We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Etiology and Pathogenesis of Aortic Aneurysms

Carl W. Kotze and Islam G. Ahmed
University College London
United Kingdom

1. Introduction

The introduction of aneurysm screening programmes in North America and Europe has led to a significant increase in the number of new diagnoses. The pathobiology of aortic aneurysm (AA) is both complex and multifactorial, and is associated with several significant developmental risk factors. Understanding current concepts in the etiology and pathogenesis of AA is therefore imperative in fueling future research studies and in aiding the development of treatment guidelines.

In 2001, the Vascular Biology Research Program of the National Heart, Lung and Blood institute (Wassef et al, 2001) summarised abdominal aortic aneurysm (AAA) pathogenic mechanism into four broad areas: proteolytic degradation of the aortic wall connective tissue, inflammation and immune response, molecular genetics and biomechanical wall stress. More recently Nordon and colleagues investigated three possible models of AAA pathogenesis not mutually exclusive: AAAs secondary to a local disease process confined to the abdominal aorta resulting from atherosclerosis; a systemic dilating diathesis primarily governed by genotype; and diseased vascular tree as a consequence of a chronic inflammatory process. They concluded that the evidence suggest AAA disease being a systemic disease of the vasculature, with a predetermined genetic susceptibility leading to a phenotype governed by environmental factors. AAAs are therefore referred to by some researchers as a degenerative disease (Nordon et al, 2011).

AAAs are associated with atherosclerosis, transmural degenerative processes, neovascularization, degeneration of vascular smooth muscle cells, and a chronic inflammation, mainly located in the outer aortic wall. Literature describes the relevant mechanisms of the formation and progression of idiopathic ascending aortic aneurysm as destructive remodeling of the aortic wall, inflammation and angiogenesis, biomechanical wall stress, and molecular genetics. Aneurysm occurrence and expansion could be further influenced by the variability of local hemodynamic factors and factors intrinsic to the arterial segment along the aorta (Kirsch et al, 2006). Observational evidence now suggests that the intraluminal thrombus (ILT), together with adventitial angiogenic and immune responses, play important roles in the evolution of atherothrombosis from the initial stages through to clinical complications, which include the formation of aneurysms (Michel et al, 2010). The role of ILT in AA pathogenesis merits further discussion and will be explored in subsequent chapters.

Uncertainty exists as to the impact of reported AA risk factors since the incidence of AAA is increasing despite a general reduction in tobacco use and an ever-increasing incidence of diabetes, which has been shown to have a protective influence. A number of other factors have also been commonly associated with aneurysm formation. They include family history, advanced age, male sex, hypertension, aortic dissection and arteriosclerosis. The significance of AA risk factors will be further explored in subsequent chapters.

2. Structural considerations in AA

Multiple factors rather than a single process are implicated in AA pathogenesis. These result in the destructive changes in the connective tissue of the media and adventitia of the aortic wall and ultimately lead to aneurysm formation and eventual rupture. The media is composed of multiple elastic laminae alternating with circularly oriented vascular smooth muscle cells (VSMCs) and surrounded by a copious ground substance. The adventitia lacks lamellar architecture but is composed of loose connective tissue with fibroblasts and associated collagen fibers and vasa vasorum. Integrity of the aortic wall is dependent on balanced remodelling of the extracellular matrix (ECM), predominantly of elastin, collagen and VSMCs. (Dobrin & Mrkvicka, 1994; Tilson, 1988).

2.1 Elastin
The chief component of the media is elastin, a lamellar ECM protein consisting of soluble tropoelastin monomers. Elastin production by the VSMCs ceases when a patient reaches maturity, therefore these soluble tropoelastin monomers, which are cross-linked by lysine residues, have a half life of 40 to 70 yrs (Rucker & Tinker, 1977). This could explain the elderly predisposition to AA formation. Normally, more than 99% of total elastin in arteries is found in an insoluble cross-linked form that can be stretched as much as 70% of its initial length (Stromberg & Wiederhielm, 1969). Elastin is responsible for the load bearing property that behaves uniformly in both the circumferential and longitudinal directions at different locations across the wall thickness (Dobrin, 1999), thereby absorbing oscillating arterial shock waves, providing recoil and maintaining arterial structure.

2.2 Collagen
Collagen is the primary structural component of the arterial adventitia and has been identified in smaller quantities in the media. It is a stable triple helix composed of three polypeptide chains with repeating tripeptide sequences (Prockop, 1990) and is responsible for tensile strength and resistance of the arterial wall. In contrast to elastin, collagen is synthesized on a continual basis throughout life, thereby collagen content represents the net effect of synthesis and degradation. Type 1 fibrillar collagen accounts for aortic wall load bearing capability (over 20 times greater than that of elastin), while Type 3 collagen provides some extensile stretch (Menashi et al, 1987). Arterial distension in response to increasing intraluminal pressures are limited through the recruitment of inextensible collagen fibers (Dobrin, 1978). Structural damage occurs when collagen is extended beyond 2–4% from its uncoiled form (Dobrin, 1988).

2.3 Vascular Smooth Muscle Cells (VSMCs)
VSMCs as part of the ECM form an important structural element and perform a mediator role in AA disease by producing TGF-beta1, ECM and inhibitors of proteolysis (O'Callaghan

& Williams, 2000). Transition of VSMCs from a contractile to a synthetic phenotype is characterized by a change in cell morphology, resulting in the production of substances such as components of the ECM, growth factors, and proteases, which are important in remodeling the vascular wall (Lesauskaite et al, 2003). This was verified by an experimental study that reported cultured VSMCs from AAAs exhibited greater elastolytic activity than VSMCs from Aortic Occlusive Disease (AOD) (Patel et al, 1996). VSMC density depends on patient age, patient gender and the location of quantification in non-atherosclerotic aneurysms. Conversely, loss of VSMCs is a characteristic of atherosclerotic aortic aneurysms (Sakalihasan et al, 2005; Kirsch et al, 2006). In particular VSMC apoptosis has been associated with fibrous cap thinning, enlargement of the necrotic core, plaque calcification, medial expansion and degeneration, elastin breaks, and failure of outward remodeling. In addition, chronic VSMC apoptosis may mimic multiple features of medial degeneration seen in a variety of human pathologies (Clarke et al, 2008).

2.4 Experimental and clinical studies

Histological examination of aneurysms reveals a thinning of the media, disruption of the medial connective tissue structure, and the loss of elastin (Campa et al, 1987) culminating in the effacement of the lamellar architecture (White et al, 1993). The role of the aortic media in contributing to wall stability is emphasized through studies demonstrating AA formation following media destruction with surgical resection, freezing, or the injection of acetrizoate or other noxious agents (Economou et al, 1960). Other studies confirmed that both elastin and collagen content is decreased in AA walls with increased collagen cross-links (Carmo et al, 2002) and an increased collagen to elastin ratio. (Cohen et al, 1988) Loss of elastin appears to be accompanied by an increase in the collagen content of the arterial wall, resulting in an overall decrease in the elastin to collagen ratio (Halloran & Baxter, 1995). This reflects in experimental studies that suggest that aortic elastase is significantly higher in patients with AAAs, multiple aneurysms, and ruptured AAAs compared with AOD. Also elastase and its major serum inhibitor, alpha 1-antitrypsin, are significantly altered in the aortic wall in different types of infrarenal aortic disease (Cohen et al, 1988).

AA development is characterised by intial elastin fragmentation responsible for aneurysmal elongation and tortuosity. There is consensus that as the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process (Shimizu et al, 2006). As the load bearing increases, more uncoiled collagen is recruited to load bear circumferentially (Goodall et al, 2002) resulting in a less distensible vessel. Collagen, because of its structural properties, must fail for significant dilatation and rupture to occur. This is confirmed as patients who are post aortic endarterectomy rarely incur AA disease. Dobrin et al. concluded that both elastin and collagen are possibly critical in AA dilatation with collagen failure resulting in gross expansion and rupture (Dobrin et al, 1994). This work confirmed experimental studies demonstrating that treatment with elastase leads to arterial dilatation and stiffening at physiologic pressures, whereas treatment with collagenase leads to arterial rupture without dilatation (Cohen et al, 1988). Cohen suggested that elastin degradation is a key step in the development of aneurysms, but that collagen degradation is ultimately required for aneurysm rupture. The integral role of VSMCs in AA disease is confirmed by an animal study that observed AAA prevention and regression after infusion with VSMCs (Allaire et al, 2002).

2.5 Structural considerations in TAA

Elastin lamellar units are found less frequently in AAA as compared to TAA, with an even more marked difference infrarenally. This relative paucity of elastin and collagen is thought to play a role, amongst other factors, in the predisposition for aneurysm development in the infrarenal aorta. The microscopic findings in TAAs are predominantly described as cystic medial degeneration, reflecting a non-inflammatory loss of medial VSMCs, fragmentation of elastic lamellae, and mucoid degeneration. In contrast, the histopathologic features of AAAs are characterized by severe intimal atherosclerosis, chronic transmural inflammation, neovascularization, and destructive remodeling of the elastic media (Diehm et al, 2007). Furthermore, ascending TAAs are associated with an underlying bicuspid aortic valve (BAV) with an estimated 75 % of patients who underwent BAV replacement demonstrating cystic medial necrosis on biopsy, compared to 14 % in patients who had tricuspid valve replacement. Inadequate levels of firillin-1 may be responsible for this weakness in aortic wall leading to BAV (Huntington et al, 1997).

	Ascending aorta	Abdominal aorta	Consequences
Elastin lamellae	–	number decreased/diameter	less provisional ECM
elastin/collagen	–	decreased	modified biomechanical properties
Embryonic origin of VSMCs	Neur-ectoderm	mesoderm	differences in responses to TGF-beta
Shear stress	–	decreased	control of inflammation
Thrombus in aneurysms	no	yes	neutrophils adsoption and protease release
VSMCs in aneurysms	unknown	decreased	homeostasis against inflammation, proteolysis

Table 1. Structural differences between TAA and AAA (Courtesy of Allaire, et al, 2009).

3. Molecular genetics in AA

Aortic aneurysms are a complex multi-factorial disease with genetic and environmental risk factors. Genetic factors have been shown to play a role in the etiology of TAA and AAA even though they are not associated aortic syndromes (Kuivaniemi al, 2008). The genetic basis of aortic aneurysms was reviewed in 1991 (Kuivaniemi et al, 1991). The major determining factor in the appearance of aortic aneurysms may be an inborn defect of collagen type III or of another component of the connective tissue matrix. At least 20% of aneurysms result from inherited disorders (Verloes et al, 1995). Medial necrosis of the proximal aorta in aneurysms or dissections is associated with a number of conditions, including inherited connective tissue disorders such as Marfan syndrome and Ehlers—Danlos syndrome type IV. It can also present along with bicuspid aortic valve, coarctation of the aorta, adult polycystic kidney disease and Turner syndrome (Caglayan & Dundar, 2009).

