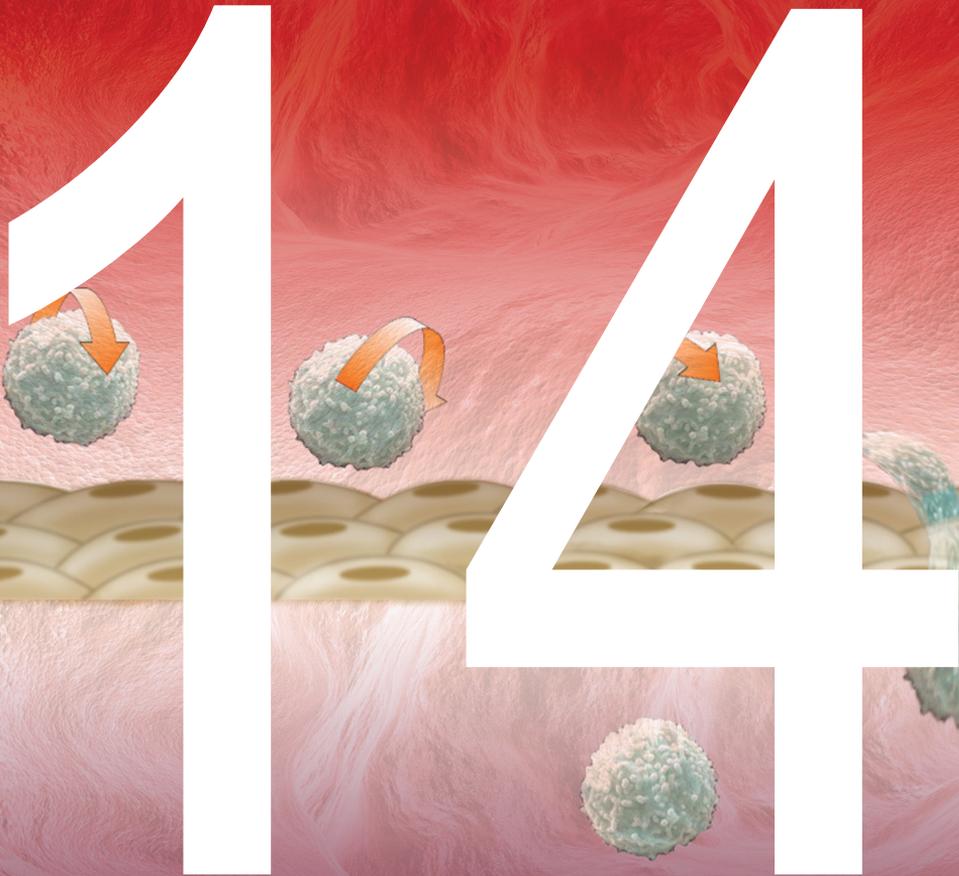


# MECHANISMS OF VASCULAR DISEASE:

A REFERENCE BOOK FOR VASCULAR SPECIALISTS



EDITED BY ROBERT FITRIDGE AND MATTHEW THOMPSON  
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# Mechanisms of Vascular Disease



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## A Reference Book for Vascular Specialists

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# Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	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	$\alpha$ -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
$\beta$ 2-GPI	$\beta$ 2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonin gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

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

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

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1 $\alpha$	Interleukin-1 alpha
IL-1 $\beta$	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 <sub>20</sub>	Myosin light chain <sub>20</sub>
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin resistant <i>Staphylococcus epidermidis</i>
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

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

PET	Positron emission tomography
PF4	Platelet factor 4
PGI <sub>2</sub>	Prostacyclin
PGG <sub>2</sub>	Prostaglandin G <sub>2</sub>
PGH <sub>2</sub>	Prostaglandin H <sub>2</sub>
PGEI <sub>2</sub> /PGI <sub>2</sub>	Prostaglandin I <sub>2</sub>
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 <sup>2+</sup> APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

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

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
T $\alpha$ CE	TNF $\alpha$ 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- $\alpha$	Transforming growth factor-alpha
TGF- $\beta$	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- $\alpha$	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

# 14 • Pathophysiology of Aortic Dissection and Connective Tissue Disorders

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## INTRODUCTION

Thoracic aortic dissection (TAD) is the most common aortic catastrophe, occurring in approximately 5 to 30 cases per 1 million persons per year.<sup>1</sup> It carries a significant morbidity and mortality risk, with 21% of patients dying prior to hospital admission.<sup>2</sup> Recent improvements in the understanding of both the molecular biology and genetics of vascular disease has led to greater clarity of the pathogenesis of acute TAD and a number of associated diseases of the thoracic aorta. Since the initiation of the International Registry of Aortic Dissection (IRAD)<sup>3</sup> in 1996 there has been an evolution of terminology in relation to TAD, and the more encompassing term acute aortic syndrome (AAS) is now utilised to include TAD and a number of other pathologies including intramural haematoma (IMH) and penetrating aortic ulcer (PAU).

In broad terms this classification reflects recent advances in understanding in relation to the pathology and natural history of TAD, and the recognition that TAD is part of a spectrum of thoracic aortic pathology. These individual processes will be discussed separately along with some of the underlying

pathologic phenomena that lead to AAS/TAD.

## Embryology of thoracic aorta and arch vessels

The formation of blood vessels occurs between the third and eighth week of embryological development. The ventral aortas fuse into the endocardial tube and circulate blood by the end of the third week. During this process a series of mesenchymal clefts lined by what will become endothelium fuse and form two pairs of longitudinal channels – one medial and one lateral. The medial channels form the primitive aortas which with elongation and folding of the embryo become paired into ventral and dorsal arrangements, joining the cephalad end of the primitive heart tubes (formed by the ventral components). Five further pairs of arterial arches pass around the developing pharynx connecting the cephalad end of the heart to the remaining unfused dorsal aortas. These branchial arch arteries in pairs form a number of components of the definitive circulation as outlined below. The paired aortas fuse over much of their length around the end of the fourth week and give a number

of intersegmental branches in dorsal, lateral and ventral patterns. During weeks 5–7 there is a significant evolution in pattern or, in particular the cephalad arches regressing and new caudad arches forming.

The aortic arches are part of this cephalad to caudal progression, with six initial sets of arches regressing in a step-wise fashion starting around weeks four to five. The first, second, and fifth arches regress and are largely gone by the start of week five having contributed to the formation of parts of the maxillary and external carotid circulation (1st), the stapedia arteries (2nd) and a pair of early regressing rudimentary vessels from the 5th. Above the level of the 3rd arch the dorsal aortas remain fused and communicate with the 3rd arch to form the definitive internal carotid artery. The common carotid artery is formed by the proximal parts of the 3rd arch (hence it is also referred to as the carotid arch). The remaining proximal external carotid artery arises as new growths of artery from the aortic sac and are not part of the arches per se, but migrate up the third arch to their final position.

Of particular relevance to the thoracic aorta, the 4th arches both persist, the left as the aortic arch and the right as the root of the right subclavian artery. The subclavian arteries initially arise as outgrowths of the terminal paired aortas just proximal to their union and subsequently the resorption of the right aorta between the origin of the subclavian and the fused trunk causes the right subclavian to be isolated.

The sixth arches fuse with the developing pulmonary arteries, the right partly regressing and partly forming the pulmonary artery with the left becoming the ductus arteriosus.

There is also a concurrent change in cardiac anatomy at this time with the heart separating into its left and right sides (aortic and pulmonary).

