

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

Robert Fitridge

The University of Adelaide, The Queen Elizabeth Hospital, Woodville, Australia

Matthew Thompson

St George's Hospital Medical School, London, UK



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List of Contributors

David G Armstrong
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Vishwanath Biradar
Intensive Care Unit
The Queen Elizabeth Hospital
Woodville, SA
Australia

Matthew Bown
Department of Vascular Surgery
University of Leicester
Leicester
UK

Andrew W Bradbury
University Department of Vascular Surgery
Birmingham Heartlands Hospital
Birmingham
UK

Edward Choke
Department of Vascular Surgery
University of Leicester
Leicester
UK

Gillian Cockerill
Department of Clinical Sciences
St George's Hospital Medical School
London
UK

Prue Cowled
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Helen Daly
Royal Perth Hospital
Perth, WA
Australia

Mital Desai
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Robert F Diegelmann
Department of Biochemistry
Medical College of Virginia
Richmond, VA
USA

Timothy K Fisher
Rashid Centre for Diabetes and Research
Sheikh Khalifa Hospital
Ajmon
UAE

Robert A Fitridge
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Gail Gillespie
Royal Perth Hospital
Perth, WA
Australia

Jonathan Golledge
Vascular Biology Unit
School of Medicine & Dentistry
James Cook University
Townsville, QLD
Australia

George Hamilton
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Mark Hamilton
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Robert J Hinchliffe
St George's Vascular Institute
St George's Hospital
London
UK

Richard D Kenagy
Department of Surgery
University of Washington
Seattle, WA
USA

Paul Kerr
Department of Pharmacology
University of Alberta
Alberta
Canada

Michael MD Lawrence-Brown
Curtin Health Innovation Research
Institute
Curtin University
Perth, WA
Australia

Brian Lepow
The University of Arizona
Department of Surgery
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Kurt Liffman
CSIRO Material Science & Engineering
and School of Mathematical Sciences
Monash University
Melbourne, Vic
Australia

Ian Loftus
Department of Vascular Surgery
St George's Hospital
London
UK

Mark J McCarthy
Department of Surgery and Cardiovascular
Sciences
University of Leicester
Leicester
UK

Greg S McMahon
Department of Surgery and Cardiovascular
Sciences
University of Leicester
Leicester
UK

Simon McRae
Adult Haemophilia Treatment Centre
SA Pathology
Adelaide, SA
Australia

Joseph L Mills
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Lyle Moldawer
Department of Surgery
University of Florida
Gainesville, FL
USA

John L Moran
Faculty of Health Sciences
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Stephen Nicholls
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Ian M Nordon
St George's Vascular Institute
St George's Hospital
London
UK

Paul E Norman
School of Surgery
University of WA
Fremantle, WA
Australia

Karlheinz Peter
Baker IDI Heart & Diabetes Institute
Melbourne, Vic
Australia

Frances Plane
Department of Pharmacology
University of Alberta
Alberta
Canada

Janet T Powell
Imperial College
London
UK

Sandeep Prabhu
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Rishi Puri
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Stephan A Schug
Royal Perth Hospital
Perth, WA
Australia

Gregory S Schultz
Department of Obstetrics and Gynaecology
University of Florida
Gainesville, FL
USA

Rahul Sharma
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Guo-Ping Shi
Department of Cardiovascular Medicine
Brigham & Women's Hospital
Harvard Medical School
Boston, MA
USA

Michael Stacey
University Department of Surgery
Fremantle Hospital
Fremantle, WA
Australia

Ilija D Sutalo
CSIRO Material Science & Engineering
and Curtin Health Innovation
Research Institute
Curtin University
Highett, Vic

Raymond Tam
Department of Pharmacology
University of Alberta
Alberta
Canada

Matthew Thompson
St Georges Hospital Medical School
London
UK

Martin Veller
Department of Surgery
University of Witwatersrand
Johannesburg
South Africa

Mauro Vicaretti
Department of Vascular Surgery
Westmead Hospital
Westmead, NSW
Australia

Matt Waltham
Academic Department of Surgery
St Thomas' Hospital
London
UK

Matthew L White
Vascular and Endovascular Surgery
University of Arizona
Tucson, AZ
USA

David P Wilson
School of Medical Sciences
Discipline of Physiology
University of Adelaide
Adelaide SA
Australia

Qingbo Xu
Department of Cardiology
Kings College
University of London
UK

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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	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-1 α	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 <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

NF κ B	Nuclear factor kappa B
NiT	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
PDGF β	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	Prothrombin 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

13 • Pharmacological Treatment of Aneurysms

MATTHEW THOMPSON, JANET T POWELL

St George's Hospital, London, UK.