3.1 AAA

3.1.1 Genetic considerations in AAA

Screening studies suggest that having a first-degree relative with a AAA is associated with an odds ratio of 1.9 to 2.4 of developing a similar problem. AAAs develop in 20% of brothers of patients with the condition (Rizzo et al, 1989). These and other findings including the presence of multiple aneurysms and systemic abnormalities in aneurysm patients e.g., increased connective tissue laxity; all emphasize a role for genetic factors in AAAs.

A small number of studies have concentrated on multiplex AAA families (with at least 2 affected members) (Platsoucas et al, 2006; Oleszak et al, 2004). Genome-wide scans of these patients have suggested a role for genes located on chromosome 19q13 and 4q31.47. Candidate genes in these regions include interleukin (IL)-15, endothelin receptor A, programmed cell death 5, and LDL receptor-related protein 3.47 (Kuivaniemi et al, 2008).

3.2 TAA

Since more than 40% of patients with TAA are asymptomatic at the time of diagnosis, such aneurysms are typically discovered accidentally through routine examination or when complications arise. Once one aneurysm has been discovered, the patient is at increased risk for developing another aneurysm (Lawrie et al, 1993; Crawford et al, 1989). Therefore, lifelong follow-up is required in these patients. If any mutation is found in the patients affected, the mutation should then be investigated in their relatives, and hence genetic counseling should be given. Because of this increased risk, according to target diseases, chromosomal and gene analysis are essential in selected cases with aneurysms or dissections, especially in inherited forms (Caglayan & Dundar, 2009).

3.2.1 Genetic considerations in TAA

Although AAA's have been well characterized in terms of familial clustering, risk factors, growth rates, and possible modes of inheritance, less is known about thoracic aortic aneurysm (TAA). Rapid advances are being made in the understanding of TAA disease at the molecular genetic level. In pedigrees with several generations of multiply affected family members, chromosomal loci have been identified. These relate to the TAA phenotype by using the methods of linkage analysis and gene sequencing. Thus far, these loci have been mapped to the 5q13-14, 11q 23.2-24, and 3p24-25 chromosome sites (Vaughan et al, 2001; Hasham et al, 2002; Kakko et al, 2003). Most recently, important work has localized the mutation on the 3p24-25 chromosome to the transforming growth factor-receptor type II (Pannu et al, 2005). Albornoz and his colleagues evaluated 88 familial pedigrees with TAA and found that 70 (79.5%) had an inheritance pattern that was most consistent with a dominant mode of inheritance: 30 were autosomal dominant, 24 were autosomal dominant versus X-linked dominant, 15 were autosomal dominant with decreased penetrance, and there was one pair of monozygotic probands with a likely autosomal dominant spontaneous mutation. The other 18 pedigrees (20.5%) were most consistent with a recessive inheritance pattern, eight being autosomal recessive versus X-linked recessive, five autosomal recessive, and five autosomal recessive versus autosomal dominant with decreased penetrance. (Albornoz et al, 2006).

Affected Aortic Segment	Familial disorder	Mode of inheritance	Gene linked
Ascending thoracic / abdominal	Ehlers-Danlos syndrome type IV	Autosomal dominant	COLA3A1
Ascending	Marfan Syndrome	Autosomal dominant	FBN1 TGFβR2
	Turner Syndrome	Chrosomal	
	Osteogenesis imperfecta	Autosomal dominant	COLA1A1
Thoracic	Autosomal dominant adult polycystic kidney disease	Autosomal dominant	PKD1,PKD2
Abdominal	Homocystinuria	Autosomal recessive	CBS
	Pseudoxanthoma elasticum	Autosomal recessive	ABCC6

Table 2. Genetic diseases and Aortic Aneurysms

3.3 General behaviour of familial aneurysms
3.3.1 Aneurysm expansion
TAA is a lethal disease and the size of the aneurysm has a profound impact on aortic dissection and death (Coady et al, 1999). The growth rate of TAA is highly variable ranging from 0.03 to 0.22 cm per year. Genetic factors may play an important role in aortic growth rates. The data suggests that genetic etiology permits more rapid aortic dilatation, thus increasing the risk for aortic dissection. Physicians must know how to distinguish between syndromic and non-syndromic forms of aortic aneurysm and dissection. As a result family history is a most important factor in evaluating the patients who have aortic aneurysms or dissection (Caglayan & Dundar, 2009).

Aneurysms affecting the thoracic aorta in patients with Marfan syndrome behave more aggressively than TAA in patients without Marfan syndrome. However, the natural history of TAA in patients who do not have Marfan syndrome but who demonstrate a family history that is positive for aortic aneurysms has not been not well-described (Coady et al, 1997). It has also been reported that the presence of an aortic dissection significantly increases the aneurysm growth rate (Coady et al, 1997). Coady and colleagues clearly demonstrated that patients with familial nonsyndromic aneurysms and superimposed aortic dissections display a faster rate of aneurysmal growth (0.33 cm/y,) when compared with the overall growth rate of aortic dissections alone. The reasons for faster growth rates in patients exhibiting familial patterns and with concomitant aortic dissections are not clear, but may reflect a compounded environmental insult on a genetically weakened aortic wall (Coady et al, 1999).

3.3.2 Dissection
In most adults, the risk of aortic dissection or rupture becomes significant when the maximal aortic dimension reaches about 5.5 cm. However, in individuals with TGFBR2 mutations, dissection of the aorta may occur before the aorta extends to 5.0 cm (Loeys et al, 2005). Even patients with Loeys-Dietz syndrome (LDS) syndrome, both transforming growth factor, beta receptor 1 (TGFBR1) and two mutations have been described and dissections may occur under 5.0 cm (Caglayan & Dundar, 2009).

In the near future, new genetic studies such as single nucleotide polymorphisms (SNP) and RNA expression studies may help underlie genetic based therapies and develop more useful, simple and cheap diagnostic genetic tests for susceptible patients.

4. Haemodynamic factors and biomechanical wall stress considerations in AA

The pathobiology of AA is thought to be a multifactorial process that includes biological, biomechanical, and biochemical processes. Contrary to current understanding of biological and biochemical factors, the role of biomechanical factors in AA pathobiology is poorly understood. It is generally recognized that AAAs can continuously expand, dissect and even potentially rupture when the stress acting on the wall exceeds the strength of the wall. Wall stress simulation based on a patient-specific AAA model appears to give a more accurate rupture risk assessment than AAA diameter alone (Li et al, 2010).

4.1 Haemodynamic forces

The artery wall is subject to three distinct fluid-induced forces: (1) pressure created by hydrostatic forces, (2) circumferential stretch exerting longitudinal forces, and (3) shear stress created by the movement of blood. The net force includes a component perpendicular to the wall, the pressure; and a component along the wall, the shear stress. Disturbed flow conditions, such as turbulence, contribute to aneurysm growth by causing injury to the endothelium and accelerating degeneration of the arterial wall. Areas of flow oscillation and extremes in shear stress (high or low) correlate with development of atherosclerosis in the aorta (Ku et al, 1985). Although clinical studies show that flow within AAAs can be smooth and laminar or irregular and turbulent, little information is available on effects of wall shear stress in aneurysms (Miller, 2002).

Intra-aneurysmal flow is affected by the geometry of the aneurysm sac and surrounding vasculature; including the existence, size, and symmetry of branches arising near the aneurysm; and the position of the aneurysm sac relative to the parent vessel (e.g. sidewall, terminal, or bifurcation). Effort has been made to correlate rupture with these various geometric features. (Zeng et al, 2011)

4.2 Effect on aneurysm expansion

Vascular endothelial cells are constantly exposed to fluid shear stress, the frictional force generated by blood flow over the vascular endothelium. The importance of shear stress in vascular biology and pathophysiology has been highlighted by the focal development patterns of atherosclerosis in hemodynamically defined regions. For example, the regions of branched and curved arteries exposed to disturbed flow conditions, including oscillatory and low mean shear stresses (OS), correspond to atheroprone areas. In contrast, straight arteries exposed to pulsatile high levels of laminar shear stress (LS) are relatively well protected from atherosclerotic plaque development (Zarins et al, 1983). Changes in blood flow have been shown to be a critical factor inducing arterial remodeling (Manu & Plattet, 2006).

The increase in shear stress is also associated with a reduction in reactive oxidative stress (ROS). The flow-mediated increase in shear stress does not decrease oxidative stress in AAAs by reducing the inflammatory cell infiltrate, but through the expression of hemeoxygenase (HO-1) in macrophages. Activation of HO-1 expression is an adaptive cellular response to survive exposure to environmental stresses (Immenschuh & Ramadori, 2000). HO-1 has anti-

inflammatory effects and may play a beneficial role in reducing oxidative reactions through the production of the antioxidants biliverdin and bilirubin (Miller, 2002).

Because of limitations in studying hemodynamics in vivo, in vitro models of AAAs have often been used to analyze pressure and flow patterns. However, these biomechanical designs often use an axisymmetric model, whereas AAAs, particularly in advanced stages, are asymmetric, resulting in growth away from the lumen's centerline. Interpretation of mechanical models can also be limited if they neglect effects of branch arteries, or by their use of steady flow, rigid walls; and homogenous and incompressible fluid. Understanding the biology of AAA development and expansion requires experiments in animal models. Unfortunately, in vivo studies are complicated by controversy regarding appropriate animal models of human AAAs (Miller, 2002).

4.3 Effect on aneurysm rupture

Rupture of the aneurysm can be seen as a structural failure when the induced mechanical stresses acting on the weakened AAA wall exceed its local mechanical failure strength. The external forces include blood pressure and wall shear stress. Stress in the AAA wall is due to the influence of other concomitant factors, including the shape of the aneurysm, the characteristics of the wall material, the shape and characteristics of the intraluminal thrombus (ILT) when present, the eccentricity of the AAA, and the interaction between the fluid and solid domains (Li et al, 2010).