There is an excellent demonstration of these embryological changes in Valentine and Wind<sup>4</sup> and a discussion of the most prevalent anomalies in a paper by Kau *et al.*<sup>5</sup> Conceptually this may give some understanding of why different segments of the aorta behave in different ways, and what the influences of the embryological derivation may be on the likelihood of differing pathologies in each segment. The embryonic origin of the vascular smooth muscle cells (VSMC) at differing levels of the aorta varies, with the predominant origin being neurectoderm in the thoracic aorta, versus mesoderm in the abdominal aorta.<sup>6</sup>

This difference in origin influences the response of VSMC's to a number of mediators such as Transforming Growth Factor Beta 1 (TGF $\beta$ 1), an important modulator of the extracellular matrix (ECM) in the thoracic aorta. Neurectodermal VSMC growth is potentiated by TGF $\beta$ 1, as is Collagen I production. This is in comparison to mesodermal VSMC's where TGF $\beta$ 1 inhibits growth and has no influence on collagen deposition. Given that VSMC's are influential in aortic strength, it would be expected that varying concentration of VSMC's and differential response to TGF $\beta$ 1 and haemodynamic strain in the aorta would influence the sites of ECM degradation and hence likelihood of aortic pathology such as dissection and/or aneurysm.<sup>7</sup> There is some evidence that VSMC's in the abdominal aorta under cyclical haemodynamic stress secrete TGF $\beta$ 1, leading to an increase in aortic wall mass (however not in the thoracic aorta).<sup>6</sup>

There is also a differential pattern of elastic lamellar units (the functional elastic unit in the aorta – combining elastin lamellae and VSMC's) through the aorta, with higher levels of elastic lamella and VSMC's in the thoracic aorta than in the abdominal. Similarly there is a decrease in the elastin to

collagen ratio in the abdominal aorta compared to the thoracic aorta.<sup>6</sup> It is interesting to note that acardiac foetus do not develop differential structure throughout the length of the aorta, suggesting that there is a significant influence of haemodynamic cyclical strain on the secretion of mediators such as TGF $\beta$ 1 and hence architecture.

### **Haemodynamics of Thoracic Compared to Abdominal Aorta**

There is convincing evidence to suggest that dissection flaps occur at the points in the aorta subject to the greatest fluctuations in pressure over time. Due to the torsional manner in which the heart contracts, and the physical effects of cardiac motion on the arch of the aorta, the areas subject to the greatest changes in pressure are the ascending aorta and the proximal descending aorta. This was demonstrated elegantly in a model created by Qiao et al based on a thoracic aortic aneurysm.<sup>8</sup> This model demonstrated differential shear and flow at varying points in the thoracic aorta, particularly the outer curves of the ascending and proximal descending aorta. There were also areas of increased transit/contact time on the concavity of the arch and proximal descending aorta (along with branch vessel origins in the arch) which as an aside may be the reason for the preponderance of atherosclerotic change at these points.

The alterations in elastic recoil ability and collagen concentrations and function in the aorta that are present in a number of aortic pathologies, combined with the magnitude of the force involved in blood flow (related to absolute blood pressure, pulse pressure and dP/dT) results in the most likely sites of dissection being where the physical forces on the aorta are greatest and the diminution in aortic strength is maximal. There is reasonable evidence that suggests that VSMC

apoptosis (which is influenced by TGF $\beta$ 1) is greatest at the convexities of the ascending and descending aorta – particularly in patients with bicuspid aortic valves, and that this may alter aortic strength at these sites,<sup>7</sup> predisposing to dissection or aneurysm at these sites.

### **Sizes of Normal Aorta**

There is an excellent outline of both the normal sizes of the thoracic aorta at differing ages, allowing a basis for sizing in different pathologies, in the European Society of Cardiology Task Force document.<sup>9</sup>

## **CLASSIFICATION OF AORTIC SYNDROMES**

The acute aortic syndromes can be classified in a number of ways, included chronicity, and anatomy and on the basis of the underlying pathology and complications.

### **Acute/Chronic**

Acute dissections are those present for less than 14 days and chronic are those present for longer.<sup>10</sup>

### **DeBakey Classification of Class 1 Dissection – Type 1, 2 and 3**

The DeBakey classification system separates TAD into three types, with subtypes of Type 3. Initially described by De Bakey and colleagues in 1965,<sup>11</sup> this classification is based on both the anatomy of the entry tear and the extent of the dissection. It is an anatomical classification and has been simplified on the basis of outcome measures and prognosis into the Stanford Classification.

**TABLE 14.1:** DeBakey Classification of Class I Dissection

Type	Tear	Extent
I	Ascending Aorta	Propagating up ascending aorta, across arch and through descending aorta
II	Ascending Aorta	Confined to ascending aorta/intrapericardial aorta
III	Distal to the Left Subclavian Artery	Descending aorta +/- retrograde across arch
Subtype IIIa		Confined to descending aorta above diaphragm
Subtype IIIb		Extends through diaphragm into visceral or abdominal aorta

**TABLE 14.2:** Relationship between Stanford and DeBakey classification of class I dissection

Stanford Type	De Bakey Equivalent	Site of Involvement
A	Type I and II	Ascending aorta +/- Arch
B	Type III	Descending thoracic aorta distal to left subclavian artery
Subtype a and b		Above or below diaphragm, similar to DeBakey

### Stanford Classification

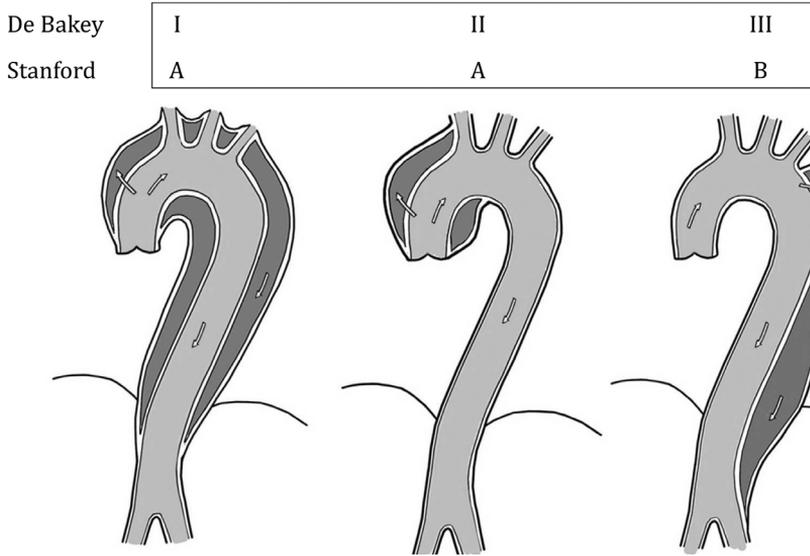
The Stanford classification arose from the recognition that prognosis was largely dependant on the involvement or not of the ascending aorta in the dissection process and was published by Dailey and colleagues in 1970.<sup>12</sup> The De Bakey Classification was thus simplified into two subclasses, Type A and B depending on involvement of the ascending aorta. Although the Stanford classification has allowed stratification into surgical treatment or conservative management groups, it fails to take into account the variations of thoracic aortic pathology that are now recognised to make up what is referred to as the Acute Aortic Syndrome. A review of recent literature proposed a more complex but inclusive classification which has been adopted by the European Task Force on Aortic Dissection.<sup>9</sup>

