Eur J Vasc Endovasc Surg **30**, 227–244 (2005)
doi:10.1016/j.ejvs.2005.03.009, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

REVIEW

A Review of Biological Factors Implicated in Abdominal Aortic Aneurysm Rupture

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Abdominal aortic aneurysm (AAA) rupture is the 13th commonest cause of death in the Western World. Although considerable research has been applied to the aetiology and mechanism of aneurysm expansion, little is known about the mechanism of rupture. Aneurysm rupture was historically considered to be a simple physical process that occurred when the aortic wall could no longer contain the haemodynamic stress of the circulation. However, AAAs do not conform to the law of Laplace and there is growing evidence that aneurysm rupture involves a complex series of biological changes in the aortic wall. This paper reviews the available data on patient variables associated with aneurysm rupture and presents the evidence implicating biological factors in AAA rupture.

Keywords: Abdominal aortic aneurysm; Rupture; Matrix metalloproteinase; Enzyme; Collagen.

Introduction

Abdominal aortic aneurysms (AAA) primarily affect elderly males with a prevalence of 5%. The natural history of aneurysms is to expand and eventually rupture. AAA rupture is responsible for 1.5% of the total mortality in males over 55 years of age, amounting to 8000 deaths per year in England.[1] Recent elucidation of the biological processes causing aneurysm development and expansion has led to translational research investigating the use of novel medication aimed at retarding aneurysm growth. The most promising drugs have been those with either anti-inflammatory or anti-matrix metalloproteinase (MMP) properties, both of which have had some success in experimental models.[2–5] However, any medication strategy for the treatment of AAA must address aneurysm rupture as well as expansion. In contrast to the expansion of AAA, the biological processes causing aortic aneurysm rupture have received little attention.

Abdominal aneurysms were traditionally considered to be a simple biomechanical problem, resulting from irreversible structural damage to the aortic wall. These changes were thought to result in dilatation and eventual rupture when wall stress from the circulation exceeded the tensile strength of the aortic wall. Focusing on aortic wall stress led to a simplistic view that aneurysm rupture was determined solely by mechanical factors. Just as the complexity of the atherosclerotic plaque has become apparent, it is now recognised that AAA rupture is a multifaceted biological process involving biochemical, cellular, and proteolytic influences in addition to biomechanical factors. The purpose of this review is to provide a summary of patient variables associated with AAA rupture and present the evidence implicating biological factors in AAA rupture. A MEDLINE search from 1966 until 2004 (OVID and Embase) was performed using the subject heading 'abdominal aortic aneurysm' and keywords 'rupture', 'matrix metalloproteinase', 'thrombus' and 'stress'. An extensive manual

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search was carried out using bibliographies from relevant key published papers.

Patient Variables Implicated in Aneurysm Rupture

Diameter

The principal determinant of AAA rupture is the maximum diameter of the aneurysm. Early investigations that attempted to stratify rupture rates according to aneurysm diameter were subjected to many problems. Initial studies relied on autopsy[6,7] which did not reflect diameter *in vivo*.[8] Studies in patients faced the problems of poor reproducibility of aneurysm diameter measurement by different scanning modalities[9] and low rates of autopsy following sudden deaths in population studies. It is therefore not unexpected that reported rupture rates varied widely, from 1% per annum[10–12] to as high as 6%[13] per annum for aneurysms <5.0 cm in diameter and from 0.8%[14] to 9.4%[15] for aneurysms 5.5–5.9 cm. The natural history data for larger aneurysms were even more difficult to obtain because most large AAA were surgically repaired. Contemporary data on the rupture risk of larger aneurysms have been derived from the non-surgical arm of the US aneurysm detection and management (ADAM) Veteran Affairs Cooperative Study.[15] This study prospectively evaluated patients with AAA larger than 5.5 cm for whom elective repair was not planned because of medical contraindications or patient refusal. Estimated annual rupture rates according to size (pooled data) are summarised in Table 1.

Table 1. Annual rupture rates of abdominal aortic aneurysms according to size (based on pooled available data)

Initial aneurysm diameter (cm)	Annual risk of rupture
3.0	0.2–0.4%[165]
4.0	0.8–1.1%[165]
4.0–5.5	0.6[26]–1.0[12]
5.5–5.9	9.4%[15*]
6.0–6.9	10.2%[15]
>7.0	30.5[166]–32.5%[15]

* The 9.4% 1-year probable rupture rate observed for initial AAA of 5.5 to 5.9 cm is 10-fold higher than the rates observed in 2 randomised trials[12,26] for AAA of 4.0 to 5.5 cm. Lederle *et al.*[15] postulated that whilst this large difference was likely due to the difference in AAA diameters, it may also reflect a difference in rupture rates between their mostly high-operative-risk patients (for whom elective repair was not planned because of medical contraindications) and the healthier patients randomised into the trials.

Expansion rates

There is evidence that rapid AAA expansion is associated with increased rupture risk. Limet *et al.*[16] reported that the risk of aortic rupture was not only related to aneurysm size but also to the rate of expansion. These findings were confirmed by Lederle *et al.*[15] who found a significantly greater mean AAA enlargement rate in patients with probable rupture than patients without rupture (0.75 vs. 0.41 cm per year) and Brown *et al.*[14] who reported increased mean and median expansion rates in patients with ruptured AAA than patients without rupture (mean 0.84 vs. 0.39 cm per year). The view that expansion rates are associated with rupture risk is not universally accepted. Cronenwett[17] argued that it is difficult to separate the influence of expansion rate on rupture risk from the effect of expansion rate on absolute diameter, which itself affects rupture risk. Nevit *et al.*[8] found that the absolute size and not expansion rate was associated with increased rupture rate, an observation which was also supported by Cronenwett *et al.*[13] To determine whether expansion rate per se is an independent predictor of rupture would require a large series of patients with similar sized aneurysms but different expansion rates to be followed without intervention. Furthermore, individual growth rates are difficult to predict and AAAs have intervals of stability, slow and rapid expansion.[18] Investigations on expansion rates should have a minimum 3 monthly follow up to monitor expansion rates accurately[19] but this is expensive, time consuming and highly dependent on patient compliance.

Cronenwett *et al.*[20] found that expansion rate was dependent on current AAA diameter, rather than a fixed rate, so that 3–6 cm diameter aneurysms expanded by 10% of their diameter per year. That expansion rate is an exponential function of initial aneurysm diameter has also been supported by other studies.[16,21–23] Limet *et al.*[16] also reported more rapid growths in larger diameter aneurysms (5.3 mm/year for AAA diameters less than 40 mm versus 7.4 mm/year for AAA diameters of 50 mm or more). Other variables that have been shown to have a positive correlation with expansion rate are pulse pressure,[20] systolic and diastolic blood pressures[24] and smoking.[25] Interestingly, the US ADAM[26] study reported that diabetes was associated with slower enlargement of aneurysms. This was consistent with previous observations that diabetes was associated with a reduced prevalence of aneurysm,[27,28] but the basis for this link remains unknown.