4.4 Haemodynamic factors and biomechanical wall stress considerations in TAA

The influence of biomechanical factors in TAA is scarcely reported, therefore the role that haemodymic factors play in TAA pathobiology remains unknown. Nevertheless, weakening of the aortic wall is compounded by increased shear stress, especially in the ascending aorta (Ramanath et al, 2009). An experimental study of a cylindrical model of TAA demonstrates that mean circumferential stress depends on the aortic diameter and systolic blood pressure but not on age or clinical diagnosis supporting the clinical importance of blood pressure control and serial evaluation of aortic diameter in these patients (Okamoto et al, 2003). Considering the functional complexity and structural differences of TAA compared to AAA, several hemodynamic factors might contribute to the development of TAA. However the predilection of aneurysm formation infrarenally suggests other factors may overrule haemodynamic factors in AA pathogenesis.

4.5 Current limitations

Although rupture is determined by the comparison of wall stress and wall strength, accurate wall strength measurement in vivo is currently not possible. Therefore, computed wall stresses at one time point may not necessarily provide an estimation of the risk of rupture without knowing the strength value at that time point. However, by following up patients and performing wall stress analysis based on follow-up images, the change in wall stresses may be more useful in identifying aneurysm stability (Li et al, 2010).

5. Enzymatic activity in AA

Proteolytic degeneration is known to cause AA formation and lead to disease progression. Proteases identified in excess in AA and other aortic diseases includes matrix metalloproteinases (MMPs), cathepsins, chymase and tryptase, neutrophil-derived serine

elastase and the enzymes of the plasmid pathway, tissue plasminogen activator (tPA), Urokinase-type Plasminogen Activator (uPA) and plasmin (Choke et al, 2005). These proteolytic enzymes are involved in regulating and remodeling the ECM.

5.1 Experimental and clinical studies

Pioneering work in animal models has demonstrated the role of proteolysis in AA. These experimental studies showed elongation and dilatation following treatment with elastase, and rupture post collagenase infusion. More recently, an in vivo study of aortic wall treated with doxycycline loaded, controlled-release, biodegradable fiber led to preservation of elastin content, decreased MMPs (most notably MMP-2 and MMP-9) and increased tissue inhibitor of metalloproteases (TIMP-1) (Yamawaki-Ogata et al, 2010). A number of MMPs, including elastases, collagenases, gelatinases and stromelysin, are found in increased concentrations in the media of the AAA and are normally inhibited by TIMP.

MMPs and other proteinases derived from macrophages and VSMCs are secreted into the extracellular matrix in response to stimulation by the products of elastin degradation (Ailawadi et al, 2003). Inflammatory infiltrates and invading neovessels are relevant sources of MMPs in the AAA wall and may substantially contribute to aneurysm wall instability (Reeps et al, 2009). In AA disease evidence suggests that the balance of vessel wall remodeling between MMPs, TIMPS, and other protease inhibitors favors elastin and collagen degradation with the net pathological effect of ECM destruction.

5.1.1 MMP-9 (92-kd gelatinase)

MMP-9 predominantly secreted by macrophages, monocytes and VSMCs is the most comprehensively studied of the metalloproteases. MMP-9 concentrations are higher in patients with AAA compared to subjects without AAA or AOD. Interestingly, Takagi observed that increased MMP-9 serum levels return to normal after aneurysm repair (Hisato Takagi et al, 2009). Furthermore, an experimental study showed that targeted gene disruption of MMP-9 prevented aneurysmal degeneration in murine models (Pyo et al, 2000). Recently, a correlation was found between AAA rupture and elevated plasma levels of MMP-9 and MMP-1 (Wilson et al, 2008).

5.1.2 MMP-2 (72-kd gelatinase)

Evidence suggests MMP-2 may be the most integral protease in ECM degeneration. MMP-2 sourced by adventitial VSMCs and fibroblasts is uniquely activated by membrane type (MT)-MMPs. MMP-2 has the ability to degrade both elastin and collagen, and possibly plays a role in early AA development. MMP-2 complements and facilitates the degenerative activity of MMP-9 in transgenic murine models, however some studies suggest that MMP-2 has greater elastolytic activity compared to MMP-9. MMP-2 levels are increased in subjects with AA compared to those with AOD or without AA disease. It is found predominantly in its active form (62-kd), which is closely associated with its substrates, which provide additional support of its role in ECM degradation. Convincing evidence from a rat aneurysm model demonstrated that the inhibition of AA formation following TIMP-1 over-expression, resulted in an activation blockade of both MMP-2 and MMP–9. Furthermore, Wilton concluded patients with larger aortic diameters have increased MMP-2/TIMP-1 ratios (Wilton et al, 2007).

5.1.3 MMP- 3

Matrix metalloproteinase-3 (MMP-3) degrades the ECM and may lead to the development of dilatative pathology of the ascending thoracic aorta (Lesauskaite et al, 2008). MMP-3 gene inactivation in mice demonstrated MMP-3 possibly causes degradation of matrix components, and promotes aneurysm formation by degradation of the elastica lamina (Silence et al, 2001).

5.1.4 MMP-12 (54-kd macrophage metalloelastase)

MMP-12 is involved in AA pathogenesis and shows a high affinity for elastin. In its active form the 22-kd enzyme degrades elastin (Longo et al, 2005). AA development in apolipoprotein E-knockout mice reported MMP-12 predominance in elastolytic activity. Deficiency of MMP-12 in the mice conferred protection against medial destruction and ectasia (Luttun et al, 2004).

5.1.5 Collagenases

Increasing collagenolytic activity has been identified in AAs, however collagen proteolysis is mostly associated with the terminal event of AA rupture. This is confirmed by greater levels of activity measured in specimens of ruptured aneurysms. (Busuttil et al, 1980).

5.1.6 MMP-1 (Collagenase-1)

MMP-1 localises within the mesenchymal cells (VSMCs, fibroblasts and endothelial cells) and is up-regulated by inflammatory mediators, however macrophage involvement has been described. Increased pro MMP-1, MMP-1 protein and mRNA levels have been reported in AAA compared to healthy aorta (Irizarry et al, 1993).

5.1.7 MMP-8 (Collagenase-2) (Matrilysin)

Studies report inconsistent expression of MMP-8 in AOD and AAA tissue, however, MMP-8 is stored as pre-formed protein in granules. Therefore MMP-8 mRNA may not accurately reflect protein concentration. Prominent expression of MMP-8 has been described in acute aortic dissection (Li et al, 2010).

5.1.8 MMP-13 (Collagenase-3)

MMP-13 is localised to VSMCs in close spatial proximity to collagen. Increased expression of MMP-13 in AAA compared to AOD tissue has been documented (Mao et al, 1999).

5.1.9 Inhibition of MMPs

Primary control of the activity of MMPs is achieved through tissue inhibitor of metalloproteinase (TIMP), by the formation of non-covalent complexes (Choke et al, 2005). TIMP-2, a broad-spectrum MMP inhibitor, and PAI-1, an inhibitor of tPA and uPA, are less expressed in AAA walls than in AOD, suggesting that ECM destruction is caused by a decrease in inhibitors and an increase in proteases (Allaire et al, 2009). Alpha-1-antitrypsin and Alpha-2-macroglobulin may suppress elastolysis, which is responsible for 90% of the inhibition of circulating MMPs, (Cohen et al, 1990). Treatment with atorvastatin decreases MMP expression and activity and leads to a reduction of TGF-beta signaling in the central region of human AAAs (Schweitzer et al, 2010). Ezetimibe combination therapy reduces aortic wall proteolysis and inflammation, key processes that drive AAA expansion (Dawson et al, 2011).

5.2 Proteolytic consideration in TAA

The hypothetical model of AAA cellular pathogenesis cannot completely explain the formation of dilatative pathology of the ascending thoracic aorta. The cellular expression of MMP-9 and their tissue inhibitors TIMP-1, TIMP-2, and TIMP-3 differ in the dilatative pathology of abdominal and thoracic aortas (Lesauskaite et al, 2006).

Overall a diminished expression of MMPs and tissue inhibitors relative to aged control AAAs in TAA, is documented. This may represent a loss of VSMCs in non-atherosclerotic TAA. Also, MT1-MMP plays a dynamic multifunctional role is TAA development (Jones et al, 2010). In Marfans syndrome MMP-2 and MMP-9 are found to be upregulated in TAA (Chung et al, 2007). Furthermore, animal studies show elevated MMP-9, MMP-2 and disintegrin and metalloproteinase domain-containing proteins 10 and 17 (ADAM-10 and -17) expressed in calcium chloride induced TAAs. Murine studies depleted of MMP-9 gene have demonstrated attenuated TAA formation (Ikonomidis et al, 2005).

6. Inflammatory changes in AA

AA is best described as a chronic inflammatory condition with an associated proteolytic imbalance. The most important pathological feature of human AA is probably the infiltration of inflammatory cells. The chronic infiltration consists mainly of macrophages, lymphocytes and plasma cells. It is suggested that these inflammatory cells and others play a regulatory role through release of a cascade of cytokines. This process results in the expression of cell adhesion molecules, increased protease expression, and the release of reactive oxygen species causing degradation of the ECM through the activation of MMPs and TIMP (Shah, 1997).

The recruitment of macrophages by chemotactic agents is possibly triggered by exposed elastin degradation products. Lymphocyte activation may be mediated by micro-organisms as well as by auto-antigens from structural degradation. TNF-alpha and INF-gamma appear to be the most consistently upregulated cytokines in patients with large AAAs. (Golledge et al, 2009). These inflammatory cytokines play multiple roles in regulating mesenchymal cell matrix metabolism, endothelial cell growth and proliferation, lymphocyte activation, antigen presenting cell (APC) function, major histocompatibility (MHC) class II molecule expression, vascular adhesion molecule expression, and even matrix degrading protease expression of surrounding cells (Wills et al, 1996).

Although AA and AOD are characterised by underlying inflammation, immunohistological studies have concluded that T- and B-cell predominance is localised to the outer media and adventitia in AA; compared to largely T–cell involvement localised to the intima and inner media in AOD. Furthermore, an autoimmune component to AA disease has been suggested after localisation of B lymphocytes in the media and considerable deposits of immunoglobulins (IgG) and complement in the wall of AA. (Lindholt & Shi, 2006).