BACKGROUND

Abdominal aortic aneurysms (AAAs) are present in 5 to 10% of men over the age of 65, and elective surgical intervention has long been the mainstay of treatment. There is widespread consensus that operative repair is the treatment of choice in larger AAAs, where the risk of rupture increases with the size of the aneurysm. However, even elective operations carry a significant mortality risk, and the UK small aneurysm trial has shown that for smaller aneurysms (between 4 and 5.5cm) there is no difference in outcome between operation and no intervention. Currently such patients are treated with best medical therapy, but there has been considerable research into finding a pharmacological treatment to prevent aneurysm expansion and rupture.

SCREENING PROGRAMMES

A major obstacle to the prevention of mortality and morbidity associated with aneurysms has been the fact that the majority are asymptomatic, and therefore often remain undetected. Abdominal aortic aneurysms have tended to present either as emergencies or as a result of their increasing size, and it has been shown that larger aneurysms grow more

rapidly than their smaller counterparts and are at greater risk of rupture.³ These patients would therefore benefit most from operative repair rather than medical intervention. In order for a medical treatment to be of benefit, it needs to be targeted at aneurysms that are small and asymptomatic. The most obvious way of doing this would be the initiation of a mass screening programme, and indeed, the Multicentre Aneurysm Screening Study (MASS)¹ has shown that as many as 88% of screen-detected aneurysms are below the threshold for surgery.

The introduction of screening programmes will identify a large population of patients with small aortic aneurysms that are at present untreated. The concept of pharmacotherapy for AAAs has evolved over the past decade, to encompass a medical treatment for aneurysms. Pharmacotherapy aims to reduce the expansion and rupture rate of aortic aneurysms by modifying aortic wall biology. A pharmacotherapeutic approach might be used to reduce the expansion rate of small, screen detected, abdominal aneurysms, and therefore reduce the proportion of patients requiring surgery. Alternatively, effective drug treatment might be able to reduce rupture rates in patients with large aneurysms unsuitable for aneurysm repair. Applications

to endovascular aneurysm repair have yet to be explored.²

PATOPHYSIOLOGY

Abdominal aortic aneurysms have long been known to be associated with increasing age, male gender, cigarette smoking, chronic lung disease, hypertension and genetic factors. Despite the fact that most of these risk factors are shared with patients with atherosclerosis, aneurysmal disease appears to be a separate entity. Diabetes is a strong risk factor for developing atherosclerosis but not for AAAs. The genetic component of aneurysm aetiology is not fully defined at present, but may be due to inborn errors of the connective tissue matrix, such as mutation of the COL3A1 gene coding for the A chain of type 3 collagen. Information from gene wide association studies is awaited to further inform the genetic basis of AAA.

The detailed pathophysiology of the developing and expanding aneurysm has been covered in Chapter 12. Abdominal aortic aneurysms are characterised by several inter-related processes; degradation of the extracellular matrix, excessive proteolysis, apoptosis, oxidative stress, angiogenesis and widespread inflammation.

An approach to developing a suitable pharmacotherapy may be considered from one of two perspectives. Firstly, the drug may be targeted to one of the specific processes that have been shown to influence aneurysm development. The second approach hinges on newer theories about the nature of arterial disease. Increasingly it has been recognised that arterial disease is neither a matter of simple deranged lipid metabolism or of isolated local mechanical effects. The current belief is that arterial disease represents a low-grade systemic inflammation, which can therefore manifest itself at any point – coronary, carotid, aneurysmal or peripheral

vascular disease. The Oxford Heart Protection Study has shown that generalised treatment of arteriopathic patients with statin therapy can reduce their chance of undergoing major adverse events including AAA rupture, regardless of their initial cholesterol level.

The majority of agents proposed to alter aneurysm expansion have been tested in animal models of aneurysm disease, and consequently there has been the typical disconnect between findings in the experimental situation and application to clinical practice. It must be remembered that humans show a great redundancy of biological processes that suggests that any effective pharmacotherapeutic agent must have pleiotropic actions. The next section of this chapter will concentrate on agents that have been tested in – albeit small scale – clinical trials. The final section will examine novel therapeutic approaches that have not yet been evaluated clinically.

