FRANCESCO SPEZIALE

Management of Abdominal Aortic Aneurysms

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Preface

The management of abdominal aortic aneurysms is one of the most investigated and interesting topics in current vascular and endovascular surgery.

This book was planned as a modern and comprehensive work on abdominal aortic aneurysms, reviewing all the relevant issues in this field: after an update on the latest aneurysms developments, an exhaustive revision of all the available Guidelines is provided. Then, all treatment modalities for infrarenal, juxtarenal and suprarenal aneurysms are illustrated in detail and commented. A place of honor has been reserved for new technologies, such as EVAS and branch of hypogastric arteries. Last, but not least, hot topics such as rupture, technical failure and infections are thoroughly discussed.

The compilation of this book was made possible by all the authors involved, who shared their great expertise and their invaluable experience. This is a reference work written by expert vascular surgeons for fellow surgeons and students interested in extending their knowledge in the field of abdominal aortic aneurysm management.

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THE EPIDEMIOLOGY OF AORTIC ANEURYSMS

Abdominal aortic aneurysm (AAA) affects around 2% of the world's population. The mortality of a ruptured AAA is as high as 80% to 90%, and rupture of an AAA accounts for a significant fraction of deaths, especially among older men. In contrast, the mortality for elective open surgery before rupture is only 2% to 6%. Early diagnosis of AAA before rupture is, therefore, important for patient survival.

Although epidemiologic and demographic risk factors for the development of aneurysms have been established in various populations, these relationships have proved less reliable in predicting significant clinical events, such as expansion and rupture, with any clinically meaningful precision. Because the risk of rupture is well understood to be proportional to the maximum diameter of the AAA, the elucidation of risk factors for aneurysm enlargement is perhaps the most effective strategy for understanding the natural history of AAA. Some authors define AAA as an infrarenal aortic diameter >30 mm. Conversely, the Society for Vascular Surgery and the International Society for Cardiovascular Surgery propose a definition for AAA as an infrarenal to normal abdominal aortic diameter ratio of ≥1.5.

The mechanism of pathogenesis of AAA is not entirely clarified, so far. Thus, in order to better understand this disease, a closer investigation of AAA and its surrounding tissue is necessary.

AAA has been classified as an extracellular matrix (EMC) remodeling disease that causes an enlargement of the abdominal segment of the aorta.

RISK FACTORS FOR THE DEVELOPMENT OF AORTIC ANEURYSMS

Epidemiologic risk factors significantly associated with the development of abdominal aortic aneurysms include cigarette smoking, advanced age, gender, family history of AAA, hypertension, central obesity, hypercholesterolemia, coronary artery disease, lower extremity peripheral arterial disease, and carotid disease. Female gender, African-American ethnicity, diabetes mellitus, and regular exercise (in men) are protective against AAA disease.

SMOKING

Hammond and Horn first described an association between smoking and aneurysms in 1958. Cigarette smoking is the major environmental risk factor for AAA, enhancing the chance of developing AAA as well as the risk of rupture, with reported odds ratios ranging from 3.0 to 12.0. AAA has a strong positive association with quantity and duration of smoking and an inverse association with the number of years after smoking cessation.

Smoking confers at least a 3.5-fold greater increase in relative risk than any other recog-

nized AAA risk factor, and the excess prevalence associated with smoking accounts for 75% of all AAAs 4.0 cm or larger. Although cessation of smoking is associated with a decline in the risk of AAA, individuals with a remote history of smoking still have a higher risk for AAA than individuals who have never smoked.

LIFESTYLE

The consumption of fruit, vegetables and nuts, as well as regular exercise, reduce the risk of AAA, as reported in a recent AAA risk factor analysis.

Also, a BMI >25 increases the risk of AAA. Lederle *et al.* accounted for both BMI and waist measures in their multivariate models and found a positive association between waist circumference and larger aneurysms (>40 mm), suggesting that waist circumference may be of more interest than BMI.

However, it is important to note that the effects of BMI and lifestyle are small compared with those of age, gender and smoking.

AAA AND WOMEN

Although the prevalence of AAAs is much lower in women than in men, with a male-to-female ratio of approximately 4:1 to 6:1, several studies have reported that women with AAAs tend to have poorer disease outcomes than men. Abdominal aneurysms in women also exhibit an elevated risk of rupture, especially if surgical therapy is reserved for AAAs more than 5.5 cm in diameter. The mean diameter at rupture for women is 5.0 cm compared with an average diameter of 6.0 cm in men. This may be accounted for by differences in the biomechanical properties of AAAs between men and women: 1) a trend towards a decrease in tensile strength in the AAA wall in women; and 2) a smaller baseline normal aortic diameter in women than in men. An earlier interventional approach for women with a smaller AAA than in men is necessary.