6.1 Experimental and clinical studies

Key features of human AA include intense inflammation, increased expression of MMP-2 and MMP-9, and local ECM destruction. It became evident that inflammation plays an integral role in aneurysm pathogenesis following novel experimental animal models that demonstrated key features of human aneurysm following transmural chemical injury induced by calcium chloride treatment of vessel adventitia. Interestingly, aneurysm formation only developed after the inflammatory response was present, suggesting that inflammation occurring in response to chemical and mechanical injury is responsible for aneurysm development, rather

than direct elastolysis. The calcium chloride murine model further indicates that CD4+ lymphocytes may be central in orchestrating production of MMP-2 and MMP-9 through interferon gamma (Xiong et al, 2004; Gertz et al, 1988). Anidjar and Dobrin recognized that exposure of the aorta caused destruction of elastic lamellae with up to a 4-fold increase in AA diameter at 6 days following elastase treatment. This increase was also associated with media infiltration of a large number of activated macrophages and T-cells (Anidjar et al, 1994). Characteristics of the elastase infusion model demonstrated that inflammatory cell infiltrate is accompanied by an increase in MMP-2 and MMP-9. Interestingly, the infiltration of macrophages and T-lymphocytes is not the prominent feature in the ruptured edges of AAAs and is even less prominent in non-ruptured areas or walls of the same AAAs. Rather, ruptured areas present significantly increased amounts of immature micro-vessels, with an excess of total and activated MMPs (Choke et al, 2006). Furthermore, prostaglandins (PG) and leukotrienes may also contribute to AAA in that the deficiency of 5-lipoxygenase attenuates aneurysm formation of atherosclerotic apolipoprotein E-deficient mice, suggesting a role for the 5-LO pathway in AAA formation (Shimizu et al, 2006).

6.2 Inflammatory cells involved in AA
6.2.1 Lymphocytes
It is suggested that Th1 and Th2-restricted T lymphocyte are the most commonly found infiltrates in AAA walls and are activated by antigen presenting cells such as macrophages, VSMCs, and endothelial cells. These inflammatory cells are integral for the regulation of the immune response in AAA. However, the specific regulatory traits of components of the inflammatory cascades and of proteases that cause aneurysmal growth remain largely unresolved. This reflects in earlier mouse studies which designated AAA disease as a T-helper (Th)-2-type inflammatory disease and identified T-helper(Th)-2-restricted CD3C T as the dominant influx. Later human studies suggested differently with AAA disease labeled as Th1-dominated or as a general pro-inflammatory condition (Abdul-Hussein et al, 2010). Local production of Th1 cytokines (Interferon-gamma (IFN-gamma), Interleukin-2 (IL-2), IL-12, IL-15 and IL-18 possibly enhances macrophage expression of MMPs, whereas Th2 cytokines (IL-4, 5, 8, and 10, Tumor necrosis factor-alpha (TNF-alpha), INF-gamma and CD40 ligand) appear to suppress macrophage MMP production and limit disease progression (Lindholt & Shi, 2006). In addition T-helper (Th)-2 cells secrete an FAS-ligand and FAP-1 resulting in apoptosis of VSMCs and Th1 cells (Shonbeck et al, 2002). Cytokines TNF-alpha and IL-8 cause inflammatory cell recruitment that is responsible for stimulating neoangiogenesis. INF-gamma stimulates cathepsin production for further Th2 activation, B-cell differentiation and Ig secretion.
In most cases, the default pathway will be a Th1-dominant for stenotic arterial lesions; however, when the local environment is skewed toward Th2 predominance, aneurysms will develop (Shimizu et al, 2006). More recently a study comparing inflammatory and proteolytic processes in AAA and popliteal artery aneurysm, characterized degenerative aneurysmal disease as a general inflammatory condition that is dominated by profound activation of the nuclear factor-kappa-B and activator protein-1 pathways. There is also hyperexpression of IL-6 and IL-8, and neutrophil involvement (Adul-Hussein et al, 2010).

6.2.2 Macrophages
Inflammation is characterised by macrophage migration from the onset of AA formation. Elastin degradation products are possibly responsible for the recruitment of macrophages

by chemotactic agents. Heamodynamic forces may regulate macrophage adhesion, transmural migration and survival (Sho et al, 2004). A recent animal study confirmed that MT1-MMP acts directly to regulate macrophage secretion (Xiong et al, 2009). This antigen presenting cell is suggested to be a central role player in the immune response and subsequent ECM destruction. It is mostly localised in the adventitia of the AA wall. Through the secretion of cytokines (IL-1b, IL-6, IL-8, and TNF-alpha) and proteases (in particular MMP-9) these macrophages recruit inflammatory cells and stimulate cytokine production, protease production, B-cell differentiation, Ig secretion, cytotoxic T-cell differentiation and neovascularization. (Lindholt & Shi, 2006). In addition to producing cytokines and proteases, these cells also produce TIMP, confirming the governing role of macrophages in AA immune response. Animal studies confirmed the paramount role of macrophages in AA inflammatory response by demonstrating human-like aortic aneurysmal degradation without further manipulation following the application of macrophages and plasmin to the aorta (Werb et al, 2001).

6.2.3 Endothelial cells
Endothelial cells have been localised in AA and are found in approximation to neovascularisation. A prominent role for endothelial cells in the inflammatory response has been suggested following histological study reports of a positive association between the degree of inflammation and the degree of neovascularisation. It is suggested that these inflammatory cells play a role in ECM remodeling through the secretion of IL-1b and IL-8, which stimulate intercellular adhesion molecule-1 (ICAM-1) presentation, thus causing recruitment of additional inflammatory cells, attraction of lymphocytes, stimulation of endothelial proliferation, stimulation of B-cell differentiation and Ig secretion. In addition, like macrophages, the proliferating endothelium also produces various MMPs and TIMP (Lindholdt & Shi, 2006). To this end an experimental study has demonstrated that doxycycline not only inhibits MMP-8 and MMP-9 activity, but also the synthesis of MMPs in human endothelial cells (Hanemaaijer et al, 1998).

6.2.4 Fibroblasts
Although fibroblasts are commonly identified in the adventitia of AAA and have a recognized function in atherosclerosis, the role of the fibroblast in aneurysm pathogenesis is uncertain. Fibroblasts secrete cytokine IL-6 which is suggested to cause a stimulatory cascade of B-cell and cytotoxic T-cell differentiation and MMP stimulation (Thompson & Parks, 1996).

6.3 Infection and AA
An infectious cause of aneurysm formation has also been suggested. Between 30% and 50% of AAAs are associated with *Chlamydia* and *Herpes* virus infections. *Chlamydia* has been shown to induce AAA in rabbits and antichlamydial antibodies are commonly detected in AAA patients, however a causal relationship remains to be established. Studies have suggested that these infections play a role in elastolysis, possibly creating and augmenting an autoimmune response through particle mimicking. Lindholt et al. found that serum antibodies against C. Pneumonia have been associated with AAA expansion and cross-reaction with AAA structural proteins. Thus, immune responses mediated by microorganisms and autoantigens may play a pivotal role in AAA pathogenesis (Lindholt et al, 1999).
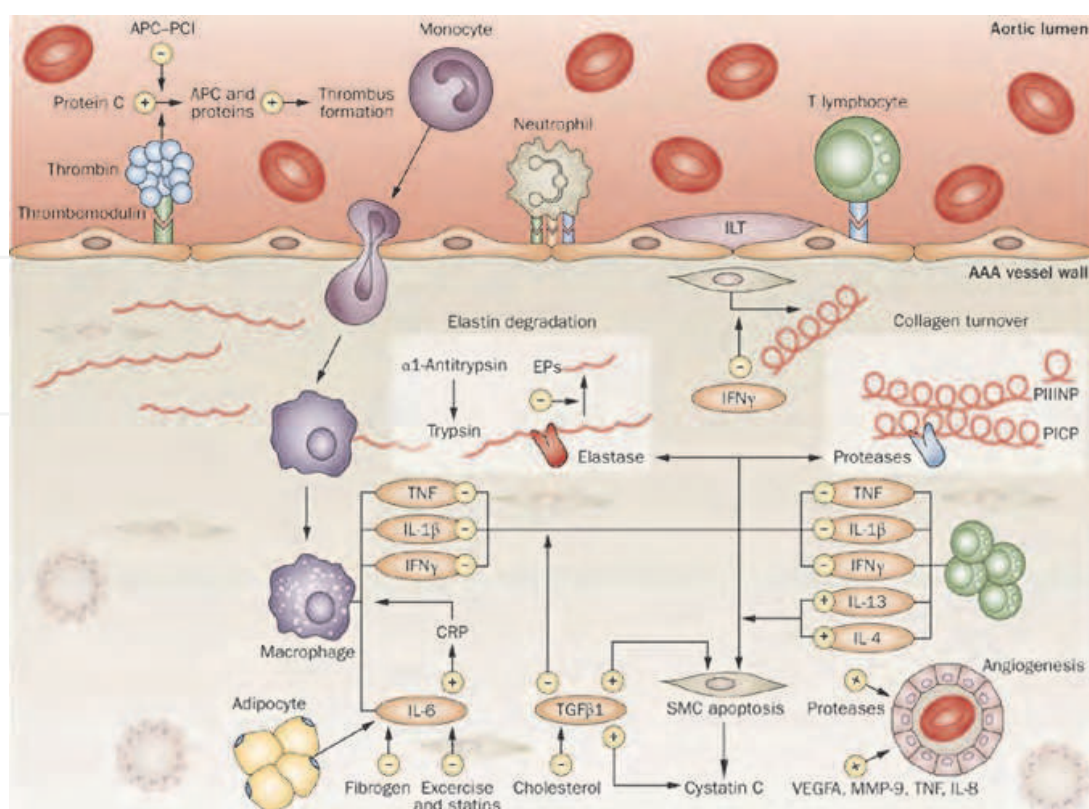
Fig. 1. Schematic diagram of the mechanisms implicated in abdominal aortic aneurysm, which primarily involve two main processes: inflammation and extracellular matrix turnover (Courtesy of Hellenthal et al, 2009).

6.4 Reactive oxygen species and AA

Reactive oxygen species such as superoxide (O2-) have also been shown to be raised in human AAAs. Elastase infusion in animal models has been shown to increase nitric oxide synthase expression and decrease the expression of the antioxidant, superoxide dismutase. O2- levels in human aneurysmal tissue are 2.5-fold higher than in adjacent nonaneurysmal aortic tissue and 10-fold higher than in control aorta (Miller et al, 2002).