### European Task Force

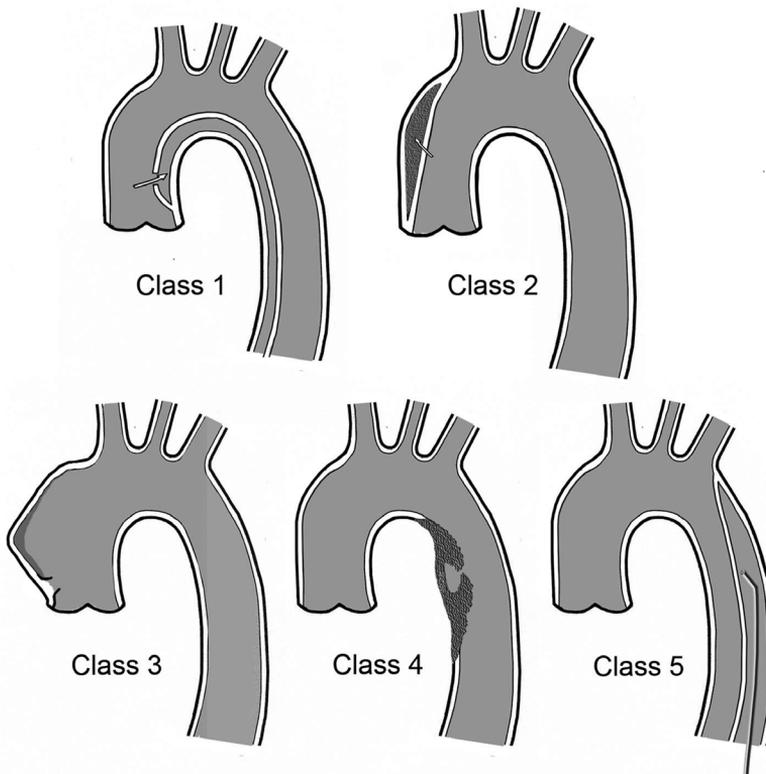
In 1999 Svensson et al<sup>13</sup> published a classification of thoracic aortic pathology that included not only classical TAD but also a number of newly recognised subtype pathologies that were felt to make up part of the continuum of aortic dissection. This system should be considered a subclassification to the Stanford and/or Debakey classifications. This classification is outlined in Figure 14.2.

### PATHOGENESIS OF THORACIC AORTIC DISSECTION

Hypertension is recognised as one of the most significant risk factors for thoracic aortic dissection, and the treatment regimes for acute dissection syndromes utilise anti-hypertensive therapy as their mainstay.



**FIGURE 14.1:** Diagrammatic representation of aortic dissection class 1 divided into De Bakey and Stanford Classifications. Based on figure 4 from Erbel *et al.* 2001.



**FIGURE 14.2:** Classes of aortic dissection. Class 1- Classical Aortic Dissection (Intimal flap between true and false lumen); Class 2 – Intramural haematoma (Medial disruption with formation of IMH); Class 3 – Discrete/ Subtle dissection without haematoma. Eccentric bulge at tear site; Class 4 – Penetrating Aortic Ulcer (Plaque rupture leading to aortic ulceration, or a classical penetrating aortic ulcer with surrounding haematoma. Usually sub-adventitial); Class 5 – Iatrogenic and Traumatic Dissection. Based on figure 5 from Erbel *et al.* 2001<sup>9</sup> and Svensson *et al.* 1999.<sup>13</sup>

**TABLE 14.3:** Summary of aortic dissection classification systems

<b>Stanford Classification</b>	
Type A	Dissection of the ascending and descending aorta
Type B	Dissection of the descending aorta
<b>De Bakey Classification</b>	
Type 1	Dissection of the entire aorta
Type 2	Dissection of the ascending aorta
Type 3	Dissection of the descending aorta
<b>New Classification</b>	
Class 1	Classical aortic dissection with an intimal flap between true and false lumen
Class 2	Medial disruption with formation of intramural haematoma/haemorrhage
Class 3	Discrete/subtle dissection without haematoma, eccentric bulge at tear site
Class 4	Plaque rupture leading to aortic ulceration, penetrating aortic atherosclerotic ulcer with surrounding haematoma, usually subadventitial
Class 5	Iatrogenic and traumatic dissection
Class 1–5 Represent a subdivision to the Stanford or De Bakey classification	

There is good evidence that suggests that aggressive blood pressure management reduces mortality, particularly the use of beta blockers. There is also evolving evidence that a number of the newer antihypertensives such as losartan, which exerts some effect on mediators such as TGF $\beta$ 1, may have extra effects on the turnover of thoracic aortic ECM, and may reduce the risk of both dissection and aneurysmal degeneration in some of the connective tissue disorders.

Smoking and hypercholesterolaemia have deleterious effects on the thoracic aorta and the catecholamine drive that is present in chronic tobacco use may exacerbate dissections and increase the risk of aneurysm disease.

Cocaine use is recognised as a risk factor for the development of the AAS, in particular in young african american males. Amphetamines similarly have a linkage with development of TAD, presumably for similar reasons to cocaine, with surges in catecholamines and concomitant acute rises in dP/dT and blood pressure in the aorta.<sup>15,16</sup>

### **Classical Thoracic Aortic Dissection (Class 1 Dissection)**

The pathognomonic lesion in aortic dissection is a tear in the intima which allows pulsatile surging of blood into the intimo-medial plane of the aorta. Typically the entry site is transverse but not involving the whole

circumference of the aorta. It usually extends down the left posterolateral plane of the aorta, in a spiral fashion.<sup>10</sup> These dissections may have communication between the false and true lumen, with intimal flap tears being present in >70% of cases at autopsy.<sup>9</sup> In a series of sudden deaths however, fenestrations were absent in 67% of cases.

Flow in the false lumen is usually antegrade but occurs retrograde in a small number of cases. Differences in the elasticity of the dissection flap and the aortic adventitia, and the increase in pressure in the false lumen predispose to collapse of the true lumen, with higher frequency of true lumen compression in non-fenestrated aortic dissection.

In 65% of cases of dissection, intimal tears occur in the ascending aorta, 20% in the descending and 10% in the arch, with 5% in the abdominal aorta.<sup>10</sup> There is a male:female ratio of 5:1 with a peak incidence of 50–60 years for proximal dissections, and 60–70yrs for distal dissection.<sup>10</sup>

There has been no particular success in defining the anatomical features of particular aortas that make them prone to dissection and long-term sequelae, despite analysis of multiple factors including tear depth and angle, local wall stress and the status of the vasa vasorum.<sup>17</sup>

### **Intramural Haematoma (Class 2 Aortic Dissection)**

Intramural haematoma (IMH) otherwise known as Class 2 aortic dissection is a less common precursor or variant form of TAD. It comprises approximately 6–10% of all acute aortic syndromes. Approximately 10–30% of patients presenting with symptoms consistent with TAD may have IMH on imaging.<sup>9</sup> Occurring in greater prevalence in Asian populations, it makes up 30–40% of AAS in Asian series. Defined as a bleed into the outer layers of aortic media

that lacks a discrete or detectable entry tear, it is usually seen on CT as a crescent shaped or concentric thickening of aortic wall. It may involve a longer segment of aorta than classical dissection. It appears as a ‘dissection without intimal tear’, and was previously described as such – however it is now recognised that there may be small atherosclerotic plaque ruptures in the wall of the vessel that are related to the proximal extent of the IMH.<sup>18</sup> There has been some suggestion that there may be focal rupture of vasa vasorum in the aortic wall which causes IMH, however with the advent of newer multidetector CT arrays, previously invisible intimal defects are now being recognised. This has led to the proposition that a ruptured vasa vasorum leads to increased focal transmural pressure and consequent ‘retrograde’ rupture of a pre-existing aortic plaque and intimal disruption.<sup>19</sup>

Two subtypes of IMH/Class 2 dissection are recognized.<sup>9</sup> The features of the two subtypes of IMH are summarized in Table 14.4.