Women present at an older age than men with similarly sized small AAAs. Mortality following the repair of AAA is also higher in women than in men, a difference that is most pronounced with endovascular repair (EVAR). Some of the observed sex differences in the incidence of AAA may be related to the protective effects of estrogen against aneurysm development, as well as the negative effects of testosterone on the aorta. The incidence in women also rises with age, although it starts later in life than in men. There are also sex differences in the risk of rupture and in the outcomes that require women to be included in AAA screening programs.

DIABETES MELLITUS

The negative association observed between diabetes mellitus and AAA has been the focus of specific attention. Several studies demonstrate this apparent protective effect, with a decreased incidence of AAA disease in diabetics as well as decreased aneurysm growth and rupture rates.

RISK OF EXPANSION AND RUPTURE OF AORTIC ANEURYSMS

After an initial diagnosis, the aim of screening is to identify the risk factors associated with AAA expansion and rupture. Although rates of enlargement vary with time and aortic diameter, the average abdominal aortic aneurysm grows at the rate of 2 mm/year to 3 mm/year. Smoking is a major risk factor for the progression and rupture of AAA, affecting collagen synthesis, oxidative stress and altered expression of metalloproteinases. Smoking also reduces estrogenic effects, ovarian function and age at menopause, increasing the vulnerability of aneurysms among smoking women compared with smoking men.

A meta-analysis using data from patients with small AAAs demonstrated that the rate of expansion increases with current smoking

status by approximately 20%. This meta-analysis reported that current smoking status doubled the risk of rupture in individuals with AAAs (hazard ratio 2.02; 95% confidence interval [CI] 1.33-3.06).

The baseline diameter of an aneurysm strongly influences its growth rate (larger AAAs grow more rapidly). Data from the UK small aneurysm trial demonstrated that AAAs with a 5 cm diameter grow approximately 70% faster than those 4 cm in diameter. As the size of the aneurysm increases, so does the risk of rupture. Several large population studies have demonstrated that the risk of aneurysm rupture is very low (0-2.5% after 5 years) for aneurysms less than 5.0 cm in diameter. For aneurysms measuring more than 5.0 cm, the 5-year risk of rupture increases well above 20%.

Recognized AAA risk factors, including peripheral vascular disease, hypertension, and hyperlipidemia, have not been consistently associated with rates of expansion. As mentioned, the presence of diabetes mellitus has a protective effect on aneurysm growth (reduction by 30%).

PATHOPHYSIOLOGY OF THE ANEURYSM WALL

Abdominal aortic aneurysm is an inflammatory-degenerative disease, characterized by aortic wall weakening and dilatation. The medial destruction characteristic of the abdominal aortic aneurysm is remarkable for the near-complete elimination of normal structural elements, particularly the typical elastic fiber sheets. Because the elastin is normally incredibly durable, investigations into the pathophysiology of the AAA have focused on the enzymatic processes of elastolysis. Elastolytic enzymes were noted to be substantially elevated within the aneurysm wall, including neutrophil elastase as well as several members of the MMP class. Specific changes in the aortic wall, including chronic adventitial and medial inflammatory cell infiltration, decrease in elastin content, and loss of integrity of ECM, have been described histologically.

MMPs are a family of extracellular matrix-degrading enzymes which are essential for a range of homeostatic physiologic processes, including wound healing, angiogenesis, tissue remodeling, and bone resorption. The activity of MMPs is inhibited by the expression and local release of biologic inhibitors of MMP activity such as tissue inhibitors of metalloproteinases (TIMPs). Pro-MMPs are secreted by neutrophils, macrophages, fibroblasts and vascular smooth muscle cells (SMCs). MMPs are controlled at several levels, including the induction and suppression of MMP gene transcription, extracellular activation, and interaction with natural inhibitors.