6.5 Inflammation considerations in TAA

Developmental variation between TAA and AAA leads to differences in cellular responses to similar biological responses (El-Hamansy & Yacoub, 2009). Similar to AAA, histological studies demonstrate inflammatory cells in the adventitia and media of the aortic wall. In particular TAA infiltrate consistently shows CD3+, CD45+, CD68+ cells in the adventitia along with a prominent vasovasorum (possibly suggesting its role as conduit) and local endothelial activation (El-Hamansy & Yacoub 2009). Immunohistochemical staining showed that T- lymphocytes followed by macrophages were the predominant inflammatory cell in sporadic TAA (Guo et al, 2000). A Th1-type immune response is predominant in TAA as mRNA levels of INF-y are significantly increased compared to controls. Specific inflammatory pathways implicated in TAA formation remain unknown. However, transforming growth factor Beta (TGF-B), a cytokine, is recognized to be central in TAA pathogenesis causing ECM degeneration through the production of plasminogen activators and the release of MMP-2 and MMP-9. Reduced or mutated forms of fibrillin 1 release active

TGF-B, which in turn activates mitogen kinase activated pathways in VSMCs. Emilin 1, however, inhibits TGF-B signaling (El-Hamamsy & Yacoub 2009). 'Mycotic' aneurysms are found in less than 1% of patients with TAA. Salmonella, Staphylococcus and Mycobacterium species are mostly identified in blood cultures and tissue samples of subjects with AA disease (Koeppel et al, 2000). The role of oxidative stress is well described in AAA, however this remains to be established in TAA disease.

7. Implications for AA management

Current treatment of AA targets risk factors and the reduction of inflammation and proteolysis in AA walls. To this extent AA repair (open or endovascular) is currently practiced when aneurysms reach the recommended size for intervention or become symptomatic. The role of in vivo imaging techniques in vascular inflammation, such as Hybrid Positron Emmission Tomography / CT, that reflects the macrophage metabolic activity, may help to clarify the role of inflammation in AA pathogenesis and aid in the evaluation of treatment response. Currently, the potential role of pharmacotherapy in attenuation of AA growth is under investigation. Evidence suggests that smoking cessation may slow aneurysm growth and reduce the risk of rupture; therefore all AA patients should be counseled on the risks of smoking.

Antihypertensive medication has been investigated in the past, as hypertension is regarded as a potential significant risk factor for AA disease. A meta-analysis did suggest a significantly attenuated growth rate by β-blockers, however randomised control trials reported no benefit in the β-blocker (propanolol) group (Guessous et al, 2008) and a greater stroke and all-cause mortality with a short peri-operative course of β-blockers. Angiotensin converting enzyme (ACE) inhibitors have been demonstrated to cause AA attenuation in animal models, however no clinical trial has been conducted to confirm this. The exact mechanism by which ACE inhibitors restrict aneurysm growth is unknown; however its ability to bind zinc, an important cofactor for MMP activity, has been suggested. Nevertheless, a population based study suggested that patients taking ACE inhibitors were less likely to present with rupture (Hackman et al, 2006). TGF-β antagonists such as TGF-β–neutralizing antibody or the angiotensin II type 1 receptor (AT1) blocker, losartan, have demonstrated prevention of AA in a mouse model of Marfan Syndrome (Habashi et al, 2006) but no significant proven effect in human AAA. Distinguishing TAA from AAAs might explain the differential findings regarding the beneficial effects of angiotensin II type 1 receptor (AT1) blocker on various aortic aneurysmal pathologies. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) restrict aneurysm growth through reduction of IL6 and MMPs (in particular MMP-9) in experimental models. However, a recent meta-analysis concluded that reduction in AAA expansion rate due to statins is not significant (Twine & Williams, 2010). Tetracyclines such as doxycycline, inhibit MMPs in animal models and have been shown to significantly reduce the growth of AAA. This has been confirmed clinically by a small scale, randomised, placebo controlled pilot study (Mosorin et al, 2001). Furthermore a macrolide antibiotic (Roxithromycin) used in a small randomised clinical trial reported a 44% reduction in AAA growth over 12 months, with the effect gradually tailing off up to 5 years (Vammen et al, 2001). Non-steroidal anti-inflammatory drug, Indomethacin prevents elastase induced AAA in animal models through CoX 2 inhibition, leading to reduction of MMP-9 and PGE2 (Miralles et al, 1999). More recently, the antioxidant properties of Vitamin E have been investigated in AAA

models. It has been shown to block the induction of AAA in Angiotensin II-infused Apo-E knockout mice via reduction of macrophage infiltration and reduction of a chemotactic cytokine, suggesting that inhibition of oxidative stress in aneurysm tissue may play a significant role in AA pathobiology and be a possible treatment target (Gavrilla et al, 2005).

8. Conclusion

Interaction of multiple factors rather than a single process is responsible for the failure of the integrity of the aortic wall, which result in AA formation and progression. Despite several similarities in etiology and pathogenic mechanisms, it appears that TAA differs in many ways from AAA. Current areas of interest include proteolytic degradation of the arterial wall, inflammation and the immune response, biomechanical wall stress, and molecular genetics. Knowledge of the pathobiology of AA has lead to more targeted imaging methods and treatment trial design to investigate various pathobiological mechanisms of AA progression. Although some agents show promise, large controlled trials are needed to demonstrate clinically significant benefits. Future research should take into consideration knowledge gained of the differences between TAA and AAA pathobiology when designing clinical trials, in order to unravel the specificities of these different events in AA. As it stands surgical treatment of AA disease continues to be the most effective means of addressing the majority of factors involved in AA formation and progression.

9. References

Abdul-Hussien, H.; Hanemaaijer, R.; Kleemann, R.; Verhaaren, B.; Hajo van Bockel, J.; Lindeman, J. (2010). The pathophysiology of abdominal aortic aneurysm growth: Corresponding and discordant inflammatory and proteolytic processes in abdominal aortic and popliteal artery aneurysms. *Journal of Vascular Surgery*, Vol.51, No.6, (June 2010), pp. 1479-87, ISSN 1097-6809

Ailawadi, G.; Eliason, J.; Upchurch, G. (2003). Current concepts in the pathogenesis of abdominal aortic aneurysm. *Journal of Vascular Surgery*, Vol.38, No.3, (September 2003), pp. 584-8, ISSN 1097-6809

Albornoz, G.; Coady, MA.; Roberts, M.; Davies, R.; Tranquilli, M.; Rizzo, J.; Elefteriades, J. (2006). Familial thoracic aortic aneurysms and dissections: incidence, modes of inheritance, and phenotypic patterns. *Annals of Thoracic Surgery*, Vol.82, No.4, (October 2006), pp. 1400 –1405, doi:10.1016/j.athoracsur.2006.04.098

Alexander J. (2004). The pathobiology of aortic aneurysms. *Journal of Surgical Research*, Vol. 117, No. 1, (March 2004), pp. 163-175. doi:10.1016/j.jss.2003.11.011.

Allaire, E.; Muscatelli-Groux, B.; Mandet, C.; Guinault, A.; Bruneval, P.; Desgranges, P.; Clowes, A.; Méllière, D.; Becquemin, J. (2002). Paracrine effect of vascular smooth muscle cells in the prevention of aortic aneurysm formation. *Journal of Vascular Surgery*, Vol.36, No.5 (November 2002), pp. 1018-26, doi:10.1067/mva.2002.12734

Allaire, E.; Schneider, F.; Saucy, F.; Dai, J.; Cochennec, F.; Michineau, S.; Zidi, M.; Becquemin, J.; Kirsch, M.; Gervais, M. (2009). New insight in aetiopathogenesis of aortic diseases. *European Journal of Vascular and Endovascular Surgery*, Vol.37, No.5 (May 2009), pp. 531-7, doi:10.1016/j.ejvs.2009.02.002

Anidjar, S.; Dobrin, P.; Chejfec, G.; Michel, J. (1994). Experimental study of determinants of aneurismal expansion of the abdominal aorta. *Annals of Vascular Surgery,* Vol.8, No.2, (March 1994), pp. 127-36, ISSN 0195-6108

Busuttil, R.; Abou-Zamzam, A.; Machleder, H. (1980). Collagenase activity of the human aorta. A comparison of patients with and without abdominal aortic aneurysms. *Archives of Surgery*, Vol.115, No.11, (November 1980), pp. 1373-8, ISSN 0004-0010

Caglayan, A.; Dundar, M. (2009). Inherited diseases and syndromes leading to aortic aneurysms and dissections. *European Journal of Cardiothoracic Surgery*, Vol.35, No.6, (June 2009), pp. 931-940 ISSN 0305-1048

Campa, J.; Greenhalgh, R.; Powell, J. (1987). Elastin degradation in abdominal aortic aneurysms. *Atherosclerosis,* Vol.65, No.1-2, (May 1987), pp.13-21, ISSN: 0021- 9150

Carmo, M.; Colombo, L.; Bruno, A.; Corsi, F.; Roncoroni, L.; Cuttin, M.; Radice, F.; Mussini, E.; Settembrini, P. (2002). Alteration of elastin, collagen and their cross-links in abdominal aortic aneurysms. *European Journal of Vascular and Endovascular Surgery*, Vol.23, No.6, (June 2002), pp. 543-549

Choke, E.; Cockerill, G.; Wilson, W.; Sayed, S.; Dawson, J.; Loftus, I.; Thompson, M. (2005). A review of biological factors implicated in abdominal aortic aneurysm rupture. *European Journal of Vascular and Endovascular Surgery*, Vol.30, No.3, (September 2005) pp. 227-44, ISSN 1078-5884

Choke, E.; Cockerill, G.; Dawson, J.; Wilson, R.; Jones, A.; Loftus, I.; Thompson, M. (2006). Increased angiogenesis at the site of abdominal aortic aneurysm rupture. *Annals of New York Academic Science*, Vol.1085, (November 2006), pp. 315-9, DOI 10.1196/annals.1383.007

Chung, A.; Au Yeung, K.; Sandor, G.; Judge, D.; Dietz, H.; van Breemen, C. (2007). Loss of elastic fiber integrity and reduction of vascular smooth muscle contraction resulting from the upregulated activities of matrix metalloproteinase-2 and -9 in the thoracic aortic aneurysm in Marfan syndrome. *Circulation Research*. Vol.101, No.5, (August 2007), pp. 512-22, ISSN 1524-4571

Clarke, M.; Littlewood, T.; Figg, N.; Maguire, J.; Davenport, A.; Goddard, M.; Bennett, M. (2008). Chronic apoptosis of vascular smooth muscle cells accelerates atherosclerosis and promotes calcification and medial degeneration. *Circulation Research*. Vol.102, No.12, (June 2008), pp. 1529-38, ISSN: 1524-4571