Other risk factors for aneurysm rupture

The UK Small Aneurysm Trial (UKSAT),[29] with a total of 1090 patients with AAA between 4.0 and 5.5 cm in diameter randomised to either surgery or serial ultrasonographic surveillance, reported that the risk of rupture was independently and significantly associated with female sex and higher mean blood pressure. When the analysis included a further 1167 patients who were ineligible for randomisation, current smoking and lower FEV_1 were also found to be associated with risk of rupture. In contrast, age, body mass index, serum cholesterol concentration, and ankle/brachial pressure index were not found to be associated with an increased risk of aneurysm rupture.

Female sex

When combined with their 1167 non-randomised patients, the UKSAT reported a three-fold higher risk of rupture in women compared to men.[29] Furthermore, the UKSAT found that the mean diameter preceding rupture was smaller in women (5.0 ± 0.8 cm) than in men (6.0 ± 1.4 cm). A smaller study[14] found the risk of rupture in women with AAA 5.0–5.9 cm to be four times that of men with AAA 5.0–5.9 cm. The US ADAM study[26] had very few women (only 34 total, with four having AAA of 4.0 cm or greater) and therefore limited conclusions could be drawn from this study regarding the risk of rupture in women.

The findings that females with AAA have a higher rupture risk suggest that when considering the indications for aneurysm repair, different thresholds might apply to women than men. In centres with low operative mortality rate, Brown *et al.*[14] recommended a threshold of no higher than 5.0 cm in women. Unfortunately, this threshold has not been tested in any randomised trial. Protocols from the UKSAT[12] and US ADAM[26] studies managed both male and female patients with an identical threshold for surgery. Furthermore, since the prevalence of AAA is much lower in women than men,[11] recruitment of large numbers of women into trials remains a challenging issue.

Blood pressure

UKSAT[29] reported that aneurysm rupture was associated with higher mean blood pressure. The UKSAT investigators speculated that weakening of aneurysmal wall by the haemodynamic burden of higher mean blood pressure was a possible reason for this link. In addition to evidence from the UKSAT,[29] the association between hypertension and AAA rupture has also previously been demonstrated in earlier studies.[13,30–32] Cronenwett[17] reported that diastolic blood pressure was a more accurate predictor of aneurysm rupture than systolic blood pressure. In a review of 75 patients with AAAs, Foster *et al.*[30] observed that 72% of patients with diastolic hypertension died from aneurysm rupture compared with 30% of the entire group. In an autopsy study, Sterpetti *et al.*[31] compared 77 patients who died from AAA rupture to 220 patients who died with an intact aneurysm and found that patients with ruptured AAA more frequently had hypertension (54 versus 28%). In a group of 156 patients, Szilagyi *et al.*[32] reported that hypertension ($>150/100$ mmHg) was present in 67% of patients with aneurysm rupture, but in only 23% of those without rupture.

Chronic obstructive pulmonary disease

Data from the UKSAT[29] showed an association between lower FEV_1 and AAA rupture. However, this association was only apparent after including in the analysis a further 1167 patients who were ineligible for randomisation. These patients mainly included those whose AAA diameter never exceeded 4.0 cm or who were considered unfit or refused surgery. The UKSAT investigators acknowledged that inclusion of these patients could have biased the results. Nevertheless, the association between COPD and AAA rupture has also been supported by earlier studies. Sterpetti *et al.*[31] found that patients with ruptured AAAs more frequently had emphysema (67 vs. 42%) and Cronenwett *et al.*[13] found that COPD was independently predictive of AAA rupture and attributed this to a possible increase in systemic proteinase activity. However, this hypothesis has never been proven in experimental studies and current evidence remains circumstantial. Van Laarhoven *et al.*[33] reported that 19% of COPD patients with severe emphysema (FEV/vital capacity ratio $<55\%$) had dilated aortas (>2.5 cm) compared with 8% of patients with less severe COPD, suggesting that patients with more severe COPD have a greater likelihood of developing AAA.

Smoking

In addition to smoking being a risk factor for AAA development[34] and expansion,[25] it has also been shown to be a risk factor for AAA rupture. Earlier studies on the relationship between smoking and AAA rupture yielded contrasting results. In a large population based study, Strachan reported the relative risk of death from AAA rupture to be increased 4.6 fold for cigarette smokers and 2.4 fold for pipe/cigar smokers.[35] On the contrary, Cronenwett *et al.*[13] and Sterpetti *et al.*[31] did not find that smoking history or

current smoking status was predictive of AAA rupture. Cronenwett[17] raised the issue that COPD was not specifically measured in the study by Strachan,[35] therefore it was not be possible to separate the potentially confounding influence of COPD. The UKSAT[29] did measure COPD specifically and reported that risk of rupture was independently and significantly associated with current cigarette smoking. In the separate analysis of the more homogeneous group of 1090 randomised patients, the UKSAT[29] investigators reported a similar association between smoking and AAA rupture when baseline plasma cotinine (a long lived metabolite of nicotine) was used as an index of smoking.

Biomechanical Factors in Aneurysm Rupture

The biomechanical approach to predicting AAA rupture views stress (internal forces per unit area) on the aneurysmal wall as the one direct factor leading to the aortic wall giving way. The basic premise of biomechanical principles is that AAA formation and enlargement are accompanied by an increase in wall stress and/or a decrease in the ability of the material of the wall to withstand these stresses (i.e. a decrease in tensile strength). To account for the well established relationship between AAA size and risk of rupture, investigators conventionally referred to the biophysical principle expressed by the law of Laplace,[36] where wall stress is directly proportional to aortic diameter and blood pressure.

$$\sigma = \frac{P \times r}{t}$$

where σ, circumferential wall stress; P, intraluminal pressure; r, vessel radius; t, thickness of wall vessel.

However, it is now known that stress distributions in aneurysms do not conform to the approximations of the law of Laplace. The law of Laplace yields only an estimate of the average stresses generated in thin wall cylinders. This equation is derived from assumptions that render it incompatible with the complex geometrical structure of an aneurysm. Mower *et al.*[37] claimed that the method of finite element analysis (FEA), a recognized discipline in engineering sciences, predicted stress distributions in hypothetical aneurysm models with greater accuracy. FEA involved dividing a large complex structure into a finite number of smaller individual elements with their own geometric shape and material properties. Engineering analysis techniques were then used to determine the behaviour of these individual elements. By studying the effects of transmission of forces of each individual element to other elements, the behaviour of a complex structure could be determined.