Moreover, an inflammatory infiltrate constituted by macrophages, and T and B lymphocytes, has been observed within the tunica media in aneurysms. The complex interaction between T lymphocytes, macrophages, and mesenchymal cells induces cytokines, chemokines, and MMP release, which deeply affect parietal integrity. Several MMPs have been involved in the process underlying aneurysm formation; in particular, an overexpression of MMP-1, MMP-2, MMP-3, MMP-9, MMP-12, and MMP-13 has been demonstrated both in plasma and within the wall in patients with both thoracic and abdominal aneurysms. Accordingly, an imbalance between MMPs and TIMPs has been related to aortic wall diseases. MMP-2 and MMP-9 have been the most studied MMPs in patients with aneurysms occurring at any aortic site, and it has been demonstrated that their levels were correlated with wall weakening. Plasma MMP-9 levels are also increased in AAA disease. Patients with large AAAs (between 5 cm and 6.9 cm) have higher circulating levels than patients with small (<4 cm) or huge (>7 cm) AAAs. Like MMP-9, MMP-2 is capable of degrading elastin and type IV collagen. It is constitutively expressed by SMCs and fibroblasts. Aortic samples obtained from smaller aneurysms demonstrate relatively greater MMP-2 than MMP-9 activ-

ity, suggesting that increased MMP-2 activity may represent an early event in the time course of AAA pathogenesis.

Recently, attention has been focused on the role of MMP-12 as a specific marker of aortic diseases; one of the most effective elastolytic enzymes in this class is MMP-12, or human macrophage elastase (HME). In particular, it has been demonstrated both in mice and humans that MMP-12 activities were related to the formation and growth of abdominal aneurysms.

Cytokines and chemokines mediate the inflammation and inflammatory cell signaling and chemotaxis. They are small extracellular proteins and glycoproteins produced by lymphocytes and macrophages. Cytokines include interleukins, interferons, and inflammatory mediators such as tumor necrosis factor and granulocyte-macrophage colony-stimulating factor. The damaged matrix itself also results in proinflammatory cellular signals.

Cathepsins are cysteine proteases that catalyze elastin degradation and depletion in experimental AAA disease. Increased amounts of cathepsins K, L, and S are present in the human aortic wall.

Oxidative stress, through the increased production of reactive oxygen species by infiltrating leukocytes, fibroblasts, and native SMCs, may also contribute to the recruitment of inflammatory cells into the aortic wall and the inhibition of plasminogen activator inhibitor-1 (PAI-1), an enzyme that limits MMP activation, leading to tissue damage and apoptosis.

Diminished density of the vascular SMCs in the media of the aortic wall is a pronounced pathologic feature of advanced AAA disease. Evidence of SMC apoptosis, including enhanced p53 production, is more pronounced in aneurysmal than in occlusive aortic disease specimens at the time of surgical repair. The remaining SMCs exhibit diminished proliferative ability.

Aortic medial SMCs may produce and secrete MMPs in response to inflammatory stimuli and may directly contribute to the progression of AAA disease. Direct participation of the vascular SMCs in the process of AAA development may be related to acquired or intrinsic enhancement of the matrix-modifying capabilities of these cells.

BIOMECHANICAL EFFECTS

The presence of differential hemodynamic conditions along the length of the aorta explains the fivefold greater incidence of AAAs.

When compared with the suprarenal segments, the infrarenal aorta shows an increased peripheral resistance and oscillatory wall shear stress, and reduced flow during resting conditions. These conditions are recognized to predispose arteries to degenerative disease.

The risk of rupture in an AAA generally increases with size. The physiologic rationale behind monitoring the maximal diameter is the Laplace equation, which states that wall tension in regular and thin-walled structures, such as symmetric cylinders and spheres, is directly proportional to their radii. However, AAAs are often fusiform, asymmetric, and tortuous, containing an intraluminal thrombus of varying thickness, all of which make the application of this equation to the AAA structure unsatisfactory.

HEMODYNAMIC FORCES ON THE AORTA

Aortic hemodynamic forces are essential contributors to progressive aneurysmal degeneration and ultimate rupture. In the consideration of biomechanical forces in the context of a pressurized tube, the term stress refers to the amount of force exerted on the arterial wall per unit area, whereas strain constitutes stress-induced mural deformation per unit area. Wall shear stress (WSS) refers to the drag exerted on the arterial wall by moving blood as a function of local flow conditions (laminar versus turbulent), as distinguished

from outward, perpendicular stress applied to the aortic wall as a result of pressure loading during the cardiac cycle. Although both shear and perpendicular stress contribute to the progression of disease, outward forces are far greater than WSS and are of paramount importance in precipitating rupture.