IMH seems to be associated with a lower risk of malperfusion syndromes than classical TAD, although complications are common. Between 28–47% of cases of IMH progress to overt false luminal dissection. Early aneurysm formation or contained rupture develops in 20–45% of patients.<sup>14</sup> There is considerable crossover between these groups. Spontaneous regression is seen in approximately 10% of patients.<sup>9</sup>

Predictors of progression to TAD include recurrent/persisting pain, and presence of PAU. Some IMH may improve spontaneously with medical management only (particularly in Asian series). Younger ages, smaller aortic diameter (<4–4.5cm) and thinner haematoma (<1cm) confer better prognosis<sup>9,20</sup> and may allow conservative/non operative treatment with close observation. In one series, a 30-fold increase in

**TABLE 14.4:** Subtypes of IMH

	IMH Type 1	IMH Type II
<b>Wall thickness</b>	≤0.5cm	0.6 – 4.0cm (median >1.3cm)
<b>Vessel diameter</b>	<3.5cm	>3.5cm
<b>Mean length in IMH</b>	<11cm	>11cm
<b>Presence of flow in IMH on echocardiography</b>	Less common	Common
<b>Association with calcified plaque</b>	Not usually associated	Commonly associated
<b>Intimal appearance</b>	Smooth	Rough / Atherosclerotic
<b>Echocardiographic appearances</b>	Echo free zones present <30%	Echo free zones present >70%

progression to rupture was demonstrated if the aortic diameter was greater than 40mm. Wall thickness >1cm was associated with a nine-fold risk of progression.<sup>21</sup>

Location of IMH is also prognostic – ascending aorta has a high risk of progression to frank dissection and usually mandates repair. Exceptions to this seem to be Japanese and Korean series where there is a more benign course with Type A IMH treated with BP control, bed rest and serial imaging.<sup>18</sup>

Given recent advances in understanding of the contribution of genetic influences to MMP concentrations, elastin and collagen turnover and risk of syndromal AAS, it may be that the genotypic differences between Asian and European groups explains the differences in prognosis, progression and prevalence in IMH.

### **Penetrating Aortic Ulcer (Class 4 Aortic Dissection)**

Penetrating aortic ulcer (PAU) was first described in 1934 by Shennan and then subsequently further characterized by Stanson et al in 1986. This condition can be defined as ulceration of an aortic atherosclerotic

plaque penetrating through the internal elastic lamina into the aortic media. It is also classified as Class 4 Aortic Dissection.<sup>9</sup>

PAU comprises around 2.3–7.6% of acute aortic syndromes but in a series of 15 patients, 40% (n = 6) suffered aortic rupture, compared to a rate of 7.3% for Type A dissection and <4% for Type B, hence it is a morbid pathology when present.<sup>22</sup> It also appears that for a given aortic diameter the presence of PAU confers a worse prognosis than for classical or Class 1 TAD.<sup>22</sup>

PAU tends to occur in patients with extensive aortic atherosclerotic disease and in an older population than those affected by Class 1 dissection (a mean age of 77 years versus 54 for Type A dissection and 67 for Type B).<sup>22</sup> It appears that the pathological lesion (haemorrhage into/through an atherosclerotic plaque) is limited in its extent around the aorta by the transmural inflammation of extensive surrounding atherosclerosis. Penetration through, and dissection towards the adventitia can occur in the setting of medial penetration of the localised plaque haemorrhage.

Both IMH and PAU are recognised to be endpoints of a degenerative aortic pathology,

and largely occur in the descending thoracic aorta. In one series,<sup>23</sup> 90% of IMH and PAU were confined to the descending aorta.

Although such focal pathology as IMH and PAU seems ideally suited to treatment by endovascular means, it is probable that most patients in these groups with pathology in the descending aorta do not require intervention, unless they fulfil criteria that would categorise them in a treatment group for classical TAD (rupture/aneurysm etc). The presence of aneurysmal dilatation is a strong predictor of the requirement for intervention in the future.

## COMPLICATIONS OF ACUTE AORTIC SYNDROME

### Visceral ischaemia/malperfusion syndromes

Visceral ischaemia is one of the most significant and catastrophic consequences of TAD. In broad terms two main pathophysiological mechanisms of ischaemia have been described.

The first is a classical proximal entry tear in the absence of a distal fenestration. This leads to rapid and significant increases in mean false luminal pressure, leading to compression of the true lumen leading to distal ischaemia. In the context of considering treatment options, this pressure differential explains why the use of a bare stent alone in treating the entry tear is unlikely to succeed. It is unlikely that a bare stent would be able to compress the highly pressurised false lumen enough to divert flow without surpassing aortic rupture pressure.

A second pattern is where there is a distal fenestration present with relatively equivalent luminal pressures. This situation has a reduced risk of distal ischaemia as flow is not compromised, however an extension into a visceral vessel can cause branch ischaemia

in one of two ways. These are described as either fixed or dynamic branch ischaemia. Fixed occlusion is caused by false luminal thrombus or pressurisation leading to a fixed impingement of the ostia. Dynamic occlusion occurs in the presence of a flap which acts as a floating valve across the ostia, particularly where there is differential pressurisation.

It is worthwhile remembering that aortic branch occlusion and malperfusion syndrome are not totally synonymous, given that partial or dynamic branch occlusion may not lead to significant end-organ ischaemia. There is some evidence that in recent times survival outcomes of branch occlusion and malperfusion syndromes have significantly improved in comparison to previous data from 1965–1985.<sup>10</sup> There is also good evidence to support mesenteric revascularisation prior to ascending aortic repair in particular, with improvements in mortality from 87% to 37% over time.

Ischaemic complications are present in up to 30% of cases of Type B dissection.<sup>10</sup> Rupture is less common but occurs in >20% of cases over the patient's lifespan. Recent literature still suggests 16–25% mortality in the patient group suffering ischaemic complications.<sup>17</sup> IRAD has demonstrated an overall mortality of 27.4% for all types of dissection, with mortality in distal dissections in the uncomplicated medical therapy cohort being 10.7%, rising to 31% in the complicated cohort. Malperfusion syndromes occur in 30–42% of dissection patients.<sup>10</sup> Spinal cord ischaemia is relatively rare as a complication of TAD but is still present in 2–3% of Type B dissections at presentation.<sup>10</sup>

### Fate of the False Lumen

False lumen thrombosis occurs in 2–3% of medically managed patients, however even with surgical treatment distal false

lumen thrombosis only occurs in 15–30% of treated patients. This has implications for recurrent dissection and aneurysmal degeneration, with progression to aneurysm formation occurring in 30–50% of patients within 4 years of diagnosis of the initial dissection.<sup>10</sup> Long-term data show that aortic death is the ultimate outcome in 30–40% of patients with medically treated dissection, despite reasonable rates of early mortality with aggressive medical therapy.<sup>17</sup>

### **Aneurysmal Degeneration and Rupture**

As outlined above, aneurysmal degeneration and rupture is one of the potential consequences of AAS. In medically managed patients who survive their initial dissection event, 25–40% will continue onwards to develop aneurysmal dilatation. Out of this group 10–20% will rupture.<sup>10</sup> Degenerative disease rates in IMH are as high as 45%, with either contained rupture or aneurysm formation.<sup>18</sup> Similarly PAU rupture or aneurysm rates are in the region of 40% – with variable reports of severity/mortality risk. As discussed earlier, predictors of worse outcomes in IMH patients are initial aortic diameter above 4cm, and aortic wall thickness >1cm. These features conferred a 30-fold and 9-fold increase in progression to aneurysm and rupture respectively.<sup>10</sup> The prognostic features for development of aneurysmal degeneration include aortic size >4cm, persistent hypertension despite medical therapy, and persistent patency of the false lumen. Interestingly the recent data from IRAD also suggests a significant increase in 3 year mortality in the group with partial thrombosis of the false lumen – a relative risk of 2.69, with a 3 year mortality rate of 31.6%.<sup>14</sup>

## **CONNECTIVE TISSUE DISORDERS AND ACUTE AORTIC SYNDROMES**

Heritable disorders such as Marfan's Syndrome (MFS), Ehlers-Danlos Syndrome (EDS) and Loeys-Dietz Syndrome (LDS) are well-recognised predisposing causes for TAD, however in large series only contribute 14–22% of dissections.<sup>1</sup> Their presence predisposes patients to early dissection and aneurysm formation compared to the atherosclerotic cohort, and identification of these patients early in life allows targeted medical therapy, surveillance and early intervention as appropriate to prevent rupture and its associated mortality.