FEA analysis of an axisymmetric and fusiform AAA model by Elger *et al.*[38] found that maximum stress was a function of the shape of the AAA wall rather than its diameter. While FEA analyses incorporated the effect of AAA shape in the determination of wall stress, this is not considered in the law of Laplace. The finding that wall stress was greatly dependent on the shape as well as the size of the aneurysm was confirmed by Vorp *et al.*[39] In their study, the peak wall stress for a hypothetical model of non-aneurysmal aorta was approximately 9 N/cm^2, whereas that for a 4-cm AAA and an 8-cm AAA was approximately 23 and 45 N/cm^2, respectively. Using a hypothetical model of a small aneurysm, FEA calculations by Mower *et al.*[37] were opposite to that predicted by the law of Laplace in that stress was greatest on the inner surface of the wall and decreased nonlinearly as the outer wall was approached.

However, these earlier studies were limited by the assumptions of idealized geometry and simplified mathematical models for aneurysmal tissue. Raghavan *et al.*[40] extended these earlier studies by using FEA to estimate AAA wall stress distribution from simultaneously determined 3D computer tomography (CT) reconstruction of abdominal aortic wall geometry and blood pressure. This study reported that in all AAA cases, the wall stress was complexly distributed, with large regional variations of high and low stress. Peak wall stress among AAA patients varied from 29 to 45 N/cm^2. Assuming that wall strength does not vary regionally within the AAA, the site of maximum stress would also likely be the site most susceptible to rupture. Peak wall stress was localised to the posterior surface in all cases studied, consistent with the observation by Darling *et al.*[41] that the majority of ruptures occurred on the posterior surface. In contrast, the wall stress on the non-aneurysmal aorta in the control subject was relatively low and uniformly distributed, with a peak wall stress of 12 N/cm^2. Statistical analysis of the computed geometric factors suggested that AAA volume, rather than AAA diameter, was the best indicator of peak wall stress and, consequently, AAA rupture.

Using 3D CT reconstruction and *in vivo* FEA analysis of peak wall stress, Fillinger *et al.*[42] and more recently, Venkatasubramaniam *et al.*[43] found that ruptured or symptomatic AAAs had a significantly higher peak wall stress compared to asymptomatic AAAs, independent of blood pressure or AAA diameter. In addition, these *in vivo* measurements of peak wall stress using FEA predicted rupture risk more accurately than law of Laplace. The smallest

ruptured AAA was 4.8 cm, but this aneurysm had a stress equivalent to the average electively repaired 6.3-cm AAA. In a later study by Fillinger *et al.*, FEA of peak wall stress was applied to 103 patients under observation.[44] This study showed that patients who later required emergent repair had higher peak wall stress during observation.

Limitations of Biomechanical Approach

Despite encouraging results, studies on FEA have limitations. Fillinger *et al.*[42] acknowledged that in some of the symptomatic patients, the only available blood pressure was at the time of symptoms and it was therefore uncertain whether the acute symptoms caused hypertension or whether hypertension caused high aneurysm wall stress that led to acute pain. Selection bias was also possible because patients who were not stable enough for a CT scan were excluded. Furthermore, these studies assume a uniform aortic wall thickness and ignored the effect of thrombus on wall stress. Some investigators have reported that intraluminal thrombus lowered the stress in the aneurysm wall[37,45–47] whilst others have reported intraluminal thrombus to increase AAA expansion/rupture risk.[48,49]

Although these studies took into account the complex geometrical shape of AAAs, the investigations did not address differences in wall tensile properties. By measuring tensile properties in aneurysmal and control tissues, Vallabhaneni *et al.*[50] reported that material properties of the aneurysm wall were markedly heterogeneous both within and between patients. These findings showed that finite element methods, by incorrectly assuming aneurysm wall to be homogeneous, might therefore be highly inaccurate. Secondly, these investigators also demonstrated clear differences in the tensile properties of non-aneurysmal aorta in the longitudinal and transverse directions and suggested that such anisotropy exists in aneurysms. If so, this highlights a further inadequacy in finite element methods that assumes aneurysm to be isotropic. The marked heterogeneity and high intersubject variation of aneurysm wall strength suggested that there are focal areas of weakened aortic wall.

Paradigm Shift in Concepts of AAA Rupture

The observation that the risk of aneurysm rupture is primarily determined by aortic diameter seems to support the concept that aortic rupture occurs when the wall stress exceeds the tensile strength of the altered aortic wall. However, the relationship between aortic rupture and wall stress is more complex than first envisaged. There are few data to support the assumption that excessive stress acting upon the aortic wall is the only cause of rupture. It has been well documented that aneurysms can rupture at virtually any size.[13,51] The traditional biomechanical notions of AAA rupture therefore appear insufficient to explain the clinical behaviour of all AAAs. Consideration must also be given to the fact that small AAAs are those in the earliest stage of evolution, when the capacity for connective tissue repair maybe high. Large AAAs, however, are also the most longstanding and will have a decreased capacity for connective tissue repair.[52] The concept of a localised process of ageing with the exhaustion of the repair potential of cells in larger AAAs seems to be supported by studies which found a pattern of accelerated replicative senescence of smooth muscle cells (SMCs) derived from AAA tissue.[53] Recent advances in our understanding of the role of enzymes in the pathobiological processes within AAA have led to a paradigm shift in our concepts of AAA rupture. Based on the findings of tensile strength heterogeneity within aneurysms, Vallabhaneni *et al.*[50] proposed that 'hot spots' of increased biologic activity (enzyme activation) within aneurysmal wall may be responsible for focal weakening and aneurysm rupture at relatively low levels of intraluminal pressure.[50]

The notion that AAA rupture may be related to increased enzymatic activity in the aortic wall was first proposed following anecdotal observations that surgical procedures precipitated AAA rupture. In a retrospective study, Swanson *et al.*[54] described 10 patients with known asymptomatic aneurysms that ruptured within an average of 10 days after laparotomy for another condition and suggested that the laparotomy may have precipitated rupture of the unresected abdominal aneurysms by raising levels of endogeneous collagenase. Nora *et al.*,[55] in their series of 17 patients with coexistent AAA and colon carcinoma, found a 14% incidence of AAA rupture in patients who underwent colon resection only. Trueblood *et al.*[56] reported an 11% incidence of AAA rupture that occurred within 3 days of operation for intraabdominal malignancy. The hypothesis that collagenase may be activated at sites distant from an initial injury was supported by an experimental study by Hawley *et al.*[57] that found increased collagenase activity within the small bowel, caecum, and stomach after colon resection in rabbits. However, other investigators have questioned these clinical and laboratory findings. Durham *et al.*[58] found a low incidence (3%) of postoperative AAA rupture in patients who underwent a

procedure other than AAA repair. Similar low rates of postoperative AAA rupture was reported by Hertzer *et al.*[59] and Acinapura *et al.*[60] Cohen *et al.*[61] showed that laparotomy, bowel resection, and even aortic mobilization had no effect on aortic collagenase activity in rats. However, these findings must be interpreted cautiously because collagenase behaviour in humans and rats may differ.