Hemodynamic stresses and their resulting strain have been studied both abdominal aneurysms in physical and computational models. Focal peak wall strain has been found to be higher in symptomatic AAAs and in ruptured AAAs than in aneurysms in patients undergoing elective AAA repair, even after matching for diameter, thus suggesting that luminal conditions may play an equal or greater role in influencing rupture than the tensile integrity of the wall itself.

Laminar intraluminal thrombus also influences aortic responses to hemodynamic conditions. Substantial layers of laminar thrombus may accumulate during aneurysmal degeneration, with the volume and density varying considerably among similarly sized AAAs in individual patients. These differences probably reflect local variations in flow conditions, WSS, and the progression of mural inflammation and degeneration.

ALTERED HEMODYNAMICS

From a biomechanical perspective, rupture can be considered a structural failure in which the wall stress of the aneurysm exceeds its wall strength. Finite element analysis (FEA), a computional structural analysis technique, has been used experimentally in the recent decade to study the biomechanics of AAA rupture. Fillinger *et al.* showed in 2003 that peak wall stress (PWS) was a superior rupture predictor to diameter, which was confirmed by a meta-analysis in 2014. Liljeqvist *et al.* has demonstrated that the maximal ratio between wall stress and wall strength, referred to here as the peak wall rupture index (PWRI), was superior to both maximal diameter and PWS as a rupture predictor.

In a recent study, infrarenal aortic volume at baseline correlated with both absolute and relative volume growth, as well as increasing estimated wall stress and biomechanical rupture risk. The correlation between baseline volume and subsequent volume growth was superior to the correlation between baseline diameter and diameter growth, suggesting a greater focus on the entire geometry of the aneurysm structure rather than sole reliance on the maximal diameter.

Laboratory experimental data show that AAA diameter varies inversely with aortic flow: increasing flow either before or after the creation of an aneurysm by surgical distal arteriovenous fistula formation or by increased daily exercise wheel access reduces aneurysm size, whereas reductions in aortic flow augment aneurysm size, all without measurable influences on aortic pressure. Clinical relevance is underscored by the recognition that major lower limb amputation and, in later studies, chronic spinal cord injury predispose patients to an increased risk of late AAA formation independent of other recognized systemic factors, such as cigarette smoking or obesity.

GENETIC DETERMINANTS

In association with environmental and acquired risk factors such as smoking, genetic predisposition influences risk of and the progression of aneurysm disease. The association between variations in genomic sequence and the risk of thoracic aneurysm disease is much more established than that related to abdominal aneurysm disease. This situation is primarily due to major differences in the underlying disease pathogenesis.

INHERITED CONNECTIVE TISSUE DISORDERS

Currently, no known monogenic disorders have been described as causing aneurysms specific to the abdominal aorta. Aortic root and ascend-

ing aortic aneurysms commonly develop as a consequence of cystic medial degeneration, often in younger patients with Marfan syndrome, Ehlers-Danlos syndrome, Turner's syndrome, bicuspid aortic valves, or familial thoracic aortic aneurysm syndromes. Inherited connective tissue disorders are a common cause of aortic aneurysms in younger patients. Approximately 20% of TAAs are attributable to syndromes associated with single-gene mutations.

In total, seven monogenic mutations have been described to cause TAA disease, including fibrillin 1 (FBN1), transforming growth factor-β (TGF-β) receptors 1 and 2 (TGFBR1, TGFBR2), myosin light chain kinase (MYLK), smooth muscle myosin heavy chain 11 (MYH11), smooth muscle alpha actin 2 (ACTA2), and SMAD family member 3 (SMAD3). Mutations in any one of these genes is usually highly penetrant and is inherited in an autosomal dominant pattern.

OTHER GENES RELATED TO AAA

If patients with generalized matrix deficiency diseases such as Marfan syndrome and Ehlers-Danlos syndrome are excluded, relevant family histories of AAA disease can be obtained from 15-20% of patients with AAAs. The risk of AAAs in males with a first degree relative affected by the disease is approximately fourfold higher than the risk in the general population.

A twin-based recent study was performed to analyze the relative etiological importance of genetic and environmental factors for AAA development. In this study, a 2.5-times higher proband-wise concordance rate was found in monozygotic twins compared with dizygotic twins, and an overall heritability of 77% was found, which suggests a substantial genetic component in the development of AAA.