### **Marfan Syndrome**

Initially described by Antoine-Bernard Marfan in 1896 as a constellation of skeletal manifestations, Marfan Syndrome (MFS) has subsequently been more clearly codified into a recognised set of cardiovascular, skeletal and ocular findings. Marfan syndrome is responsible for approximately 5% of all aortic dissections and is the most common cause of dissection in patients under 40 years of age.

The classification of the syndrome was initially described in the Berlin Nosology (1986) but due to advances in molecular biology and further understanding of the disease and its sub-types, there was a new nosology developed in 1996 – the Ghent Nosology. This has recently been revised and was published in 2010.<sup>24</sup> This allows some differentiation from previously overlapping syndromes such as the Mitral Valve Prolapse Syndrome (MVPS) and the MASS (Myopia, Mitral Valve Prolapse, Non-progressive Aortic Root Dilatation, skeletal findings and striae), and also further differentiation from some of the more recently described overlap

syndromes such as Loeys-Deitz Syndrome. These other syndromes do not all carry the same vascular implications as MFS. Unfortunately in the past the laxity of diagnostic criteria meant that many people had the diagnosis of MFS applied, when in actuality their vascular mortality was lower than that of MFS.

The previously identified genetic basis of MFS is a mutation in the gene coding for fibrillin 1 – a cysteine-rich glycoprotein important in the manufacture of connective tissues. In the aorta, fibrillin 1 is prevalent in the aortic adventitia, and to a lesser degree in the media where fibrillin 2, a similar but functionally different protein, is more prevalent.<sup>25</sup> The anatomic abnormalities in the MFS aorta are those of ‘cystic medial degeneration’ – loss of VSMC numbers, increased collagen content and elastic fiber disarray.<sup>7</sup>

The current diagnostic criteria include a series of major and minor criteria. Major criteria include aortic root dilatation/dissection, Ectopia Lentis,  $\geq 4$  particular skeletal manifestations and dural ectasia as defining characteristics, and the presence of the fibrillin 1 mutation as a component of diagnosis when these are not clear. In index patients the diagnosis must involve major involvement in at least two organ systems and minor involvement in one more. In the presence of a fibrillin 1 mutation that is known to cause the MFS, or when there has previously been a first degree relative with MFS based on the Ghent Nosology – there need be only one major and one minor manifestation in different organ systems. The presence of the fibrillin1 mutation is now given more weight in light of the increased ease of detection.

The 2010 Ghent nosology has been developed based on a more evidence-based approach, and in a more patient centric fashion with an alteration in the weighting of different criteria and development of more meaningful diagnostic thresholds.

Cardinal features such as aortic root dilatation and ectopia lentis are now given more weight, and in combination can be diagnostic. Other systemic manifestations (in other organ systems) contribute to an overall systemic risk score that assists in diagnosis.

MFS has variable time of onset, tissue distribution and severity of clinical manifestation, even in patients with identical fibrillin gene mutation.

Of interest in MFS, levels of proteases such as MMP-9 are actually quite low, particularly in comparison to AAA phenotypes, and there is some suggestion that MFS-related dissection and aneurysm are not as strongly influenced by proteases as had previously been thought.<sup>6</sup>

### *Fibrillin and Marfan Syndrome*

Fibrillin1 is a fundamental component of the vascular ECM. Fibrillin-rich microfibrils play a significant role in linking vascular SMC to adjacent elastin fibrils. They are thought to regulate tissue development and turnover of elastin, and are a template for the construction of elastin microfibrils.<sup>6</sup>

The FBN-1 gene is a large gene on the q arm of Chromosome 15 at position 21.1. The description of this location is 15q21.1. It is closely associated with the gene for TGF $\beta$ 1. There are more than 600 described mutations in the FBN-1 gene that can cause MFS with varying degrees of penetrance. The majority (around 2/3) of fibrillin 1 mutations are missense mutations that alter one amino acid out of the 2871 that make up the protein. Approximately 20% are frameshift mutations, and 12% are side splice mutations. Around 25% of the presentations of MFS have a new and previously unidentified mutation in the fibrillin 1 gene.<sup>25</sup>

It was previously felt that the abnormality of the fibrillin1 gene led to structural abnormalities in ECM and elastin through fibrillin 1 weakness which were the cause of the

aneurysmal degeneration seen in MFS. This rather simplistic concept has been partly refuted, particularly in light of syndromes such as Williams-Beuren syndrome where a microdeletion of the elastin gene is actually characterised by aortic stenosis rather than aneurysm and dissection.<sup>6</sup> It is now postulated that there is both a structural and a signalling component to the pathophysiology. This has led to a change in the definition of Marfan's from a purely connective tissue disorder to a developmental abnormality with effects on the development and morphogenesis of multiple organ systems.

There is some evidence from mouse knockout models that underexpression of the fibrillin 1 gene results in increased MMP expression and elastin fragmentation, leading to reduced structural integrity of the aorta.<sup>26</sup> There is also upregulation of MMPs when mutated fibrillin 1 (which is more prone to proteolysis) undergoes degradation. There is similarly an increase in macrophage numbers in the setting of elevated concentrations of fibrillin 1 fragments.<sup>6</sup> There is some evidence of a degree of a threshold phenomenon for the deterioration in vessel structure in relation to proportional amounts of normal and abnormal fibrillin 1 microfibrils.

One of the proposed mechanisms by which fibrillin 1 mutation causes loss of tissue integrity is the documented impact of abnormal fibrillin 1 on the action of normal fibrillin-1 in the formation of microfibrils. This is a case of a heterozygote disorder where there is a dominant-negative pattern of activity caused by the mutated gene product.<sup>6,27</sup>

Fibrillin 1 gene mutations on their own (ie in absence of Marfan's) that result in decreased fibrillin1 gene expression have also been linked to thoracic aortic aneurysm (TAA) and TAD. A reduction in fibrillin 1 abundance, but with normal protein structure may lead to similar but less severe

phenotype to Marfan's that is restricted to the vascular system.<sup>26</sup> Similarly there appears to be a relationship between fibrillin 1 mutation and upregulation of TGF $\beta$ 1 signalling pathways. This may be because of structural and functional similarities between latent TGF $\beta$ 1 binding protein (LTBP) and fibrillin 1 and the possibility that abnormalities in the fibrillin 1 gene cause decreased affinity for TGF $\beta$ 1 in LTBP – hence releasing greater amounts of TGF $\beta$ 1 to increase signalling of TGF $\beta$ 1 and therefore increase VSMC apoptosis.<sup>6</sup>

Given the large number of unique mutations, genotypic/phenotypic correlations are difficult. There are also additions to the fibrillin 1 gene which can cause the related phenotypic abnormality that is MASS. The recently described interplay between fibrillin 1 and TGF $\beta$  has similarly provided new insight into potential mechanisms for and explanations of the variable penetrance and phenotypic appearance of MFS and related disorders.