Role of Enzymes in the Pathophysiology of AAA

It is widely accepted that an AAA is the end result of a multifactorial process culminating in irreversible pathological remodelling of the aortic wall connective tissue[62] (Fig. 1). The most prevalent features of endstage AAA segments are: degradation of the viscoelastic protein elastin, compensatory increased collagen synthesis and content, excessive inflammatory infiltration consisting of T-cells, B-cells and macrophages, apoptosis of vascular smooth muscle cells (VSMCs) and excessive medial neovascularisation. The overall result is gradual imbalance between the synthesis and degradation of elastin and collagen leading to permanent diffuse alteration of the matrix structure of the vessel wall in aneurysms.[63–66] Although the exact mechanisms are unknown, there is compelling evidence to indicate that the pathophysiology of AAAs is associated with increased proteolytic capacity within the abdominal wall, which is primarily attributed to elevated concentration and activity of matrix metalloproteinases (MMPs). MMPs are a family of endopeptidases with proteolytic activity towards the important structural elements in the aortic wall—elastin and interstitial collagen.[67] Four MMPs, including 72-kD gelatinase (MMP-2), 92-kD gelatinase (MMP-9), matrilysin (MMP-7), and macrophage elastase (MMP-12), are predominantly elastases, whereas at least three other MMPs (MMP-1, -8 and -13) are enzymes specific for interstititial collagens.[68] Based on substrate specificity the MMPs are categorized into 6 groups (Table 2). Other enzymes that may participate in connective tissue degeneration are plasmin, plasminogen activators,[69] their inhibitors,[70,71] serine elastases and cathepsins.[72] In different laboratories and with various experimental approaches, MMPs have consistently materialised as key participants in aneurysm disease. The role of MMPs in the pathophysiology of AAAs has been comprehensively reviewed elsewhere[68,73,74] and will therefore be limited in this review to a table summary (Table 3) of a series of published experimental studies on MMPs and AAAs.

Role of Enzymes in AAA Rupture

Protein content of the aortic wall

Ex vivo mechanical testing of healthy and aneurysmal abdominal aortic wall specimens[75,76] revealed that the failure strength of a typical AAA wall was lower than that of non-aneurysmal aorta. It seems likely that the increased local production of enzymes capable of degrading elastin and interstitial collagen[67] alters the structural integrity and predisposes the aortic wall to weakening.[65] During the formation of AAAs, the elastin concentration decreases whilst the collagen concentration increases.[63] Sumner *et al.*[77] demonstrated the relative depletion of elastin in aneurysmal tissue, a finding that was confirmed by subsequent studies.[51,78] This phenomenon reflected the increased elastin disruption by elastases and insufficient elastin production by senescent VSMCs. In contrast, the collagen concentration of aneurysmal aorta was found to be elevated in several studies.[63,79,80] McGee *et al.*[81] showed that mRNA levels for ∝ 1-procollagen were increased in AAA tissue extracts and suggested that the increase in collagen concentration in aneurysmal tissue was due to increased collagen synthesis and deposition. This was thought to be due to a compensatory response to increase in wall stretch,[82] a phenomenon which has been observed *in vitro*.[83] Others claimed that the increase in collagen concentration was a dilutional effect caused by selective degradation of elastin in the aneurysmal media.[79]

It is generally accepted that the distensible elastic fibres of the aortic media are responsible for load-bearing at physiologic pressures whereas adventitial collagen acquires load-bearing function at higher pressures[84] In the normal aorta, collagen and elastin are arranged in such a way that confers resistance to stretch, with the main load being placed upon the elastin fibres.[85] The degradation of elastin in aneurysmal tissue is thought to initiate arterial dilatation. Elastic fibres are distributed to a larger area as the collagen concentration and aortic diameter increase.[63,80] All these changes result in the gradual increase of both aortic diameter[63] and haemodynamic stress, and the transfer of tensile stress in the aortic wall to collagen fibres.[65,86,87] The collagen content increases as the aneurysm increases in size.[80,88] This network contains predominantly type I and III collagen,[89,90] with collagen type III responsible for most of its tensile characteristics.[79]

However, these compensatory processes have an endpoint. Beyond this threshold, the collagen network cannot maintain the biophysical properties of