A meta-analysis of candidate genes demonstrated that single nucleotide polymorphisms (SNPs) in the genes encoding angiotensin-converting enzyme (ACE), angiotensin type 1 receptor (AT1R), MMP-9, and methlyenetetrahydrofolate reductase (MTHFR) have been consistently associated with AAAs.

Genome-wide association studies provide a more robust method for identifying genes associated with disease processes such as AAA. These studies scan the entire genome, in an unbiased fashion, for SNPs associated with a particular disease, and have identified SNPs associated with AAA disease.

Currently, the strongest genomic association with AAA that has been described relates to a SNP on 9p21, previously associated with coronary artery disease. Another locus for AAA has been identified on 9q33. This SNP also demonstrated an association with coronary artery disease, peripheral artery disease, and pulmonary embolism but not with intracranial aneurysms.

Ogata *et al.* reported results on an unbiased, comprehensive genome-wide approach, namely a DNA linkage study for familial AAA using sex and family history as covariates, and identified linkage to chromosomes 19q13 and 4q31, suggesting that these regions of the human genome harbor genetic risk factors for AAA. They also found that the prevalence of AAA in the brothers of the AAA probands was almost three times that in the sisters; a similar trend was observed in the group of siblings of the spouses.

Finally, in another large genome-wide association study, a specific association between a variant in low-density-lipoprotein receptor-related protein 1 (LRP1) and AAA was reported. Despite several polymorphisms recognized to influence disease risk, the risk attributable to these SNPs is relatively small. It is unlikely that any single gene is essential for the initiation of AAA. A combination of predisposing polymorphisms is probably responsible for the majority of heritable risk for the development of AAA in any individual patient.

ROLE OF AORTIC THROMBUS

Intraluminal thrombus (ILT) is a natural phenomenon that is based on the deposition of

blood components when an abdominal aortic aneurysm grows to a certain size. Whether the presence of ILT has any influence on the natural history of the AAA continues to be a matter of debate.

In 1965, Martin surmised that as an aneurysm develops, it becomes lined with thrombus, which weakens it by interfering with nutrition of that segment of the wall. Intraluminal thrombus is not protective and weakens the aneurysm wall. In 2000, using a pressure transducer during open aneurysm repair, Schurink *et al.* confirmed that intraluminal thrombus does not reduce pressure close to the aneurysm wall. Vorp *et al.* also confirmed localized hypoxia in regions of thicker thrombus that might lead to localized wall neovascularization, inflammation, and regional wall thinning. Hypoxia also affects the function of vascular smooth muscle cells, causing them to secrete more collagenase than in normoxic conditions, with less elastin and collagen production. Furthermore, the accumulation of thrombus may impair the diffusion of oxygen across the aortic wall, resulting in relative hypoxia and potential SMC apoptosis/necrosis. Biologically active substances infiltrate through the aortic wall by centrifugal convection and centripetal filtration, destabilizing the matrix-rich aortic media, increasing the inflammatory response and therefore increasing the risk of progression and rupture.

In addition to being an indirect marker of disease progression, intraluminal thrombus may also directly mediate progression of aneurysms through by plasmin. Activation of proteolytic MMPs degrades extracellular tissues, cleaves cell surface receptors, and are involved in tissue remodeling. Intraluminal thrombus contains high levels of MMP-2 and MMP-9, trapped neutrophils rich in MMP-9, and neutrophil gelatinase-associated lipocalin, which neutralizes the defensive actions of tissue inhibitors of metalloproteinases. Laminar thrombus may also alter peak wall strain in AAAs. The balance of thrombus-related influences on AAA disease remains uncertain, with most investigators concluding that laminar thrombus generally increases the progression of disease and risk of rupture in AAAs of similar diameter.

An autopsy study of 78 patients who died of infrarenal ruptured AAAs showed that 80% of ruptures occurred at the site of mural thrombus. This was supported by CT studies of patients admitted with rupture, which showed that most of the wall disruption occurred through the thrombus or at its edge. Others argue that cracks or fissures in the intraluminal thrombus due to proteolytic enzymes on the luminal surface of the clot are what really cause rupture. However, a definitive consensus has not been gained. A Dutch report in 2013, while accepting a role for initial disruption formation, confirmed that intraluminal thrombus thickness was associated with vascular smooth muscle cell apoptosis (or cell death), elastin degradation, and high levels of MMP-2 and correlated with aneurysm rupture.

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