SMADs are intracellular proteins that transduce extracellular signals from TGF $\beta$  ligands to the nucleus where they activate TGF $\beta$  gene transcription. Some recent evidence suggests that the majority of the vascular end points in MFS are related to the influence of fibrillin 1 mutation on TGF $\beta$ 1 levels and the subsequent TGF $\beta$ 1/SMAD2 signalling interaction. The downstream effect of this on elastin manufacture and disorganisation via upregulation of TGF $\beta$  responsive gene expression leads to elastolysis and ECM degradation.

### ***The Role of Transforming Growth Factor Beta (TGF $\beta$ ) in the Development of Vascular System in Health and Disease***

The TGF $\beta$  signalling pathway is important in both embryologic development – particularly in relation to body morphology and patterning, tissue differentiation and body

axis; as well as having a potent role in the differentiation and proliferation of a number of cell lines, and the stimulation of apoptosis – particularly in VSMCs. TGF $\beta$  mutations therefore have the potential to cause a number of congenitally acquired disorders of development and function of the skeletal, muscular and cardiovascular systems. This applies to both TGF $\beta$  and TGF $\beta$  receptors (TGF $\beta$ R) or components of the signaling pathway. This includes a number of ligands that are currently of particular interest to researchers in TAA/AAA/TAD.

The TGF $\beta$  superfamily is large, and signals via two main pathways – TGF $\beta$ /activin/nodal receptor to downstream intracellular transduction proteins SMAD2 and 3, or alternatively bone morphogenetic proteins (BMPs) to SMAD1 and 5.<sup>7,28</sup>

TGF $\beta$  has three ligand subtypes -1, -2 and -3. These are secreted as what is termed a large latent complex (LLC) comprising 3 polypeptide chains. These chains are the small dimeric TGF $\beta$  ligand, a latency associated peptide (LAP) to which TGF $\beta$  is non-covalently bonded and a latent TGF $\beta$  binding protein (LTGF $\beta$ BP) of which there are three subtypes which are covalently bound to the LAP.<sup>28</sup>

After secretion, the LLC is sequestered in the ECM in association with fibrillin 1. This provides a pool of stable, largely inactive TGF $\beta$  which can be released under stimulus from a reservoir. The TGF $\beta$  receptors and ECM with a reservoir are widespread and the effects of TGF $\beta$  occur both locally and systemically. This explains why the regulation of TGF $\beta$  secretion at local level by variation in levels of ECM components such as fibrillin 1 can have significant effects.

The mechanism of TGF $\beta$  ligand signaling is reasonably well understood and appears to occur via two families of TGF $\beta$  receptor, type 1 and type 2 (of which there are further subtypes within each family). TGF $\beta$  binding

to the type 2 receptor causes recruitment and subsequent phosphorylation of the type 1 receptor, leading to the formation of an activated receptor complex. TGF $\beta$  affinity for the receptor is variable, and there are a number of transmembrane co-receptors such as betaglycan (TGFBR3), which is high affinity but non-signalling, that enhance TGF $\beta$  binding to the type 2 receptor complex.<sup>28</sup>

The formation of the activated receptor complex leads to further cascading phosphorylation of receptor-associated SMADs (r-smads or smad 2/3). The type of SMAD activated depends on which TGF $\beta$ 1 receptor subtype is activated. Once the r-smad is activated it binds with a co-smad (SMAD4) to shuttle it to the nucleus to allow transcription of the target TGF $\beta$  gene.

Clearly this is a complex pathway, and furthermore there are a number of other intracellular kinases which can influence the phosphorylation and hence activity of the SMAD family, all of which can have outside influences.<sup>7,28,29</sup>

## Ehlers-Danlos Syndrome

Ehlers-Danlos Syndrome (EDS) is a hereditary disorder of connective tissue related to abnormalities in the gene for collagen, with six different types described.<sup>30,31</sup> It has an overall prevalence of approximately 1 in 25,000 live births.<sup>31</sup> Original descriptions were by Edward Ehlers in 1899 and Henri Alexandre Danlos in 1908. The most important subtype from the vascular perspective, and the most catastrophic in terms of presentation remains Type IV or what is now known as the vascular type, described by Andras Barbaras in 1967, in which he noted increased vascular fragility. The prevalence of the vascular type is <4% of all EDS cases. Presentations are heterogenous, and are not always entirely clear, and the distribution of clinical presentation reflects that of Type III collagen.

Children with EDS are often misdiagnosed as having coagulation disorders due to easy bruising.<sup>30</sup> Skeletal manifestations are consistent with abnormality in manufacture of Type III collagen with a defect in the pro- $\alpha$ -1 Type III collagen chain, coded for by the COL3A1 gene. Abnormalities in these collagens lead to ligamentous laxity.

The biochemical basis for EDS was described by Pope in 1975. It is a heterozygous mutation of the gene for Type III collagen, which is located on the long arm of chromosome 2, and is inherited in an autosomal dominant fashion.<sup>31</sup> Vascular EDS is best described as a monogenic orphan disease transmitted as an autosomal dominant trait. There is therefore a 50% chance of affected individuals passing on EDS to each child. Sporadic cases do however, account for up to half of all reported cases.

### ***Diagnosis of Ehlers-Danlos Syndrome***

Clinical diagnostic features of vascular EDS include typical facial features (although these may be absent in some cases), skin abnormalities with a thin translucent appearance and more visible veins, rupture of hollow viscera and vessels and easy bruising or ecchymoses. The classical facies of EDS are described as acrogeria, an appearance of slim face, thin long nose, sunken cheeks and often bulging or protruberant eyes. There may be periorbital pigmentation and/or telangiectasis. The upper lip is often fine and lacks puckering.<sup>30</sup> This is present in around 30% of patients.<sup>31</sup>

Skin manifestations vary from the other types of EDS, in particular the hypermobility and classical types, in that skin hyperextensibility is a less prominent feature. The skin does feel softer and is more translucent, and the subcutaneous vessels are often very prominent and visible – particularly on the trunk. Skin on the hands and feet is often more aged appearing than expected. With

previous scarring, the appearance is quite stretched and there may be deposits of haemosiderin and enlargement of scars over mobile areas.

Easy bruising is a common finding, particularly in the younger group – in fact it is the most consistent clinical feature, being present in 66% of reported cases in one series.<sup>32</sup> These bruises and subcutaneous haematomas are often huge – much larger than the inciting injury would account for. The presence of these bruises often prompts investigation of platelet function and coagulation, however the underlying pathology is vascular fragility rather than any haematological abnormality.

Vascular complications in EDS are relatively rare in infancy but prevalent in teens and in the third and fourth decades of life. More than 80% of people have had a vascular complication by the age of 40.<sup>31</sup> Median survival of vascular type EDS patients is only 48 years. Vessel complications are the leading cause of mortality in patients with vascular EDS; with aortic tears, dissection, and arteriovenous fistulas being seen along with classical arterial rupture. These events are often spontaneous with no apparent cause and can occur in otherwise normal appearing blood vessels. The thoracic aorta and abdominal aorta are the main sites of involvement with more than 50% of these events occurring in the distal thoracic aorta.<sup>31</sup> Middle-sized arteries appear to be the main vessels in which these events otherwise occur. Extremity vessel events contribute approximately 25% of the complications that are seen in vascular EDS.<sup>31</sup> Spontaneous arterial rupture into closed spaces can lead to compartment syndrome and limb loss. Sudden onset of flank or abdominal pain should mandate non-invasive imaging as it is a common presentation of intestinal, uterine or arterial rupture.