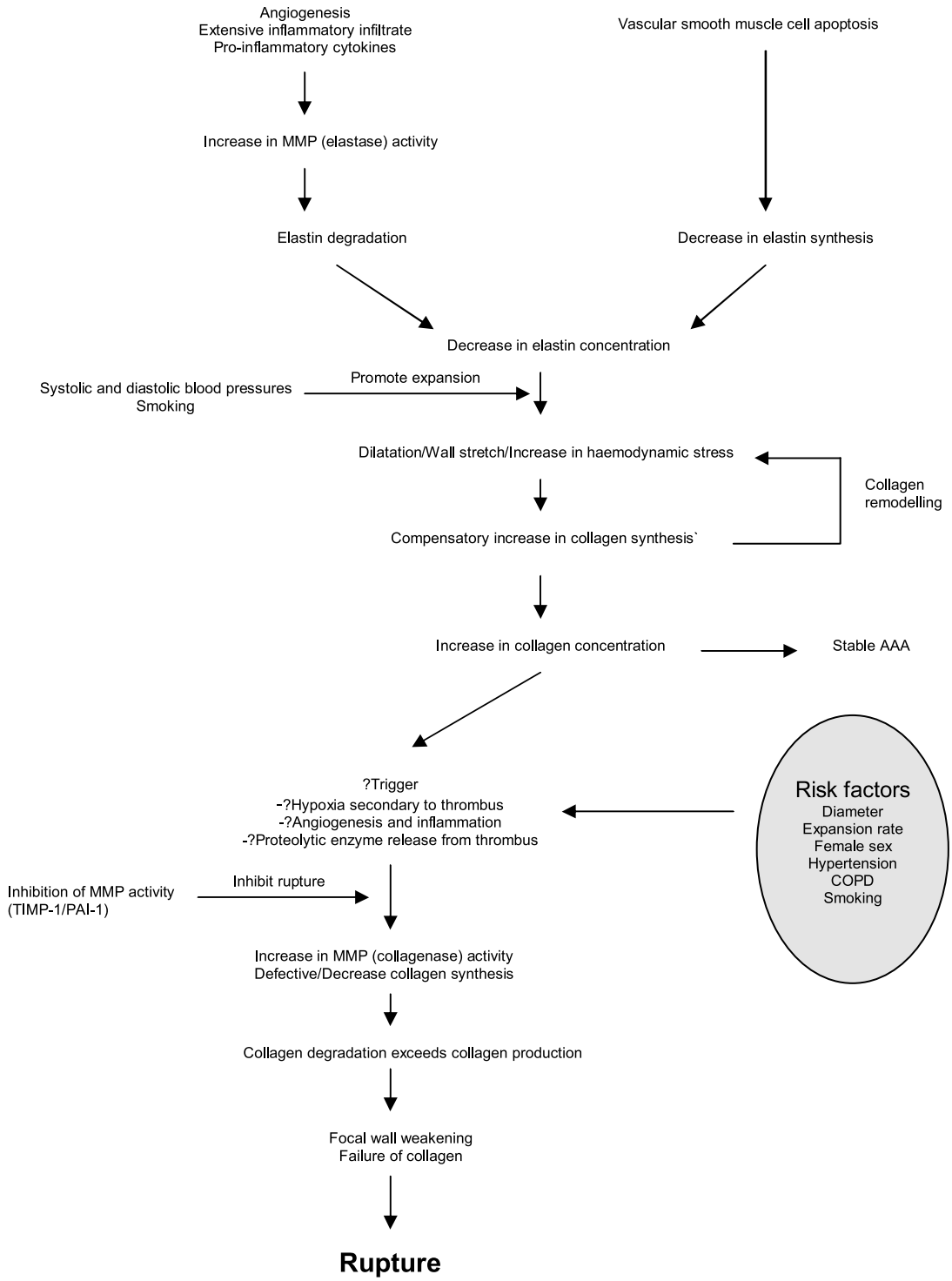

Fig. 1. Chain of biological events leading to abdominal aortic aneurysm rupture.

the aneurysm[65,66,91] and the aneurysm becomes at high risk of rupture. Once an AAA becomes established and prior to rupture, it is primarily composed of types I and III collagen. Naturally, AAA resistance to rupture must be dependent upon the tensile strength provided by these collagen networks.[92] It therefore seems likely that the final common pathway of clinical progression of AAAs to rupture involves proteolytic degradation of aortic collagen fibres.

Table 2. The major MMP subtypes and their substrates

MMP	Enzyme	Principal substrates
Collagenases		
MMP-1	Collagenase-1 (Interstitial collagenase)	Collagens I, II, III, VII, VIII, X, gelatin, aggrecan, MMPs-2 and -9
MMP-8	Collagenase-2 (Neutrophil collagenase)	Collagens I, II, III, V, VII, VIII, X, gelatin, aggrecan
MMP-13	Collagenase-3	Collagens I, II, III, IV, gelatin, aggrecan, PAI2
MMP-18	Collagenase-4 (*Xenopus* collagenase)	Collagen I
Gelatinases		
MMP-2	Gelatinase A (72 kDa gelatinase)	Gelatin, collagens I, IV, V, VII, X, XI, XIV, elastin, fibronectin, aggrecan
MMP-9	Gelatinase B (92 kDa gelatinase)	Gelatin, collagens IV, V, VII, X, elastin
Stromelysins		
MMP-3	Stromelysin-1	Collagens III, IV, IX, X, gelatin, aggrecan, MMPs-1, -7, -8, -9, -13
MMP-10	Stromelysin-2	Collagens III, IV, V, gelatin, casein, MMPs-1 and -8
MMP-11	Stromelysin-3	Gelatin, collagen IV, fibronectin, casein, proteoglycans
Matrilysins		
MMP-7	Matrilysin-1 (PUMP-1)	Collagens IV, X, fibronectin, gelatin
MMP-26	Matrilysin-2	Collagen IV, fibronectin, gelatin, proMMP-9, fibrinogen
Membrane type MMPs		
MMP-14	MT1-MMP	Collagens I, II, III, gelatins, MMPs-2 and -13
MMP-15	MT2-MMP	MMP-2, gelatin
MMP-16	MT3-MMP	MMP-2
MMP-17	MT4-MMP	Gelatin, proMMP-2
MMP-24	MT5-MMP	Proteoglycans, proMMP2, collagen I, gelatin, fibronectin, laminin
MMP-25	MT6-MMP	Collagen IV, proMMP-8, proMMP-9
Others		
MMP-12	Macrophage metalloelastase	Collagen IV, gelatin, elastin, fibronectin

Experimental studies

Dobrin *et al.*[93] investigated the proteolytic effects of purified collagenase and elastase on arterial tissue. At supraphysiological pressures, collagen and elastin were degraded differentially in isolated canine common carotid arteries and human external, internal and common iliac arteries. Treatment with collagenase caused the blood vessels to dilate, become more compliant and rupture. In contrast, treatment with elastase caused the vessels to dilate markedly and become stiffer (probably due to recruitment of previously unstretched collagen fibres) but was not related to rupture. These findings have fostered the notion that elastin degradation is a key step in the development of aneurysmal dilatation but collagen degradation is ultimately required for aneurysm rupture. It must be recognised when interpreting these studies that there is some collagenase activity in elastase and some of the results could therefore be related to changes in collagen. The investigators stated that they used the most purified elastase and collagenase available, and that the results were reproducible; every vessel treated with elastase dilated but never ruptured, whereas every vessel treated with collagenase dilated only slightly but did rupture.

Animal studies provided evidence for the role of tissue inhibitor of matrix metalloproteinases (TIMP)-1 in preventing medial degradation and aneurysm formation by inhibiting the MMPs involved in the disruption of the media. Silence *et al.*[94] showed that aneurysms in thoracic and abdominal aortas were more frequent in mice with combined deficiency of apoE and TIMP-I genes compared with single deficiency of ApoE genes. In their experiments, MMP activity was most pronounced at sites where degradation of the elastic lamina occurred. Lemaitre *et al.*[95] showed that mice with combined deficiency of apoE and TIMP-I genes, fed on a cholesterol-rich diet, developed aortic medial ruptures and formed pseudoaneurysms. In these mice, the elastic lamellae were degraded and infiltrated with macrophages. The gelatinolytic activity associated with the macrophages was abolished by the addition of TIMP-1.

Allaire *et al.*[96] demonstrated that local inhibition of MMP activity by TIMP-1 had the potential to inhibit aneurysm rupture. This group seeded vessels with rat SMCs, transfected with a retroviral vector containing TIMP-1 cDNA. This had the effect of preventing aneurysmal degeneration and rupture. This group argued that it was very likely that TIMP-1 inhibited destruction of the wall by blocking MMPs since the elastic layers were preserved and the activity of MMP-9, activated MMP-2 and 28 kD caseinase and elastase were all decreased. In a similar experiment, the same group demonstrated that blockade of plasminogen

Table 3. Summary of published series reporting the role of enzymes in the pathophysiology of AAA