THERAPEUTIC STRATEGIES

Beta blockade

Hypertension has been associated with AAAs, and investigations have shown that hypertension increases the development of aneurysms in the Anidjar/Dobrin rat model.

Since beta-blockers have been used successfully in the treatment of hypertension, it was not unreasonable to investigate the effect of beta-blockade on aneurysm expansion, as these agents have been shown to slow aneurysm progression in both experimental models and retrospective studies of patients with AAAs. Initially this was thought to be purely due to the drugs' effects on blood pressure, but there is considerable evidence to support the theory that beta-blockers may exert any beneficial effects on AAAs through enhancing

the cross linkage of elastin molecules, making them less prone to degradation.

A randomised clinical trial was instigated by the Propanolol Aneurysm Trial Investigators and reported in January 2002.³ 548 patients with asymptomatic aneurysms between 3 and 5cm in diameter were randomised to receive either placebo ($n = 272$) or propanolol ($n = 276$) and were followed for a mean of 2.5 years. The primary criterion was the mean growth rate of the aneurysm. There was no significant difference in the growth rates of the two groups, although there was a trend towards more elective operations in the placebo group. There was no difference in death rates, but patients in the treatment arm of the study reported a poorer quality of life, and more of this group stopped taking their medication.

In this robust study it was clear that propanolol has little, if any, effect on the growth rate of AAAs. Subsequent studies of other beta-blockers have suggested that beta-blockade has little effect on the growth rate of AAA.⁴

Modification of the inflammatory response

With considerable evidence to support the theory that aneurysm expansion and rupture are both mediated by the immune system, it is unsurprising that there has been interest in modifying this response as a means of attenuating growth.

In the rat elastase perfusion model of AAA, the effect of treating experimental aneurysms with powerful immunosuppression was tested. At nine days post infusion, a significant difference in the diameters of the aortas was observed, with the control group having expanded to approximately three times their pre-infusion size, but the treatment groups only grew to around twice their original size. These findings indicate

that, at least in this experimental model, preventing the infiltration of inflammatory cells could halt the main spurt of aneurysm growth. Similar results were seen by Ricci et al when using a monoclonal antibody against the macrophage adhesion molecule CD-18.⁵

The one constant factor in these experiments on immune-modification has been that the compounds used have been unacceptable as clinical treatment strategies due to their wide range of action and many side effects.

Non steroid anti-inflammatories

Indomethacin is a powerful anti-inflammatory drug that has been investigated both in the rodent elastase model and in human aortic aneurysmal tissue. Indomethacin reduced both aneurysm growth and MMP-9 activity in the rat and the levels of prostaglandin E2 (PGE-2), interleukin 1 beta (IL-1 β) and interleukin 6 (IL-6) in human tissue.

In a retrospective analysis of the large group of patients in the UK small aneurysm trial, indomethacin was also shown to inhibit aneurysm growth *in vivo*.⁶ The trial was not designed for this purpose and was the result of sub-group analysis, so further trials would be required. There is preliminary evidence that non-selective COX inhibition by indomethacin prevents aneurysm growth, but the side effects of this treatment on the gastrointestinal, renal and hepatic systems are well known.

Matrix metalloproteinase (MMP) inhibition

Many observers have noted an imbalance between MMPs and their naturally occurring inhibitors (TIMPs) in aortic disease, and one of the modes of action of indomethacin is to reduce the activity of matrix metalloproteinases. Many other compounds

have also been investigated for their anti-MMP properties and most have been effective in the experimental setting.

Tetracyclines have long been known to prevent connective tissue breakdown by their inhibitory effect on MMPs and several experimental studies have suggested that doxycycline reduced the growth of degenerative aneurysms and suppressed MMP-9 production in the rat elastase model. In a clinical trial, preoperative treatment with doxycycline caused a reduction in both the expression of macrophage MMP-9 mRNA and the activity of MMP-2 in aneurysm tissue.⁷ Also, a small double-blinded, randomised and placebo controlled pilot study from Finland has shown that treatment with doxycycline for a three month period significantly reduced the rate of aneurysm growth in a cohort of patients as measured by serial ultrasound scans.⁸ At six months, there was also a significant reduction in the serum C-reactive protein levels of the treatment group. Although the sample size was small and preoperative confounding effects are not taken into consideration, this trial has provided evidence to support further research into this area. In recent years a clinical trial has demonstrated that administration of doxycycline can produce a profound but selective effect on vascular inflammation that reduces aortic wall neutrophil and cytotoxic T-cell content.⁹ Additionally a clinical trial of doxycycline after endovascular aneurysm repair demonstrated that patients treated with doxycycline exhibited greater decreases in maximum aortic diameter and significantly reduced aortic neck dilatation at 6 months.¹⁰ Large-scale clinical trials of this agent appear warranted.