The most commonly seen intra-cerebral

catastrophe related to vascular Ehlers-Danlos Syndrome is carotid-cavernous fistula.<sup>30,32</sup> This is an exceedingly uncommon presentation in the normal population, and is seen almost exclusively in patients with traumatic injury. The occurrence of this in an atraumatic setting should lead to a high clinical suspicion of the presence of a collagen-vascular disorder. The mean age of occurrence of carotid-cavernous fistula in this population is 31 years compared with 58 years in the general population. Less common presentations include intracranial haemorrhage in approximately 4% of cases.<sup>7</sup> Most of these cases have a previously identified intracranial aneurysm. Extracranial dissection of both the vertebral and carotid arteries is also seen. As with carotid-cavernous fistula the presence of this pathology in the absence of trauma should suggest the presence of a collagen vascular disorder. Other vascular anomalies include prominent varicose veins and these are widely seen in EDS patients. Surgical treatment of varicose veins is contraindicated.

Gastrointestinal and obstetric complications are also common—both of these tissue types being rich in type III collagen. From the gastrointestinal point of view, the sigmoid colon is the most regularly involved site of perforation. In contrast to the hypermobility of classical types of EDS, joint hypermobility is not a prominent feature in vascular EDS. In some studies there is an increased risk of congenital hip dysplasia and congenital clubfoot in comparison to the general population.<sup>30</sup> Differential diagnosis of EDS includes a number of paediatric coagulation disturbances and Silverman Syndrome, which can also have easy bruising and haematoma. In adults, Marfan's disease should also be considered.<sup>30,33</sup>

The diagnostic criteria for EDS were outlined most recently in the Villefranche nosology<sup>34</sup> that breaks the more classical

description of EDS into six main types based on clinical presentation and the pathognomonic manifestations of each type. The presence of two or more major criteria is highly indicative of the disease and laboratory testing is recommended.<sup>34</sup>

Laboratory diagnosis involves the demonstration of structurally abnormal type III collagen produced by fibroblasts, and demonstration of an abnormal COL3A1 gene. The most reliable study is assessment of procollagen III deficiency using gel electrophoresis. This requires skin biopsy and has a risk of wound complications, thus site selection should be careful. Qualitative abnormalities in type III collagen can be seen by measuring secretion of type III collagen in cultured skin fibroblasts.<sup>30</sup>

Unfortunately although COL3A1 gene analysis is intuitively more accurate and would seem easier, it suffers the problem of lack of concordance between the mutation type and severity. There are numerous mutations possible in the gene given its large size, and there may be a greater prevalence of mutations than is currently recognised. Some mutations may have a degree of phenotypic correlation. Unfortunately the site of the mutation within the collagen gene has not been useful in predicting tissue integrity—one series of 135 EDS vascular type patients had no correlation between location of mutation and degree or presence of tissue fragility.<sup>35</sup>

From a biochemical perspective the most common point mutation that has been demonstrated is the replacement of a glycine in the collagen triple helix chain with another amino acid. Unfortunately the amino acid substitution does not correlate with phenotypic expression or clinical outcome. A proposed hypothesis in the aetiology of the clinical syndrome is that the abnormal procollagen components are either degraded in a form of 'protein suicide'<sup>35</sup> or are retained but their presence causes disruption of the

**TABLE 14.5:** The diagnostic criteria for the vascular subtype of EDS.

<b>Inheritance Pattern</b>	Autosomal dominant
<b>Major Diagnostic Criteria</b>	Thin, translucent skin
	Arterial/Intestinal/uterine fragility or rupture
	Extensive bruising
	Characteristic facial appearance
<b>Minor Diagnostic Criteria</b>	Acrogeria
	Hypermobility of small joints
	Tendon and muscle rupture
	Talipes equinovarus
	Early onset varicose veins
	Arteriovenous / carotid-cavernous sinus fistula
	Pneumothorax/haemopneumothorax
	Gingival recession
	Positive family history, sudden death in (a) close relative(s)

normal organisation and deposition of other types of collagens. This may explain the spectrum of differences in tissue fragility that are present with the same mutation. This is an evolving area of knowledge.<sup>31</sup>

Although controversial, some experts recommend ongoing surveillance to determine whether there is an incidental vascular lesion.<sup>31</sup> The controversy in this area arises from the fact that the majority of lesions will be treated conservatively and diagnosing them may increase patient anxiety unnecessarily. Arteriography is relatively contraindicated as an investigative modality in these patients as it is associated with a 67% complication rate and mortality rate of 17%,<sup>32</sup> however there is evolving discussion about its use as a treatment modality with the utilisation of endovascular coils or stents to minimise the use of arterial sutures. Similarly much of the previous evidence in relation to intervention in these patients was with larger sheaths

and the advent of lower profile devices may minimise these risks.

The prognosis of Vascular EDS is dismal, with 92% of late deaths in a cohort of 220 index patients being due to vascular catastrophes, with median survival being 48–54 years, and patient survival to 60 years being as low as 55–68%.<sup>31</sup> The average age of first vascular or visceral complication is 24yrs with a 12% mortality. Pregnancy has a 25% risk of death with each pregnancy and an associated 50% chance of passing on the mutated COL3A1 gene.<sup>32</sup>

### Loeys-Deitz Syndrome

Although MFS and EDS are by far the most commonly recognised connective tissue disorders (CTD) associated with AAS/TAD, recent understanding in the molecular biology of dissection has allowed recognition of a new disorder described by Bart Loeys and

Harry Deitz in 2005. This autosomal dominant CTD is recognised to be caused by mutation in the transforming growth factor beta (TGF $\beta$ ) receptor 1 or 2 gene. LDS prevalence is currently not well-described. LDS does appear to be intimately related to MFS, and this becomes clear when it is understood that the genetic anomaly in LDS is a loss-of-function mutation in the TGF $\beta$ R2 receptor – hence this mimics some of the effects of alteration in the levels of available TGF $\beta$  seen in fibrillin 1 deficiency syndromes such as MFS.

Phenotypic features of LDS include hypertelorism (90%), bifid uvula, cleft palate, generalised arterial tortuosity, craniosynostosis (50%), PDA and ASD. Mental retardation is often present. These features contrast with some of the features of MFS such as narrow high arched palate in MFS versus cleft, but there are a significant number of shared features such as ascending aortic aneurysm and dissection.

LDS falls into two types, LDS type 1 and LDS type 2. LDS1 has a number of similarities and overlap with MFS, including aortic root dilation, arachnodactyly (long thin fingers), dolichostenomelia (thin body and long extremities), pectus deformity and joint laxity. These patients are now discriminated from MFS patients in the new revised Ghent nosology by the absence of ectopia lentis (present in 40–56% of MFS patients) and other more stringent diagnostic criteria. LDS type 2 shares a number of similar features to vascular EDS, including soft, velvety skin and the presence of aortic aneurysm or dissection, however EDS lacks a significant number of features present in LDS including excessive vascular tortuosity, and bifid uvula. The table below outlines the major differences between the syndromes.

The vascular degenerative changes associated with LDS are significantly more malignant than those in MFS and occur

at a younger age, hence early recognition is vital. Aortic root aneurysm is reported in patients as young as 6 years of age. The underlying genetic abnormality of LDS leads to altered signaling in the TGF- $\beta$  cytokine family. TGF- $\beta$  plays an important role in ECM formation and turnover, as well as cell proliferation and differentiation, along with apoptosis. This influence on proliferation and differentiation is particularly apparent in cardiovascular embryogenesis, including ventricular myocardial genesis.

