual site of thrombosis, or a strong family history (>1 first degree relative) of venous thrombosis.

As previously mentioned, patients with antiphospholipid antibody syndrome have been demonstrated to have an increased risk of recurrent thrombosis, with estimates of risk ranging from 10 to 60% per annum.[34] In addition, patients with antiphospholipid antibody syndrome have been demonstrated to have an increased risk of death after ceasing anticoagulation, contributed to by the fact that this patient group is at increased risk of not only recurrent venous thrombosis but also arterial complications.[41] Therefore long-term anticoagulation is generally recommended for patients who meet the diagnostic criteria for this condition.

Determining the need for primary prophylaxis in asymptomatic family members

Another possible role for thrombophilia testing is determined if the baseline risk of venous thrombosis is sufficient to warrant primary prophylaxis with anticoagulation. Given the lack of evidence supporting a role for anti-platelet therapy in preventing venous thromboembolism, at present this would require a sufficiently high risk to justify exposure to the 2 to 3% annual risk of major haemorrhage associated with vitamin K antagonist therapy of which approximately 20% will be fatal.

As shown in Table 10.2, the annual risk of venous thrombosis in previously asymptomatic patients with venous thrombosis varies from approximately 0.3% with the PGM to up to 2% in patients with AT or protein S deficiency.[8,9,40] This is against a background rate of approximately 0.1% per annum in the general population, with incidence increasing with age. It is generally accepted that given the risk associated with oral anticoagulation, that primary prophylaxis is therefore not justified in patients with any of the known inherited thrombophilias. It has been shown that between 50 to 60% of episodes of venous thrombosis in previously asymptomatic family members with thrombophilia will occur in

TABLE 10.2: Risk of venous thrombosis in asymptomatic family members with inherited thrombophilia.

	AT Deficiency	Protein C Deficiency	Protein S Deficiency	FVL mutation*	PGM mutation*
Overall risk (risk / year)	1.5–2.0%	1.0–1.5%	1.5–2.0%	0.5%	0.3–0.4%
Oral Contraception (risk / yr exposure)	4 to 5% (pooled data)			0.3–0.5%	0.2%
Pregnancy (risk / pregnancy)	~ 4.0% (pooled data)			~2.0%	~2.0%

*Refers to heterozygote state

the context of an additional environmental risk factor such as surgery. While not clearly demonstrated in clinical trials, it is possible that more aggressive thromboprophylaxis may be justified particularly in patients with type 1 thrombophilic conditions.[9] Again, if testing is performed for this indication, care must be taken to avoid over-interpretation of the test result by both patient and other clinicians.

Making decisions regarding the use of the oral contraceptive pill

Knowledge of whether a previously asymptomatic individual is a carrier of a known inherited thrombophilia may influence decision-making regarding exposure to the pro-thrombotic effects of oral contraception. Estimates of the annual risk of thrombosis with use of a combined oestrogen/progesterone oral contraceptive (OCP) are shown in Table 10.2.[8] Generally women of child bearing age have a low annual risk of thrombosis of approximately 1 to 2 per 10000 per year. Therefore despite the combination of oral contraceptive use and being heterozygous for the FVL mutation producing an approximate 30-fold increase in risk, the absolute risk per year is still relatively low at no greater than 0.5% per annum.

Most clinicians would accept that the degree of risk associated with OCP use in patients with type 1 thrombophilic conditions justifies avoidance and use of other contraceptive measures, including progesterone only pills or intrauterine devices that do not increase the risk of thrombosis. The decision regarding OCP use in women heterozygous for FVL and PGM is less black and white, and will be influenced by patient perception of the benefit obtained from OCP use, and the presence of other risk factors for venous thrombosis such as obesity.

Determining the need for thromboprophylaxis during pregnancy

The risk of venous thrombosis during pregnancy in women with no prior history of thrombosis associated with the presence of common inherited thrombophilic conditions is shown in Table 10.2.[8,9] Two-thirds of pregnancy related episodes of venous thrombosis will occur during the post-partum period. Again the case for prophylactic anticoagulation during pregnancy can be made most strongly for women with type 1 conditions, particularly for antithrombin deficiency that in some studies is associated with a risk of ante-partum events of up to 10%. As a minimum, post-partum prophylaxis should be administered for 6 to 8 weeks. In FVL and PGM heterozygotes ante-partum prophylaxis is generally not recommended in women with no prior history of events. Post-partum prophylaxis should be considered, particularly in women with additional risk factors.

Patients with arterial thrombosis

The association between inherited thrombophilic conditions and arterial disease has not been clearly demonstrated. Case reports and small studies have linked antithrombin, protein C and protein S deficiency to arterial disease, however the data are inconclusive.[8] Larger studies have evaluated the link between the FVL and PGM mutations with both coronary artery disease, myocardial infarction and stroke. Generally the findings have been of either no link or a weak association with odds ratios of < 1.5,[8,9] with some data suggesting a stronger association with myocardial infarction in younger patients with the additional risk factor of smoking. There is also no conclusive evidence supporting an association of thrombophilia with peripheral arterial disease. Based on the lack of a clear association of inherited

thrombophilia with arterial disease, and no data supporting a change in management based on the knowledge that the presence of a thrombophilic condition improves patients outcome, is has been strongly recommended that testing for inherited thrombophilia should not be performed in patients with arterial disease.

As stated above, the association of antiphospholipid antibodies with an increased risk of arterial disease is more definitive. It is generally recommended that patients with APLAS and arterial disease should be treated with warfarin rather than antiplatelet agents, although the evidence supporting this approach remains minimal.[34]

The clinical utility of measuring homocysteine levels in patients with arterial disease at present remains unclear. While a number of trials have shown benefit of B-vitamin supplementation on surrogate end-points of arterial disease, a recent meta-analysis found no reduction in clinical end-points in patients with either cardiovascular disease or stroke with supplementation therapy.[42]

POTENTIAL DETRIMENTAL EFFECTS OF THROMBOPHILIA TESTING

A small number of studies have examined the potential psychological impact on patients of performing thrombophilia testing.[43] While the general conclusion was that the impact was low, it was clear that many patients were unclear that they had been tested, and the knowledge of having a thrombophilia did cause significant distress in some individuals. Other potential drawbacks to testing for inherited thrombophilia may include difficulty with obtaining or changes to the cost of life-insurance, and questionable cost-effectiveness.[8]

CONCLUSION

It can be concluded that despite the ability to detect an underlying thrombophilia in up to 50% of patients with venous thrombosis, it is doubtful that performing laboratory testing for thrombophilias has a positive effect on patient outcome in the majority of patients. The strongest case for testing for inherited thrombophilia can be made for type 1 conditions, although these conditions will be detected in only approximately 5% of patients. The evidence that testing for FVL and the PGM abnormalities improves patient outcome is limited. Widespread testing in unselected patients is recommended against, and a stronger case can be made for patients with female first-degree relatives of child-bearing age. Prior to any testing being performed, the clinician involved in test-ordering should counsel the patient regarding the implications of both a positive and negative test result, and how this will change patient management. If it is unclear how the test result will change treatment for the individual or relatives, then testing should not be performed.

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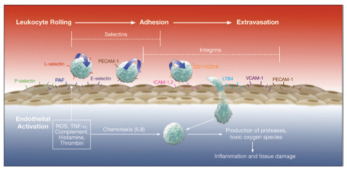

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