Anti-chlamydial therapy

The hypothesis that atherosclerosis may have an infective aetiology is not new, and it is clear that AAAs and atherosclerosis share some of the same risk factors. These associations were the rationale for clinical trials of anti-chlamydial therapy for AAA.

One RCT examined the effect of roxithromycin on aneurysm growth.¹¹ Patients with small aneurysms were given either roxithromycin or placebo for four weeks, and subsequently followed up for a mean of 1.5 years. Once adjustments had been made for smoking, blood pressure and IgA, there was a significant difference in aneurysm growth between treatment and placebo groups.

DRUGS ACTING ON THE RENIN/ANGIOTENSIN AXIS

In 1998 a French group reported the effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists in a strain of rat prone to rupture of the internal elastic lamina of the aorta. To ensure any beneficial effects were not due to the antihypertensive properties of the drugs, they were compared to hydralazine and two calcium channel antagonists. Both ACE inhibitor and angiotensin II antagonists prevented rupture of the internal elastic lamina, suggesting this was due to the effect on angiotensin II and not on another part of the renin/angiotensin system.

In recent years there has been some intriguing, and contrasting clinical evidence regarding ACE inhibition in AAA. A Canadian group using epidemiological methodology reported that patients who received ACE inhibitors before admission to hospital were significantly less likely to present with ruptured aneurysm (odds ratio 0.82) than those who did not receive ACE inhibitors.¹²

Similar associations were not observed for beta blockers, calcium channel blockers or angiotensin receptor blockers. Conversely, analysis of patients taking ACE inhibitors in the UK small aneurysm trial demonstrated that these patients had enhanced aneurysm growth.¹³ A clinical trial is underway in the UK to define the action of ACE inhibitors in AAA expansion.

HMG CO-A REDUCTASE INHIBITORS

The HMG Co-A reductase inhibitors (statins) are a group of drugs in which there has been considerable interest recently. The statins have been used successfully for their lipid-lowering properties for some time now, but have also exhibited beneficial effects in cardiovascular disease unrelated to this. In laboratory experiments, statins have been proven to reduce MMP-9 expression by human macrophages, and their anti-inflammatory effects are well documented. Their pleiotropic actions are well suited to target aneurysm expansion and experimental effects are encouraging in reducing aortic inflammation and proteolysis.^{14,15}

A small scale clinical trial of statin therapy in AAA demonstrated a reduced expansion rate in the treatment group¹⁶ and a recent systematic review and meta-analysis suggested that there is evidence to suggest that statins reduce aneurysm growth.⁴ However, aside from aneurysm expansion, there is now overwhelming evidence that patients with aneurysms and peripheral vascular disease derive benefit from statins with regard to cardiovascular death and outcome following surgery.¹⁷ In this regard all patients with aortic aneurysms should be on statin therapy if tolerated.

THE FUTURE – DATA FROM RECENT EXPERIMENTAL STUDIES

Recent experimental data have suggested some possible significant advances in pharmacotherapy for AAA. A recent study by Satoh *et al*¹⁸ demonstrated the significant role that oxidative stress plays in the development of experimental aneurysms. This study revealed that angiotensin II, through induction of reactive oxygen species, induces cyclophilin A in smooth muscle cells which then stimulates recruitment of inflammatory cells, activation of MMPs and production of reactive oxygen species. These factors then initiate the biological events responsible for aneurysm formation. This study and subsequent commentaries have illustrated the importance of oxidative stress in aneurysm formation and suggest a target for pharmacotherapy.

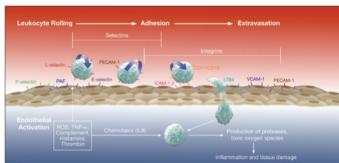
Perhaps the most significant new studies in aneurysm biology over the last few years have been those investigating the effect of inhibiting signalling pathways. As stated previously, aneurysms form by multiple pathways in the milieu of extensive biological redundancy. Two recent reports using inhibition of signalling pathways (JNK and NF κ B) have reported that inhibition of crucial signalling mechanisms can actually result in regression of established experimental aneurysms.^{19,20} These results clearly represent a paradigm shift in aneurysm pharmacotherapy and offer the potential goal of aneurysm regression. The inhibitors used would not be safe in clinical use but recently, drugs with the potential to inhibit signalling pathways have been investigated experimentally. Rosiglitazone – a drug used extensively in diabetic control – has the ability to inhibit JNK and MAPK and has been effective in reducing aneurysm formation in the experimental setting.²¹

Clearly the goal over the next few years will be to discover drugs with the potential ability to regress established aneurysms.