TGF- $\beta$  signal alterations lead to disarrayed elastin fibres, with loss of elastin content, and dilation and dissection as a consequence. In comparison to MFS, aortic and vascular aneurysms and dissections happen throughout the vascular tree, not just in the aortic root. Rupture has also been demonstrated in vessels <4.5 cm in diameter, in comparison to MFS where this would usually be considered a 'safe' size to manage conservatively.

Histological evaluation of vessels in LDS has shown excessive aortic wall collagen, along with increased levels of phosphorylated nuclear smad2. This indicates increased TGF $\beta$  signalling despite some degree of deficiency in the receptor.<sup>29</sup> In contrast to other CTD's, in particular EDS Vascular type, the surgical prognosis for LDS is quite good with reasonable surgical outcomes achievable as these patients lack the inherent tissue fragility of vascular EDS patients.<sup>35</sup>

### **Familial Thoracic Aortic Aneurysm Disease**

Recent research shows that there are a significant number of patients who do not have typical named syndromes such as MFS but who have familial clustering of thoracic aortic aneurysm disease (TAAD). These patients display features of aortic pathology including ascending aortic or root dilation

**TABLE 14.6:** Major clinical features of Loeys-Dietz Syndrome (LDS) type 1 and 2, Marfan syndrome and the vascular type of Ehlers Danlos Syndrome (EDS type IV). Modified from Aalberts et al., 2008.

	Marfan	LDS 1	LDS 2	EDS 4
<b>Vascular</b>				
Aortic aneurysm/dissection	++	+++	+++	+++
<i>Aortic Tortuosity</i>	-	+++	+++	-
ASD	-	+	+	-
<b>Skeletal</b>				
Arachnodactyly <sup>a</sup>	+++	++	++	-
Dolichostenomelia <sup>b</sup>	++	+		-
Pectus abnormalities	++	++	++	-
Joint laxity	++	++	+++	+ (small joints)
<i>Pes equinovarus</i> <sup>c</sup>	-	+		+
<b>Facial</b>				
Craniosynostosis <sup>d</sup>	-	+ /+++	-	-
Hypertelorism <sup>e</sup>	-	+++	-	-
<i>Cleft palate/bifid uvula</i>	-	+++	+	-
<b>Skin</b>				
Excessive striae	+	-	-	-
<i>Easy bruising</i>	-		+++	++
<i>Soft, velvety, translucent</i>	-	+	+/+++	+++
<b>Eyes</b>				
<i>Ectopia lentis</i> <sup>f</sup>	++	-	-	-
<b>Other</b>				
<i>Rupture large organs</i>	-	-	+/+++	++
<p>The presence or absence of the features in italics might help to differentiate from Marfan syndrome, - infrequently, + around 25–50%, ++ around 50–75%, +++ &gt;75%, <sup>a</sup>long slender fingers, <sup>b</sup>thin body habitus and long extremities, <sup>c</sup>clubfeet, <sup>d</sup>premature closure of cranial sutures, <sup>e</sup>increased distance between pupils, <sup>f</sup>lens subluxation</p>				

and aneurysms or dissection of the ascending or descending aorta. They appear to have an autosomal dominant pattern of inheritance but with variable penetrance and expression. That is, some carriers do not demonstrate the pathology, and those that develop the

pathology within a family do so at different severities. There is no gender bias. This is largely a diagnosis of exclusion, with a focus being on ruling out other named congenital or genetic anomalies that predispose to AAS/TAAD. The age of presentation provides some

hint as to the likely underlying pathology, with familial thoracic aortic aneurysm disease (FTAAD) patients presenting on average at older age than MFS patients, but younger age than sporadic TAAD patients.

Familial TAAD has been linked to a number of chromosomal abnormalities, some of which appear to be allelic with the mutations seen in well-characterised diseases such as MFS.

FTAAD type 1 is related to a gene defect on chromosome 11q23.3-4. This is an autosomal dominant inheritance pattern gene, but in comparison to a number of other syndromes, is a vascular-only syndrome with multiple segmental involvement of the thoracic and abdominal aorta commonly seen. This disease is highly penetrant in comparison to such diseases as MFS.

FTAAD type 2 has been linked to a 5q13-q14 mutation which is inherited in autosomal dominant fashion. In comparison to type 1 FTAAD, there is variable penetrance of this disorder, particularly in women. In comparison to type 1 FTAAD this process also carries with it a number of cardiovascular abnormalities which are similar to those seen in MFS. The postulation is that the 5q locus codes for a connective tissue protein of some kind.

FTAAD type 3 has a locus of mutation that maps to the 3p25-p24 site. This seems to be the site of the TGFBR2 gene, and the mutations that cause vascular anomalies appear to occur in the functionally important kinase domain leading to loss of function. This also overlaps a locus for a Marfan-like syndrome (the MFS2 locus). This mutation is found in approximately 5% of TAD patients. The phenotype is predominantly ascending aortic disease, however other site disease is also seen. Rupture and dissection at smaller sizes than usual is also recognised in the FTAAD type 3 patients.

## Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly (1–2% of the population) and predisposes patients to increased risk of dissection, dilatation and aneurysm, independent of valvular function.<sup>26</sup> It displays an autosomal dominant inheritance pattern and has been shown to have a strong link with TAA in a cohort of 13 families.<sup>25</sup>

Similar medial degeneration is seen in BAV as that seen in fibrillin1 knockout mice. There is a measurable deficiency of fibrillin 1 and elevated levels of MMP-2 in bicuspid aortic valves compared to the control population.<sup>26</sup> There is similarly evidence of decreased amounts of fibrillin 1 in aortic media in BAV patients, but normal elastin and collagen levels. This is in comparison to atherosclerotic dilation where fibrillin 1 levels are increased. This suggests that the underlying pathology in BAV is similar to that in fibrillin 1 knockout mice – increases in TGF $\beta$ 1 concentration and activity.

## Turners Syndrome

Monosomy X, or Turners syndrome (TS) is a moderately common chromosomal disorder, (1 in 2500 live births), that carries with it an increased risk of aortic coarctation and dissection. The most commonly seen cardiovascular anomaly in TS is bicuspid aortic valve, and as discussed earlier, this independently increases the risk of TAD. BAV is seen in 13–34% of TS patients compared with 1–2% of the general population. The risk of aortic dissection in young Turners patients is significantly higher than the general population and dissection occurs at sizes below that at which dissection would normally be considered a risk (<5cm). Dissection is usually Type A, although there is a correlation between aortic coarctation

(present in 4–14% of TS patients) and Type B dissection. Given the short stature of TS patients, the aortic size index rather than the raw aortic size is preferred for calculating aortic dissection risk in these patients.

## SUMMARY

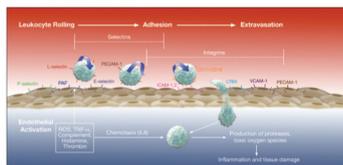
Although previously considered a simple haemodynamic consequence of chronic hypertension, thoracic aortic dissection in the classical sense is now recognised as being part of a continuum of aortic pathologies that include intramural haematoma, penetrating aortic ulcer and a number of congenital connective tissue disorders. The recent advances in the molecular understanding of aspects of ECM turnover – particularly relating to fibrillin 1 and transforming growth factor – beta have allowed us to expand our diagnostic and treatment options into new areas.

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## MECHANISMS OF VASCULAR DISEASE

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