Coady, M.; Rizzo, J.; Hammond, G. (1997). What is the appropriate size criterion for resection of thoracic aortic aneurysms? *Journal of Thoracic and Cardiovascular Surgery*, Vol.113, No.3, (March 1997), pp. 476-91, ISSN 0022-5223

Cohen, J.; Mandell, C.; Chang, J.; Wise, L. (1988). Elastin metabolism of the infrarenal aorta. *Journal of Vascular Surgery*, Vol. 7, No. 2, (February 1988), pp. 210-214

Cohen, J.; Sarfati, I.; Ratner, L.; Tilson, D. (1990). Alpha 1-antitrypsin phenotypes in patients With abdominal aortic aneurysms. *Journal of Surgical Research*, Vol. 49, No. 4, (October 1990), pp. 319-21, ISSN 0022-4804

Crawford, E.; Svensson, L.; Coselli, J.; Safi, H.; Hess, K. (1989). Surgical treatment of aneurysm and/or dissection of the ascending aorta, transverse aortic arch, and ascending aorta and transverse aortic arch. Factors influencing survival in 717 patients . *Journal of Thoracic and Cardiovascular Surgery*, Vol.98, No.5 pt 1, (November 1989), pp.659-73, ISSN 0022-5223

Dawson, J.; Choke, E.; Loftus, I.; Cockerill, G.; Thompson, M. (2011). A randomised placebo-controlled double-blind trial to evaluate lipid-lowering pharmacotherapy on

proteolysis and inflammation in abdominal aortic aneurysms. *European Journal of Vascular and Endovascular Surgery*, Vol.41, No.1, (January 2011), pp. 28-35, doi:10.1016/j.ejvs.2010.08.023

Diehm, N.; Dick, F.; Schaffner, T.; Schmidli, J.; Kalka, C.; Di Santo, S.; Voelzmann, J.; Baumgartner, I. (2007). Novel Insight Into the Pathobiology of Abdominal Aortic Aneurysm and Potential Future Treatment Concepts. *Progress in Cardiovascular Diseases*, Vol.50, No.3, (November 2007), pp. 209-217,doi:10.1016/j.pcad.2007.05.001

Dobrin, P. (1978). Physiological Properties of Arteries. *Physiological Reviews,* Vol.58, No.2, (April 1978), pp. 397-460

Dobrin, P. (1988). Mechanics of normal and diseased blood vessels. *Annals of Vascular Surgery*, Vol.2, No.3, (July 1988), pp. 283-94.

Dobrin, P.; Mrkvicka R. (1994). Failure of elastin or collagen as possible critical connective Tissue alterations underlying aneurysmal dilatation. *Cardiovascular Surgery,* Vol.2, No.4, (August 1994), pp.484–488

Dobrin, P. (1999). Distribution of lamellar deformations: implications for properties of the arterial media. *Hypertension,* Vol.33, No.3, (March 1999), pp. 806-810

Economou, S.; Taylor, C.; Beattie, E.; Davis, C. Persistent experimental aortic aneurysms in dogs. *Surgery*, Vol.47, (January 1960), pp. 21-8

El-Hamamsy, I.; Yacoub, M. (2009). Cellular and molecular mechanisms of thoracic aortic aneurysms. *Nature Review Cardiology*, Vol.6, No.12, (December 2009), pp. 771-86, ISSN 1759-5002

Gavrila, D.; Li, W.; McCormick, M.; Thomas, M.; Daugherty, A.; Cassis, L.; Miller, F.; Oberley, L.; Dellsperger, K.; Weintraub, N. (2005). Vitamin E inhibits abdominal aortic aneurysm formation in angiotensin II-infused apolipoprotein E-deficient mice. *Arteriosclerosis Thrombosis Vascular Biology*, Vol.25, No.8, (August 2005), pp. 1671-7, ISSN 1524-4636

Gertz, S.; Kurgan, A.; Eisenberg, D. (1988). Aneurysm of the rabbit common carotid artery induced by periarterial application of calcium chloride in vivo. *Journal of Clinical Investigation*, Vol.81, No.3, (March 1988), pp. 649-56, doi: 10.1172/JCI113368

Golledge, A.; Walker, P.; Norman, P.; Golledge, J. (2009). A systematic review of studies examining inflammation associated cytokines in human abdominal aortic aneurysm samples. *Disease Markers,* Vol.26, No.4, (September 2009), pp. 181-8. Review. ISSN 0278-0240.

Goodall, S.; Porter, K.; Bell, P.; Thompson, M. (2002) Enhanced invasive properties exhibited by smooth muscle cells are associated with elevated production of MMP-2 in patients with aortic aneurysms. *European Journal of Vascular and Endovascular Surgery*, Vol.24, No.1, (July 2002), pp. 72-80

Guessous, I.; Periard, D.; Lorenzetti, D.; Cornuz, J.; Ghali, W. The efficacy of pharmacotherapy for decreasing the expansion rate of abdominal aortic aneurysms: a systematic review and meta-analysis. *PLoS One*, Vol.26, No.3, (March 2008), e1895.

Guo, D.; Papke, C.; He, R.; Milewicz, D. (2006). Pathogenesis of thoracic and abdominal aortic aneurysms. *Annals of the New York Academy of Science*, Vol.1085, (November 2006), pp. 339-52. Review

Habashi, J.; Judge, D.; Holm, T.; Cohn, R.; Loeys, B.; Cooper, T.; Myers, L.; Klein, E.; Liu, G.; Calvi, C.; Podowski, M.; Neptune, E.; Halushka, M.; Bedja, D.; Gabrielson, K.; Rifkin, D.; Carta, L.; Ramirez, F.; Huso, D.; Dietz, H. (2005). Losartan, an AT1 antagonist,

prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science,* Vol.7, No.312, (April 2006), pp.117-21, ISSN 0036-8075

Hackman, D.; Thiruchelvam, D.; Redelmeier, D. (2006). Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet,* Vol.368, No.9536, (August 2006), pp. 659–65

Halloran, B.; Baxter, B. (1995) Pathogenesis of aneurysms. *Seminars in Vascular Surgery*, Vol.8, No.2, (June 1995), pp. 85–92

Hanemaaijer, R.; Visser, H.; Koolwijk, P.; Sorsa, T.; Salo, T.; Golub, L.; van Hinsbergh, V. Inhibition of MMP synthesis by doxycycline and chemically modified tetracyclines (CMTs) in human endothelial cells. *Advances in Dental Research*, Vol.12, No.2, (November 1998), pp. 114-8, doi 10.1177/08959374980120010301.

Hasham, S.; Guo, D.; Milewicz, D. (2002). Genetic basis of thoracic aortic aneurysms and dissections. *Current Opinion in Cardiology,* Vol.17, No. 6, (November 2002), pp.677–683, ISSN 0268-4705

Hellenthal, F.; Buurman, W.; Wodzig, W.; Schurink, G. (2009). Biomarkers of abdominal Aortic aneurysm progression. Part 2: inflammation. *Nature Review Cardiology,* Vol.6, No.8, (August 2009), pp. 543-52, doi:10.1038/nrcardio.2009.102

Huntington, K.; Hunter, A.; Chan, K. (1997). A prospective study to assess the frequency of Familial clustering of congenital bicuspid aortic valve. *Journal of The American College of Cardiology*, Vol.30, No.7, (December 1997), pp. 1809-12

Ikonomidis, J.; Barbour, J.; Amani, Z.; Stroud, R.; Herron, A.; McClister, D.; Camens, S.; Lindsey, M.; Mukherjee, R.; Spinale, F. (2005). Effects of deletion of the matrix metalloproteinase 9 gene on development of murine thoracic aortic aneurysms. *Circulation,* Vol.112, No.9, (August 2005), pp. I242-8, doi: 10.1161/CIRCULATIONAHA.104.526152.

Immenschuh, S.; Ramadori, G. (2000). Gene regulation of heme oxygenase-1 as a therapeutic target. *Biochemical Pharmacology*, Vol.60, No.8, (October 2000), pp.1121–1128, doi:10.1016/S0006-2952(00)00443-3

Inzoli, F.; Boschetti, F.; Zappa, M.; Longo, T.; Fumero, R. (1993). Biomechanical factors in abdominal aortic aneurysm rupture. *European Journal of Vascular Surgery*, Vol.7, No.6, (November 1993), pp.667–674, ISSN 0950-821X

Irizarry, E.; Newman, K.; Gandhi, R.; Nackman, G.; Halpern, V.; Wishner, S.; Scholes, J.; Tilson, M. (1993). Demonstration of interstitial collagenase in abdominal aortic aneurysm disease. *Journal of Surgical Research*, Vol.54, No.6, (June 1993), pp. 571-4, doi 10.1006/jsre.1993.1087

Jones, J.; Zavadzkas, J.; Chang, E.; Sheats, N.; Koval, C.; Stroud, R.; Spinale, F.; Ikonomidis, J. (2010). Cellular phenotype transformation occurs during thoracic aortic aneurysm development. *Journal of Thoracic Cardiovascular Surgery*, Vol.140, No.3, (September 2010), pp. 653-9, doi 10.1016/j.jtcvs.2009.12.033

Kakko, S.; Raisanen, T.; Tamminen, M. (2003). Candidate locus analysis of familial ascending aortic aneurysms and dissections confirms the linkage to the chromosome 5q13-14 in Finnish families. *Journal of Thoracic and Cardiovascular Surgery*, Vol.126, No. 1, (July 2003), pp. 106-13, doi 10.1016/S0022-5223(03)00037-0

Kirsch, M.; Radu, C.; Allaire, E.; Loisance, D. (2006) Pathobiology of Idiopathic Ascending Aortic Aneurysms. *Asian Cardiovascular Thoracic Annals*, vol.14 no.3, (June 2006), pp. 254-260

Koeppel, T.; Gahlen, J.; Diehl, S.; Prosst, R.; Dueber, C. (2004). Mycotic aneurysm of the abdominal aorta with retroperitoneal abscess: successful endovascular repair. *Journal of Vascular Surgery*, Vol.40, No.1, (July 2004), pp. 164-6, doi:10.1016/j.jvs.2004.02.046.