Enzymes	Summary of findings	Author	Year
MMP-9	Increased levels MMP-9 in explant AAA than AOD or normal aorta. MMP-9 localised to macrophages	Thompson *et al.*[167]	1995
	MMP-9 expression localised to macrophages	McMillan *et al.*[128]	1995
	Increased expression MMP-9 mRNA in AAA	Tamarina *et al.*[168]	1997
	Increased expression and activity of MMP-9 in AAA	Elmore *et al.*[169]	1998
		Freestone *et al.*[98]	1995
		Saito *et al.*[170]	2002
		Tung *et al.*[171]	2001
		Yamashita *et al.*[172]	2001
	Significant proportion of MMP-9 found to be active in AAA wall	Sakalihasan *et al.*[173]	1996
	Monocytes cultured with aortic explants infiltrated tissue, produced MMP-9 and degraded elastic fibres	Katsuda *et al.*[174]	1994
	Targeted gene disruption of MMP-9 prevented aneurysmal degeneration in mice	Pyo *et al.*[175]	2000
	No significant difference in MMP-9 mRNA and protein between AAA and AOD tissue*	Davis *et al.*[176]	1998
MMP-2	Increased MMP-2 protein and mRNA in AAA compared to AOD tissues	Davis *et al.*[176]	1998
		McMillan *et al.*[129]	1995
	Increased MMP-2 activation and binding to tissue matrix in AAA compared to AOD aorta	Davis *et al.*[176]	1998
	Increased levels MMP-2 in vasculature (inferior mesenteric veins) remote from the aorta in patients with AAA	Goodall *et al.*[177]	2001
	MMP-2 complemented and facilitated the degenerative activity of MMP-9 in transgenic murine models	Longo *et al.*[178]	2002
	Increased amounts of MMP-2 protein and mRNA production by cultured aortic SMCs compared to SMCs from AOD tissues	Crowther *et al.*[179]	2000
	No significant difference between MMP-2 mRNA level between AAA and control (AOD and organ donor aorta)*	Elmore *et al.*[169]	1998
	No significant difference in MMP-2 staining by immunohistochemistry between AAA and AOD tissue*	Knox *et al.*[180]	1997
MMP-12	Increased MMP-12 in AAA compared to normal aorta and localisation of MMP-12 to residual elastin especially areas adjacent to nondilated normal aorta	Curci *et al.*[181]	1998
	Deficiency of MMP-12 in mice conferred protection against medial destruction and ectasia	Luttun *et al.*[182]	2004
	Targeted gene disruption of MMP-12 did not suppress elastase-induced aneurysmal degeneration*	Pyo *et al.*[175]	2000
MT1-MMP	Increased MT1-MMP protein and mRNA in AAA compared with normal and AOD tissue	Nollendorfs *et al.*[183]	2001
	MT1-MMP localised to the media in the same distribution as MMP-2 giving indirect evidence for its role in MMP-2 regulation	Crowther *et al.*[184]	2000
	Immunodepletion of MT1-MMP blocked a significant portion of the proteolytic activation of pro-MMP2	Rajavashisth *et al.*[185]	1999
Collagenase -1 (MMP-1)	Increased pro MMP-1, MMP-1 protein and mRNA levels in AAA compared to healthy aorta	Irizarry *et al.*[186]	1993
		Annabi *et al.*[187]	2002
		Tamarina *et al.*[168]	1997
	MMP-1 localised within mesenchymal cells (SMCs and fibroblasts)	Newman *et al.*[130]	1994
	Capillary endothelial cells synthesised MMP-1 in response to cytokine stimulation	Rifkin *et al.*[188]	1990
	No significant difference in MMP-1 mRNA in AAA compared to AOD tissue*	Mao *et al.*[158]	1999
	Variable expression of MMP-1 in AAA and difficulty in demonstrating excess collagenase activity in soluble tissue extracts*	Evans *et al.*[189]	1991
		Herron *et al.*[190]	1991
		Menashi *et al.*[79]	1987
		Bussutil *et al.*[191]	1980
		Webster *et al.*[192]	1991
Collagenase -2 (MMP-8)	Inconsistent expression of MMP-8 in AOD and AAA tissue. However, MMP-8 is stored as preformed protein in granules[154,155] and therefore MMP-8 mRNA may not accurately reflect protein concentration	Mao *et al.*[158]	1999
Collagenase -3 (MMP-13)	Increased expression of MMP-13 in AAA compared to AOD tissue and localisation of MMP-13 to SMCs in close spatial proximity to collagen	Mao *et al.*[158]	1999
Tissue inhibitors of MMPs (TIMPs)	Increased ratio between enzyme (MMP-2 and -9) and inhibitor (TIMP-1 and -2) mRNA in AAA	Tamarina *et al.*[168]	1997
	Increased ratio between MMP-2 and its inhibitor TIMP-2 and between MMP-1 and -3 and their inhibitor TIMP-1 in AAA	Knox *et al.*[180]	1997
	More frequent abdominal aneurysms in mice with combined deficiency of apoE and TIMP-1 compared with single deficiency of apoE	Silence *et al.*[94]	2002
	Gelatinolytic activity associated with macrophages in mice aorta abolished by the addition of TIMP-1	Lemaitre *et al.*[95]	2003

* Contrary evidence.

activators also inhibited MMP activity and prevented formation of aneurysms and arterial rupture.[70] Guinea pig-to-rat aortic xenografts seeded with syngeneic rat SMCs, retrovirally transduced with the rat plasminogen activator inhibitor-1 (PAI-1) gene, did not rupture or become aneurysmal whereas all grafts not seeded with cells ruptured within 14 days. Overexpression of PAI-1 was related to decreased levels of tissue plasminogen activator (t-PA), 28-kD caseinase, and activated MMP-9, and preservation of elastin.

Clinical evidence

The pathological processes associated with the natural history of aneurysms to dilate and rupture are not well documented in clinical studies. The relationship between aortic diameter and MMP activity and expression has been examined in several studies.[98,84] Data from these investigations provided circumstantial evidence that MMP-2 promoted propagation of smaller AAA, but MMP-9 activity was associated with larger aneurysms. Freestone *et al.*[98] used zymography and immunassay to show increased concentrations of MMP-2 in small aneurysms (4–5.5 cm in diameter), and increased activity of MMP-9 in larger aneurysms (>5.5 cm). It was therefore postulated that increased expression and activation of MMP-2 played a role in early aneurysmal dilatation by degrading elastin, whereas MMP-9, by its association with larger aneurysms, predisposed the aneurysm to rapid growth and rupture. McMillan *et al.*[84] used polymerase chain reaction (PCR) methodology to show that moderate-diameter AAAs (5–7 cm) had significantly higher MMP-9 mRNA expression than either small (<5 cm) or large (>7 cm) AAAs. These authors speculated that the increased MMP-9 expression was related to the continued expansion of moderate sized aneurysms but the lower levels of MMP-9 expression in aneurysms >7 cm suggested that the rapid expansion and higher rupture rates that characterise very large aneurysms were probably related to other factors.

Anderton *et al.*[99] showed that serum MMP-1 levels were increased 2.5 fold and serum MMP-9 levels were increased 6 fold in ruptured compared to non-ruptured AAA. Petersen *et al.* investigated the activity of MMP-2 and -9 in 20 medium sized (diameter 5< 7 cm) AAAs, 20 large sized (>7 cm) AAAs and 20 ruptured AAAs using semi-quantitative substrate gel zymography. Their results showed a significantly higher MMP-9 activity in ruptured AAA compared to large non-ruptured AAA but no difference in MMP-2 activity. These investigators concluded that high MMP-9 activity was associated with AAA rupture. However, this study was limited in the selection of patients and the methodology employed to define MMP activity or concentrations.