REFERENCES

- Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002; **360**(9345): 1531–9.
- Thompson MM. Controlling the expansion of abdominal aortic aneurysms. *Br J Surg* 2003; **90**(8): 897–8.
- Propranolol for small abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg* 2002; **35**(1): 72–9.
- Guessous I, Periard D, Lorenzetti D, Cornuz J, Ghali WA. The efficacy of pharmacotherapy for decreasing the expansion rate of abdominal aortic aneurysms: a systematic review and meta-analysis. *PLoS One* 2008; **3**(3): e1895.
- Ricci MA, Strindberg G, Slaiby JM, et al. Anti-CD 18 monoclonal antibody slows experimental aortic aneurysm expansion. *J Vasc Surg* 1996; **23**(2): 301–7.
- Walton LJ, Franklin IJ, Bayston T, et al. Inhibition of prostaglandin E2 synthesis in abdominal aortic aneurysms: implications for smooth muscle cell viability, inflammatory processes, and the expansion of abdominal aortic aneurysms. *Circulation* 1999; **100**(1): 48–54.
- Curci JA, Mao D, Bohner DG, et al. Preoperative treatment with doxycycline reduces aortic wall expression and activation of matrix metalloproteinases in patients with abdominal aortic aneurysms. *J Vasc Surg* 2000; **31**(2): 325–42.
- Mosorin M, Juvonen J, Biancari F, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J Vasc Surg* 2001; **34**(4): 606–10.
- Lindeman JH, Abdul-Hussien H, van Bockel JH, Wolterbeek R, Kleemann R. Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells. *Circulation* 2009; **119**(16): 2209–16.
- Hackmann AE, Rubin BG, Sanchez LA, Geraghty PA, Thompson RW, Curci JA. A randomized, placebo-controlled trial of doxycycline after endoluminal aneurysm repair. *J Vasc Surg* 2008; **48**(3): 519–26; discussion 26.
- Hogh A, Vammen S, Ostergaard L, Joensen JB, Henneberg EW, Lindholt JS. Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. *Vasc Endovascular Surg* 2009; **43**(5): 452–6.
- Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006; **368**(9536): 659–65.
- Sweeting MJ, Thompson SG, Brown LC, Greenhalgh RM, Powell JT. Use of angiotensin converting enzyme inhibitors is associated with increased growth rate of abdominal aortic aneurysms. *J Vasc Surg* 2010; **52**(1): 1–4.

14. Wilson WR, Evans J, Bell PR, Thompson MM. HMG-CoA reductase inhibitors (statins) decrease MMP-3 and MMP-9 concentrations in abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2005; **30**(3): 259–62.
15. Evans J, Powell JT, Schwalbe E, Loftus IM, Thompson MM. Simvastatin attenuates the activity of matrix metalloprotease-9 in aneurysmal aortic tissue. *Eur J Vasc Endovasc Surg* 2007; **34**(3): 302–3.
16. Schouten O, van Laanen JH, Boersma E, et al. Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. *Eur J Vasc Endovasc Surg* 2006; **32**(1): 21–6.
17. Schouten O, Boersma E, Hoeks SE, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med* 2009; **361**(10): 980–9.
18. Satoh K, Nigro P, Matoba T, et al. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. *Nat Med* 2009; **15**(6): 649–56.
19. Yoshimura K, Aoki H, Ikeda Y, et al. Regression of abdominal aortic aneurysm by inhibition of c-Jun N-terminal kinase. *Nat Med* 2005; **11**(12): 1330–8.
20. Miyake T, Aoki M, Masaki H, et al. Regression of abdominal aortic aneurysms by simultaneous inhibition of nuclear factor kappaB and ets in a rabbit model. *Circ Res* 2007; **101**(11): 1175–84.
21. Jones A, Deb R, Torsney E, et al. Rosiglitazone reduces the development and rupture of experimental aortic aneurysms. *Circulation* 2009; **119**(24): 3125–32.



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MECHANISMS OF VASCULAR DISEASE

Edited by Robert Fitridge and Matthew Thompson

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