Ku, D.; Giddens, D.; Zarins, C.; Glagov, S. (1985). Pulsatile flow and atherosclerosis in the human carotid bifurcation: positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis,* Vol.5, No.3, (June 1985), pp. 293–302, ISSN: 1079-5642

Kuivaniemi, H.; Tromp, G.; Prockop, D. (1991). Genetic causes of aortic aneurysms. Unlearning at least part of what the textbooks say. *Journal of Clinical Investigation,* Vol.88, No.5, (November 1991), pp. 1441-1444, ISSN 0268-4705

Kuivaniemi, H.; Platsoucas, C.; Tilson; M. (2008). Aortic Aneurysms: An Immune Disease with a Strong Genetic Component. *Circulation*, Vol.117, No.2, (Jan 2008), pp. 242-252, ISSN 1524-4539

Lawrie, G.; Earle, N.; DeBakey, M.(1993). Long-term fate of the aortic root and aortic valve after ascending aneurysm surgery. *Annals of Surgery,* Vol.217, No.6 , (June 1993), pp.711-20. ISSN 0003-4932

Lesauskaite, V.; Ivanoviene, I.; Valanciute, A. (2003). Programmed cellular death and atherogenesis: from molecular mechanisms to clinical aspects. *Medicina*, Vol.39, No.6, (January 2003), pp. 529-34

Lesauskaite, V.; Epistolato, M.; Castagnini, M.; Urbonavicius, S.; Tanganelli P. (2006). Expression of matrix metalloproteinases, their tissue inhibitors, and osteopontin in the wall of thoracic and abdominal aortas with dilatative pathology. *Human Pathololy*, Vol.37, No.8, (August 2006), pp. 1076-84, doi:10.1016/j.humpath.2006.03.017

Lesauskaite, V.; Sinkūnaite, G.; Benetis, R.; Grabauskas, V.; Vaskelyte, J.; Smalinskiene, A.; Simonyte, S.; Jariene, G.; Tatarūnas, V.; Klumbiene, J.; Petkeviciene, J.; Kinduris, S.; Giedraitis, S.; Sakalauskas, J.; Bolys, R.; Sirvinskas, E.; Lenkutis, T.; Pangonyte, D. (2008). Matrix metalloproteinase-3 gene polymorphism and dilatative pathology of ascending thoracic aorta. *Medicina* (Kaunas), Vol.44, No.5, (February 2008), pp. 386-91

Li, Z.; Sadat, U.; U-King-Im, J.; Tang, T.; Bowden, D.; Hayes, P, Gillard, J. (2010). Association between aneurysm shoulder stress and abdominal aortic aneurysm expansion: A Longitudinal Follow-Up Study. *Circulation,* Vol.122, No.18, (November 2010), pp. 1815-1822, doi 10.1161/CIRCULATIONAHA.110.93981

Li, Y.; Shao, A.; Jiang, H.; Dong, G.; Xu, B.; Yi, J.; Jing, H. (2010). The prominent expression of plasma matrix metalloproteinase-8 in acute thoracic aortic dissection. *Journal of Surgical Research*, Vol.163, No.2, (October 2010), e99-104, Epub 2010, doi 10.1016/j.jss.2010.05.030

Lindholt, J.; Fasting, H.; Henneberg, E.; Ostergaard, L. (1999). A review of Chlamydia pneumoniae and atherosclerosis. *European Journal of Vascular and Endovascular Surgery*, Vol.17, No.4, (April 1999), pp. 283-9, Review, doi 10.1053/ejvs.1998.0757

Lindholt, J.; Shi, G. Chronic inflammation, immune response, and infection in abdominal aortic aneurysms. *European Journal of Vascular and Endovascular Surgery*, Vol.31, No.5, (May 2006), pp. 453-63, Review, doi 10.1016/j.ejvs.2005.10.030

Loeys, B.; Chen, J.; Neptune, E.; Judge, D.; Podowski, M.; Holm, T.; Meyers, J.; Leitch, C.; Katsanis, N.; Sharifi, N.; Xu, F.; Myers, L.; Spevak, P.; Cameron, D.; De Backer, J.; Hellemans, J.; Chen, Y.; Davis, E.; Webb, C.; Kress, W.; Coucke, P.; Rifkin, D.; De Paepe A.; Dietz H. (2005). A syndrome of altered cardiovascular, craniofacial,

neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nature Genetics*,Vol.37, No.3, (March 2005), pp. 275−81, doi:10.1038/ng1511

Longo, G.; Buda, S.; Fiotta, N.; Xiong, W.; Griener, T.; Shapiro, S.; Baxter, B. (2005). MMP-12 has a role in abdominal aortic aneurysms in mice. *Surgery*, Vol.137, No.4, (April 2005), pp. 457-62.

Luttun ,A.; Lutgens, E.; Manderveld, A.; Maris, K.; Collen, D.; Carmeliet, P.; Moons, L. (2004). Loss of matrix metalloproteinase-9 or matrix metalloproteinase-12 protects apolipoprotein E-deficient mice against atherosclerotic media destruction but differentially affects plaque growth. *Circulation*, Vol.109, No.11, (March 2004), pp. 1408-14, ISSN 1524-4539

Mao, D.; Lee, J.; VanVickle, S.; Thompson, R. (1999). Expression of collagenase-3 (MMP-13) in human abdominal aortic aneurysms and vascular smooth muscle cells in culture. *Biochemistry Biophysics Research Communications,* Vol.261, No.3, (August 1999), pp. 904-10., doi10.1006/bbrc.1999.1142

Menashi, S.; Campa, J.; Greenhalgh, R.; Powell, J. (1987). Collagen in abdominal aortic aneurysm: Typing, content, and degradation. *Journal of Vascular Surgery*, Vol.6, No.6, (December 1987), pp. 578-582

Michel, J.; Ventura, J.; Egido, J.; Sakalihasan, N.; Treska, V.; Lindholt, J.; Allaire, E.; Thorsteinsdottir, U.; Cockerill, G.; Swedenborg, J. For the FAD EU consortium. (2011) Novel aspects of the pathogenesis of Aneurysms of the Abdominal Aorta in humans. *Cardiovascular Research,* Vol. 90 No.1, (April 2011), pp. 18-27 ISSN 0008-636

Miller, F.; Sharp, W.; Fang, X.; Oberley, L.; Oberley, T.; Weintraub, N. (2002). Oxidative stress in human abdominal aortic aneurysms: a potential mediator of aneurysmal remodeling. *Arteriosclerosis Thrombosis Vascular Biololy,* Vol.22, No.1, (April 2002), pp. 560–565, ISSN 1524-4636

Miller, F. (2002). Aortic Aneurysms: It's All About the Stress. *Arteriosclerosis, Thrombosis and Vascular Biology*, Vol.22, No.12, (December 2002), pp. 1948-1949, DOI 10.1161/01.ATV.0000047947.37203.82

Miralles, M.; Wester, W.; Sicard, G.; Thompson, R.; Reilly, J. (1999) Indomethacin inhibits expansion of experimental aortic aneurysms via inhibition of the cox2 isoform of cyclooxygenase. *Journal of Vascular Surgery,* Vol.29, No.5, (May1999), pp.884-92

Mosorin, M.; Juvonen, J.; Biancari, F.; Satta, J.; Surcel, H.; Leinonen, M.; Saikku, P.; Juvonen, T. (2001). Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *Journal of Vascular Surgery*, Vol.34, No,4, (October 2001), pp 606-10

Nordon, I.; Hinchliffe, R.; Loftus, I.; Thompson, M. (2011). Pathophysiology and epidemiology of abdominal aortic aneurysms. *Nature Reviews Cardiology,* Vol.8, No.2, (February 2011), pp. 92-102, ISSN 1759-5002

O'Callaghan, C.; Williams, B. (2000) Mechanical strain-induced extracellular matrix production by human vascular smooth muscle cells: role of TGF-ß1. *Hypertension,* Vol.36, No.3, (September 2000), pp. 319–324, ISSN 1524-4563

Okamoto, R.; Xu, H.; Kouchoukos, N.; Moon, M.; Sundt, T. (2003). The influence of Mechanical properties on wall stress and distensibility of the dilated ascending aorta. *Journal of Thoracic Cardiovascular Surgery*, Vol.126, No.3, (September 2003), pp. 842-50, ISSN 0022-5223

Oleszak, E.; Chang J.; Friedman, H.; Katsetos, C.; Platsoucas, C. (2004). Theiler's virus infection: a model for multiple sclerosis. *Clinical Microbiology Reviews*, Vol.17, No.1, (January 2004), pp.174 –207, ISSN 0079-645X

Pannu, H.; Fadulu, V.; Chang, J. (2005). Mutations in transforming growth factor-_ receptor type ii cause familial thoracic aortic aneurysms and dissections. *Circulation*, Vol.112, No.4, (July 2005), pp. 513–20, ISSN 0009-7322

Patel, M.; Melrose, J.; Ghosh, P.; Appleberg, M. (1996). Increased synthesis of matrix Metalloproteinases by aortic smooth muscle cells is implicated in the etiopathogenesis of abdominal aortic aneurysms. *Journal of Vascular Surgery*, Vol.24, No.1, (July 1996), pp. 82-92

Platsoucas, C.; Lu, S.; Nwaneshiudu, I.; Solomides, C.; Agelan, A.; Ntaoula, N.; Purev, E.; Li, L.; Kratsios, P.; Mylonas, E.; Jung, W.; Evans, K.; Roberts, S.; Lu, Y.; Layvi, R.; Lin, W.; Zhang, X.; Gaughan, J.; Monos, D.; Oleszak, E.; White, J. (2006). Abdominal aortic aneurysm is a specific antigen-driven T cell disease. *Annals of the New York Academy of Sciences*, Vol.1085, (November 2006), pp. 224 –235, ISSN 0077-8923

Prockop, D. (1990). Mutations that alter the primary structure of type I collagen. The perils of a system for generating large structures by the principle of nucleated growth. *The Journal of Biological Chemistry*, Vol.265, No.26, (September 1990), pp. 15349 -15352. ISSN: 0021-9258

Pyo, R.; Lee, J.; Shipley, J.; Curci, J.; Mao, D.; Ziporin, S.; Ennis, T.; Shapiro, S.; Senior, R.; Thompson R. (2000). Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. *Journal of Clinical Investigation*, Vol.105, No.11, (June 2000), pp. 1641-9, doi 10.1172/JC18931

Ramanath, V.; Oh, J.; Sundt, T.; Eagle, K. (2009). Acute aortic syndromes and thoracic aortic aneurysm. *Mayo Clinical Proceedings*, Vol.84, No.5, (May 2009), pp. 465-81, ISSN 0025-6196

Ramanath, V.; Oh, J.; Sundt, T.; Eagle, K. (2009). Acute aortic syndromes and thoracic aortic aneurysm. *Mayo Clinical Proceedings*, Vol.84, No.5, (May 2009), pp. 465-81, ISSN 0025-6196

Reeps, C.; Gee, M.; Maier, A.; Pelisek, J.; Gurdan, M.; Wall, W.; Mariss, J.; Eckstein, H.; Essler, M. (2009). Glucose metabolism in the vessel wall correlates with mechanical instability and inflammatory changes in a patient with a growing aneurysm of the abdominal aorta. *Circulation: Cardiovascular Imaging*, Vol. 2, No. 6, (November 2009) pp. 507-9. doi 10.1161/CIRCIMAGING.109.858712

Rizzo, R.; McCarthy, W.; Dixit, S.; Lilly, M.; Shively, V.; Flinn, W.; Yao, J. (1989). Collagen types and matrix protein content in human abdominal aortic aneurysms. *Journal of Vascular Surgery*, Vol.10, No.4, (October 1989), pp.365–373, ISSN 1018–1172

Rucker, R.; Tinker, D. (1977) Structure and metabolism of arterial elastin. *International Review of Experimental Pathology,* Vol.17, (January 1977), pp. 1-47.