Anderton *et al.*[100] used enzyme linked immunosorbent assay (ELISA) to quantify levels of MMP-1, -2, -3, -9 and -13 and TIMPs-1 and -2 and found no significant differences in these levels in the AAA sac of large (>6.5 cm) and medium (5–6.5 cm) sized aneurysms, or ruptured and non-ruptured AAA sac. When the same group analysed paired samples of aortic sac obtained from the anterior sac and the site of rupture in nine patients with ruptured AAA, MMP-9 was seven times higher at the site of rupture than in the anterior sac, suggesting that localised elevations in MMP-9 may have a role in focal aortic wall weakening and AAA rupture. This concept of localised 'hot spots' of MMP hyperactivity was supported by Vallabhaneni *et al.*[50] This group demonstrated marked heterogeneity of tensile strength and MMP activity in aneurysmal walls but failed to correlate MMP-2 and -9 activities to the physical properties of the wall. The absence of this correlation could be due to the fact that these investigators were unable to measure the MMP activity and physical properties in the same specimen. Instead, MMP assay was conducted from an area close to the specimen subjected to tensile strength testing.

Role of Inflammation and Immune Response in AAA Rupture

A prominent histologic feature of end stage AAAs is extensive inflammatory infiltration consisting of T-cells, B-cells and macrophages. The cause of the inflammatory process is unknown, and possibilities include autoimmune reaction[101,102] or an infectious agent such as *Chlamydia pneumoniae*.[103] Soluble peptide fragments derived from the degradation of extracellular matrix components, including elastin, laminin and fibronectin, may serve as a chemotactic agent for infiltrating macrophages through interactions with the 67-kD cell surface elastin-binding protein found on inflammatory cells.[104] The trigger for the recruitment of leukocytes is not yet known, but may include the local production of chemotactic cytokines (chemokines) such as interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1) and RANTES (regulated on activation normal T-cell expressed and secreted).[105] Their elevated levels in human and experimental AAA tissues[105,106] coupled with their potent chemotactic properties suggest that they are likely to play a role in the influx and migration

of inflammatory cells, especially T-lymphocytes and monocytes.

Anidjar *et al.*[107] used elastase-induced model of AAA in rats to demonstrate that inflammation correlated with aneurysm formation. It is likely that inflammatory cells release a cascade of pro-inflammatory cytokines that results in the activation of proteolytic enzymes.[108] Human and experimental AAA tissues have been shown to produce abundant amounts of prostaglandin E2 (PGE2), tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6).[109–113] These cytokines may play a major role in tissue injury by inducing the expression and activation of MMPs and TIMPs.[105]

Although chronic inflammation is a dominant feature of established AAAs, evidence for the role of inflammation in AAA rupture is lacking. Domanovits *et al.*[114] compared laboratory parameters of inflammation (C-reactive protein [CRP] and white blood count [WBC]) in 111 asymptomatic outpatients, 52 symptomatic patients without rupture and 62 patients with aneurysm rupture. These authors reported that patients with symptomatic and ruptured AAA had significantly elevated serum CRP and WBC levels compared to asymptomatic patients. As aneurysmal pain was associated with elevated CRP and WBC, Domanovits *et al.* proposed that an inflammatory process is present in the aortic wall that promoted rupture. However, their study failed to distinguish whether the elevations in serum markers of inflammation were due to a local vascular inflammatory process or due to acute phase reaction accompanying the systemic inflammatory response syndrome.

The functional importance of the immune response in AAAs is not fully understood. The immune response in AAAs may be primarily destructive, encouraging connective tissue break down and vascular smooth muscle cells apoptosis. On the other hand, anti-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-10 (IL-10), can inhibit macrophage activation and expression of MMPs and may represent endogeneous mechanisms that counter aneurysmal degeneration.[105] These cytokines are produced by CD4+ T-cells within aneurysms[115,116] and have been demonstrated to be elevated in human AAAs.[117,118]

There is evidence linking immunosuppression to AAA rupture but this is largely limited to anecdotal accounts. Palm *et al.*[119] reported rapid growth and rupture of AAA in a patient who received chemotherapy with gemcitabine, cisplatinum, prednisolone, and dexamethasone for metastatic pancreatic carcinoma. Fastest aneurysm growth coincided with chemotherapy administration and when chemotherapy was not given for 3 months, there was no aneurysm growth observed. Piotrowski *et al.*[120] reported an increased aneurysm growth rate and rupture at 4 cm diameter in a cardiac transplant patient who was on a cyclosporine, steroid and azathioprine immunosuppressive regimen. The mechanism for the disadvantageous effects of chemotherapy on AAA is unknown. At present, the literature on the effect of chemotherapy on the extracellular matrix is sparse. Furthermore, these reports were unable to distinguish if aneurysm rupture may be related to other effects of chemotherapy, such as increased arterial pressure induced by cyclosporine therapy, or due to the immunosuppressive effects of chemotherapy per se. Reilly *et al.*[121] showed that steroids induced aortic aneurysm rupture in 90% of heterozygous female blotchy mice within 2 weeks and that this response was dose dependent. On the contrary, Dobrin *et al.*[122] showed that treatment with corticosteroids effectively suppressed aneurysmal dilatation and reduced aortic wall elastin degradation.

Role of Intraluminal Thrombus in AAA Rupture

Intraluminal thrombus (ILT) is found in about 75% of all AAAs.[123] Some authors have suggested that rupture is associated with growth of thrombus in the aneurysm.[124] Acute haemorrhage seen in the mural thrombus of patients with ruptured AAAs has led others to suggest that blood entering thrombus may have a role in rupture.[125] Vorp *et al.*[126] showed that aneurysms with ILT thickness equal or greater than 4 mm had lower pO2 compared with aneurysms with ILT less than 4 mm thick, consistent with their earlier observation that ILT attenuated oxygen flow from the lumen to the aortic wall.[127] Vorp *et al.*[126] also reported that AAAs with thick ILT had greater inflammation, increased expression of ORP (hypoxia specific polypeptide) and lower tensile strength. They postulated that ILT, by creating a hypoxic environment may lead to a compensatory inflammatory response, an increase in local proteolytic activity of the wall,[128–130] local wall weakening and subsequent rupture.

In addition, early studies have shown that hypoxia induced macrophages to enhance their bioreactivity,[131–135] with subsequent increase in elastase production.[136] Adolph *et al.*[137] reported ILT to be an active and complex biological entity, containing many inflammatory cells, including macrophages and neutrophils. Fontaine *et al.*[138] showed that ILT was a possible site of proteolytic enzyme release and activation, and hypothesised that mural thrombus

acted as a source of proteolytic enzymes by aggregating platelets and trapping circulating cells and adsorbing plasma components. The observation by Jean-Claude *et al.*[139] that elevated levels of plasmin were present in the inner layers of the AAA wall near the interface with ILT, supported this phenomenon of proteolytic enzymes leeching from ILT. A more recent study by Fontaine *et al.*[140] showed that leukocytes in the luminal pole of thrombus released MMP-9 and MMP-8.

Early experimental work suggested that the availability of oxygen affected both the quantity and quality of ECM synthesis.[141–148] Aortic endothelial cells cultured in hypoxic conditions exhibited a decrease in collagen synthesis,[145] whereas hypoxic arterial SMCs exhibited a decrease in both collagen synthesis[146,149] and tropoelastin mRNA expression and synthesis.[142] Fibroblasts exposed to hypoxic conditions also produced less collagen.[143,147] Furthermore, hypoxic cells synthesised abnormal collagen, because oxygen is needed for the hydroxylation of proline.[143] Kazi *et al.*[150] compared the morphology of aneurysm wall covered with thrombus to segments exposed to flowing blood and illustrated the following features to be associated with thrombus: thinner aneurysm wall, fragmentation and decreased number of elastin fibres, decreased numbers of SMCs, increased number of inflammatory cells, and increased SMC apoptosis. The thinner thrombus-covered wall with less structural integrity may therefore predispose this wall segment to rupture.

On the contrary, other investigators have reported that intraluminal thrombus exerted protective influences against aneurysm rupture. Kushihashi *et al.*[151] observed from CT images that mural thrombus was significantly thinner in ruptured than in non-ruptured aneurysms (9 vs. 19 mm). In another series of CT analysis, Pillari *et al.*[152] noted that aneurysm expansion was associated with a synchronous increase in the volume of intraluminal thrombus in those aneurysms measuring 5–7 cm. However, expansion of aneurysms greater than 7 cm was not associated with increase in thrombus volume. The lower thrombus to lumen ratio associated with larger (>7 cm) aneurysms suggested that the thrombus may reach a point of maximum relative volume and thus maximum protection for the aneurysm.

Some studies have reported that ILT significantly lowered aneurysm wall stress.[45] However, Schurink *et al.*[48] demonstrated that the thrombus within an aortic aneurysm failed to reduce transmission of pressure to the aneurysm wall. Thubrikar *et al.*[47] described a different mechanism by which thrombus reduced wall stress. Similar to the observations by Schurink *et al.*,[48] Thubrikar *et al.*[47] reported that thrombus readily transmitted pressure to the vessel wall. *In vivo* measurements of pressure through mural thrombus revealed that the aneurysm wall was subjected to almost all ($91 \pm 10\%$) of the intraluminal pressure. However, when these investigators measured *in vitro* dilatation of aneurysms during pressurisation before and after the thrombus was removed, they observed that the presence of thrombus was responsible for an overall marked reduction in the aneurysm dilation. It was proposed that mural thrombus acted as a fibrous network adherent to the aneurysm wall and since this network also had to stretch with the aneurysm, the dilation of the aneurysm under pressure was reduced in the presence of thrombus. Although the thrombus transmitted most of the luminal pressure to the aneurysm wall, the reduction in dilation (strain) was thought to be important in reducing the overall wall stress.

Future Work

Several opportunities exist to advance our understanding of the biological processes underlying AAA rupture.

Collagenases

Given that the final common pathway of clinical progression of AAAs to rupture is likely to involve proteolytic degradation of aortic collagen fibres, research efforts should focus on collagenases. The triple-helix domains of interstitial collagens confer intrinsic stability and resistance to enzymatic breakdown. The biologic degradation of interstitial collagen requires two types of extracellular proteinases; collagenases that cleave the triple helix domains of intact collagen fibres in a characteristic locus, resulting in a mixture of 1/4- and 3/4-length degradation fragments, and secondly, gelatinases that subsequently cleave denatured or partially hydrolysed forms of collagen to more soluble peptides.[153] Both types of collagen-degrading activity are attributed to enzymes of the MMP family, of which MMP-1, -8 and -13 function as interstitial collagenases under physiologic conditions.[153]

The proteolytic capacity of collagenases in ruptured AAAs has not been well documented in experimental or clinical studies. Investigations on the role of MMP-8 (collagenase-2) are not straightforward. MMP-8 is produced by polymorphonuclear neutrophils (PMNs), and is sequestered in storage granules to be

released upon cellular activation.[154,155] In addition, chondrocytes, synovial fibroblasts and vascular endothelium can also express MMP-8.[156,157] Mao *et al.*[158] reported an inconsistent expression of MMP-8 in AOD (2 of 4) and AAA (1 of 4) tissues. They postulated that this inconsistent pattern could be attributed to the fact that MMP-8 is stored as preformed protein in granules in PMNs and therefore MMP-8 mRNA may not accurately reflect protein concentration.

Angiogenesis

Previous histological studies have demonstrated that AAAs were associated with angiogenesis (formation of new blood vessels from pre-existing blood vessels).[159,160] The role of angiogenesis in aneurysm disease however remains undefined. Thompson *et al*.[160] demonstrated that the extent of angiogenesis correlated with the degree of inflammation in the aortic wall. There is evidence that hypoxia may induce inflammatory cells to aggregate and secrete angiogenic factors resulting in neovascularisation.[126] In addition to permitting oxygen and nutrient supply to the hypoxic regions, neovascularisation will also result in further inflammatory cell migration to aneurysmal tissue and subsequent secretion of proteolytic enzymes, potentially leading to wall weakening and aortic rupture. Kobayashi *et al.*[161] have demonstrated that vascular endothelial growth factor (VEGF) expressing cells were strongly related to the degree of neovascularisation in AAAs. VEGF possesses several unique attributes that make it an attractive target for AAA rupture research. Specifically, it promotes mitogenesis of vascular endothelial cells and vascular permeability, and it also modulates production of a number of proteolytic enzymes involved in the process of neo-vascularisation. As a result, VEGF plays a pivotal role in the initiation and maintenance of angiogenesis, and is crucial in the activation of pathways causing enzymatic breakdown of matrix protein.[162–164]

Conclusions

Collective endeavours in basic science research in the past two decades have led to an accelerated pace of progress in the understanding of aneurysm disease as a unique pathophysiological process. In contrast, research into biological factors involved in AAA rupture is still at an early stage. Nevertheless, recent developments are encouraging and the progress made is beginning to alter our concepts of AAA rupture.

It can be expected that clinical management will eventual shift to include new medical therapeutic strategies that limit aneurysm growth. It is hoped that new insights into the processes underlying aneurysmal rupture will lead to novel medical therapies. A model incorporating how biochemical, cellular, haemodynamic and proteolytic influences can conspire to cause AAA rupture will be essential to the development of pharmacologic agents that will not only retard aneurysm growth but will more importantly, directly inhibit aneurysm rupture.

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Accepted 16 March 2005
Available online 11 May 2005