Sakalihasan, N.; Limet, R.; Defawe, O. (2005). Abdominal aortic aneurysm. *The Lancet,* Vol.365, No.9470, (January 2005), pp. 1577-1589, doi:10.1016/S0140-6736(05)66459-8

Schönbeck, U.; Sukhova, G.; Gerdes, N.; Libby, P. T(H)2 predominant immune responses prevail in human abdominal aortic aneurysm. *American Journal of Pathology*, Vol.161, No.2, (August 2002), pp. 499-506, ISSN 0002-9440

Schweitzer, M.; Mitmaker, B.; Obrand, D.; Sheiner, N.; Abraham, C.; Dostanic, S.; Meilleur, M.; Sugahara, T.; Chalifour, L.; (2010). Atorvastatin modulates matrix metalloproteinase

expression, activity, and signaling in abdominal aortic aneurysms. *Vascular and Endovascular Surgery*, Vol.44, No.2, (February 2010), pp116-22, doi:10.1177/1538574409348352

Shimizu, K.; Shichiri, M.; Libby, P.; Lee, R.; Mitchell, R. (2004). Th2-predominant inflammation and blockade of IFN-gamma signaling induce aneurysms in allografted aortas. *Journal of Clinical Investigation*, Vol.114, No.2, (July 2004), pp.300-8, doi 10.1172/JC1200419855

Shimizu, K.; Mitchell, R.; Libby, P. (2006). Inflammation and cellular immune responses in Abdominal aortic aneurysms. *Arteriosclerosis Thrombosis and Vascular Biology*, Vol.26, No.5, (May 2006), pp. 987-94. ISSN: 1524-4636

Shah, P. (1997). Inflammation, metalloproteinases, and increased proteolysis: an emerging pathophysiological paradigm in aortic aneurysm. *Circulation*, Vol.96, No.7, (October 1997), pp. 2115-7.

Sho, E.; Sho, M.; Hoshina. K.; Kimura, H.; Nakahashi, T.; Dalman, R. (2004). Hemodynamic Forces regulate mural macrophage infiltration in experimental aortic aneurysms. *Experimental Molecular Pathology*. Vol.76, No.6, (April 2004), pp. 108-16, doi10.1016/j.yexmp.2003.11.003

Silence, J.; Lupu, F.; Collen, D.; Lijnen, H. (2001). Persistence of atherosclerotic plaque but reduced aneurysm formation in mice with stromelysin-1 (MMP-3) gene inactivation. *Arteriosclerosis Thrombosis Vascular Biololoy*, Vol.21, No.9, (September 2001), pp. 1440-5, ISSN 1524-4636

Stromberg, D.; Wiederhielm, C. (1969). Viscoelastic description of a collagenous tissue in simple elongation. *Journal of Applied Physiology,* Vol.26, No.6, (June 1969), pp. 857-62

Takagi, H.; Manabe, H.; Kawai, N.; Goto, S.; Umemoto, T. (2009). Circulating matrix metalloproteinase-9 concentrations and abdominal aortic aneurysm presence: a meta-analysis. *Interacteractive Cardiovascular Thoracacic Surgery*, Vol.9, No.3, (September 2009), pp. 437-40, Review, doi 10.1510/icvts.2009.208835

Thompson, R.; Parks, W. (1996). Role of matrix metalloproteinases in abdominal aortic aneurysms. *Annals of the New York Academy of Sciences*, Vol.18, No.800, (November1996), pp. 157-74, Review, doi 10.1111/j.1749-6632.1996.tb33307.x

Twine, C.; Williams I. (2010) Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms. *British Journal of Surgery*, Vol.98, No.3, (March 2011), pp 346-53, doi 10.1002/bjs.7343

Vammen, S.; Lindholt, J.; Ostergaard, L.; Fasting, H.; Henneberg, E. (2001). Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. *British Journal of Surgery*, Vol.88, No.8, (August 2001), pp. 1066-72, ISSN 1365-2168

Vaughan, C.; Casey, M.; He, J. (2001). Identification of a chromosome 11q23.2-q24 locus for Familial aortic aneurysm disease, a genetically heterogeneous disorder. *Circulation*, Vol.103, No.20, (May 2001), pp. 2469 –2475, ISSN 0009-7322

Verloes, A.; Sakalihasan, N.; Koulischer, L.; Limet, R. (1995). Aneurysms of the abdominal aorta: familial and genetic aspects in three hundred thirteen pedigrees. *Journal of Vascular Surgery*, Vol.21, No.4, (April 1995), pp.646-655, ISSN 0741-5214

Wassef, M.; Baxter, T.; Chisholm, R.; Dalman, R.; Fillinger, M.; Heinecke, J.; Humphrey, J.; Kuivaniemi, H.; Parks, W.; Pearce, W.; Platsoucas, C.; Sukhova, G.; Thompson, R.; Tilson, D.; & Zarins, C. (2001). Pathogenesis of abdominal aortic aneurysms: A multidisciplinary research program supported by the National Heart, Lung, and

Blood Institute. *Journal of Vascular Surgery*, Vol.34, No 4, (October 2001), pp. 730-8. doi:10.1067/mva.2001.116966

Werb, Z.; Bainton, D.; Jones, P. (1980). Degradation of connective tissue matrices by macrophages. III. Morphological and biochemical studies on extracellular, pericellular, and intracellular events in matrix proteolysis by macrophages in culture. *Journal of Experimental Medicine,* Vol.152, No.6, (December 1980), pp. 1537-53. ISSN: 1540-9538

White, J.; Haas, K.; Phillips, S.; Comerota, A. (1993). Adventitial elastolysis is a primary event in aneurysm formation. *Journal of Vascular Surgery,* Vol.17, No. 2, (February 1993), pp. 371-80. doi:10.1067/mva.1993.43023

Wills, A.; Thompson, M.; Crowther, M.; Sayers, R.; Bell, P. (1996). Pathogenesis of abdominal aortic aneurysms-cellular and biochemical mechanisms. *European Journal of Vascular and Endovascular Surgery,* Vol.12, No.4, (November 1996), pp. 391-400, Review, ISSN 0741-5214

Wilson, W.; Anderton, M.; Choke, E.; Dawson, J.; Loftus, I.; Thompson, M. (2008). Elevated plasma MMP1 and MMP9 are associated with abdominal aortic aneurysm rupture. *European Journal of Vascular an Endovascular Surgery*. Vol.35, No.5, (May 2008), pp. 580-4, doi:10.1016/j.ejvs.2007.12.004

Wilton, E.; Bland, M.; Thompson, M.; Jahangiri, M. (2008). Matrix metalloproteinase expression in the ascending aorta and aortic valve. *Interactive Cardiovascular Thoracic Surgery*, Vol.7, No.1, (February 2008), pp. 37-4, doi:10.1510/icvts.2007.163311

Xiong, W.; Zhao, Y.; Prall, A.; Greiner, T.; Baxter, B. (2004). Key roles of CD4+ T cells and IFN-γ in the development of abdominal aortic aneurysms in a murine model. *Journal of Immunology*, Vol.172, No.4, (February 2004), pp. 2607–12. ISSN: 0022-1767

Xiong, W.; Knispel, R.; MacTaggart, J.; Greiner, T.; Weiss, S.; Baxter, B. (2009). Membrane-type 1 matrix metalloproteinase regulates macrophage-dependent elastolytic activity and aneurysm formation in vivo. *Journal of Biological Chemistry,* Vol. 284, No.3, (January 2009), pp. 1765-71, doi 10.1074/jbc.M806239200

Yamawaki-Ogata, A.; Hashizume, R.; Satake, M.; Kaneko, H.; Mizutani, S.; Moritan, T.; Ueda, Y.; Narita, Y. (2010). A doxycycline loaded, controlled-release, biodegradable fiber for the treatment of aortic aneurysms. *Biomaterials*, Vol.31, No.36, (December 2010), pp. 9554-64. ISSN:0142-9612

Zarins, C.; Giddens, D.; Bharadvaj, B.; Sottiurai, V.; Mabon, R.; Glagov, S. (1983). Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. *Circulation Research*. Vol.53, No.4, (October 1983), pp. 502–514, ISSN 0009-7330

Zeng, Z.; Kallmes, D.; Durka, M.; Ding, Y.; Lewis, D.; Kadirvel, R.; Robertson, A. (2011). Hemodynamics and anatomy of elastase-induced rabbit aneurysm models: similarity to human cerebral aneurysms? *American Journal of Neuroradiology*, Vol.32, No.3, (March 2011), pp. 595-601, doi 10.3174/ajnr.A2324
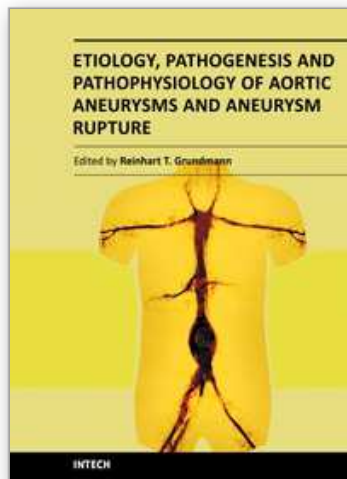
Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

Edited by Prof. Reinhart Grundmann

ISBN 978-953-307-523-5

Hard cover, 222 pages

Publisher InTech

Published online 27, July, 2011

Published in print edition July, 2011

This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

INTECH
open science | open minds