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N. Weiss et al.: Medical management of aneurysms
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Medical management of abdominal aortic aneurysms

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Summary

Abdominal aortic aneurysms (AAA) are the most common arterial aneurysms. Endovascular or open surgical aneurysm repair is indicated in patients with large AAA ≥ 5.5 cm in diameter as this prevents aneurysm rupture. The presence even of small AAAs not in need of immediate repair is associated with a very high cardiovascular risk including myocardial infarction, stroke or cardiovascular death. This risk by far exceeds the risk of aneurysm rupture. These patients therefore should be considered as high-risk patients and receive optimal medical treatment and life-style modificiation of their cardiovascular risk factors to improve their prognosis. In addition, these patients should be followed-up for aneurysm growth and receive medical treatment to decrease aneurym progression and rupture rate. Treatment with statins has been shown to reduce cardiovascular mortality in these patients, and also slows the rate of AAA growth. Use of beta-blockers, ACE inhibitors and AT_1–receptor antagonists does not affect AAA growth but may be indicated for comorbidities. Antibiotic therapy with roxithromycin has a small effect on AAA growth, but this effect must be critically weighed against the potential risk of wide-spread use of antibiotics.

Key words: Abdominal aortic aneurysm, medical therapy, statins, cardiovascular risk

Zusammenfassung

Medikamentöse Therapie bei Bauchaortenaneurysma

Bauchaortenaneurysmen (BAA) sind die häufigste Manifestation arterieller Aneurysmen. Eine endovaskuläre oder offene chirurgische Aneurysmaausschaltung ist bei großen BAA von ≥ 5,5 cm Durchmesser indiziert, da damit eine Ruptur verhindert werden kann. Kleine BAA ohne Indikation für sofortige chirurgische oder interventionelle Intervention sind assoziiert mit einem sehr hohen Risiko für kardiovaskuläre Ereignisse, wie Myokardinfarkt, Schlaganfall oder kardiovaskulärem Tod. Dieses Risiko überwiegt bei kleinem BAA das Risiko einer Ruptur bei Weitem. Diese Patienten müssen daher als Hochrisikopatienten betrachtet werden und sollen eine optimale medikamentöse Behandlung und Lebensstilmodifikation ihrer kardiovaskulären Risikofaktoren erhalten, um die Prognose zu verbessern. Zudem sollten diese Patienten überwacht werden bzgl. Wachstum des Aneurysmas und eine medikamentöse Therapie erhalten, welche das Aneurysmawachstum verzögert und die Rupturrate verringert. Eine Behandlung mit Statinen reduziert die kardiovaskuläre Mortalität dieser Patienten und verringert zudem das Wachstum von BAA. Betablocker, ACE Inhibitoren und AT_1–Rezeptor Antagonisten haben keinen Einfluss auf die Wachstumsrate von BAA, können aber aufgrund von Komorbiditäten indiziert sein. Eine antibiotische Behandlung mit Roxithromycin hat einen geringen Effekt auf die Wachstumsrate von BAA. Dieser Effekt muss jedoch kritisch abgewogen werden gegen das potentielle Risiko eines breiten Einsatzes von Antibiotika.

Introduction

A healthy infrarenal aorta has a diameter of around 2 cm, which slightly increases with age. An aortic diameter of 3 cm or more is defined as an aortic aneurysm. The rupture rate increases with size. Open surgical or endovascular repair of an aneurysmatic abdominal aortic aneurysma (AAA) is indicated when the maximal diameter equals or exceeds 5.5 cm, when the growth rate of the aneurysm is faster than 0.5 cm in 6 months, or when it is symptomatic. Medical management is recommended for aneurysms that do not meet the above mentioned criteria for repair. Its aim is to retard aneurysm growth and prevent rupture. Furthermore, patients with AAA carry a very high cardiovascular risk. Five year mortality of patients enrolled in the United Kingdom Small Aneurysma Trial was around 25 %. Thereby the participants were five- to six times more likely to die from myocardial infarction, stroke, heart failure or cancer than dying from aneurysm rupture [1]. The presence of AAA is therefore considered to be a coronary heart disease risk equivalent as stated in recent European and US-American guidelines [2, 3]. The purpose of this review is to summarize currently available clinical data on the effect of medical management of patients with small AAA on aneurysm progression, rupture rate and mortality.

Epidemiology

Abdominal aortic aneurysm (AAA) is the most common aneurysm of large arteries, constituting more than 60 % of all the cases. The incidence of asymptomatic AAA varies in the literature from 3 to 117 per 100.000 person-years and for ruptured AAA – from 1 to 21 per

Vasa 2014; 43: 415–421

100.000 person-years [4]. The disease is more common in males than in females and has a prevalence of 3 % in individuals older than 50 years and 10 % in males older than 65 years. In the year 2012 there were 13,898 hospitalizations of patients with asymptomatic AAA (ICD I71.4) and 2,260 cases with ruptured AAA (ICD I71.3) in Germany [5]. Half of the patients with ruptured AAA die before reaching the hospital, while the total mortality of patients with ruptured AAA reaches 85 % [6]. The risk factors linked with the incidence of AAA in epidemiological studies include age (1,7 fold increase of the incidence of AAA larger than 4 cm every 7 years), male gender (3 times higher risk than women), positive family history, smoking and hypertension [7 – 9]. The role of dyslipidemia as a risk factor remains controversial [10, 11], while the presence of diabetes mellitus may even play a protective role [12].

Risk of rupture and indications for repair

The risk of AAA rupture increases exponentially with increasing aneurysm diameter (Figure 1). The Cochrane analysis of the 3,314 patients from UKSAT (United Kingdom Small Aneurysm Trial), ADAM (Aneurysm Detection and Management), CAESAR (Comparison of Surveillance versus Aortic Endografting for Small Aneurysm Repair) and PIVOTAL (Positive Impact of Endovascular Options for Treating Aneurysms Early) trials showed that preventive endovascular or surgical aneurysm repair on asymptomatic AAAs with maximal diameter of less than 5.5 cm does not lead to any survival benefits compared to conservative treatment in combination with regular ultrasound controls and repair only after exceeding this critical diameter [13]. According to this metaanalysis patients with AAA less than 5.5 cm in diameter are five to six times more likely to die from acute myocardial infarction, heart failure, stroke or cancer than from rupture of the AAA. Based on these data, repair of AAA is indicated only when the maximal diameter equals or exceeds 5.5 cm or when the growth rate of the aneurysm is faster than 0.5 cm in 6 months. Medical management is recommended for aneurysms, which do not meet the above-mentioned criteria for repair.

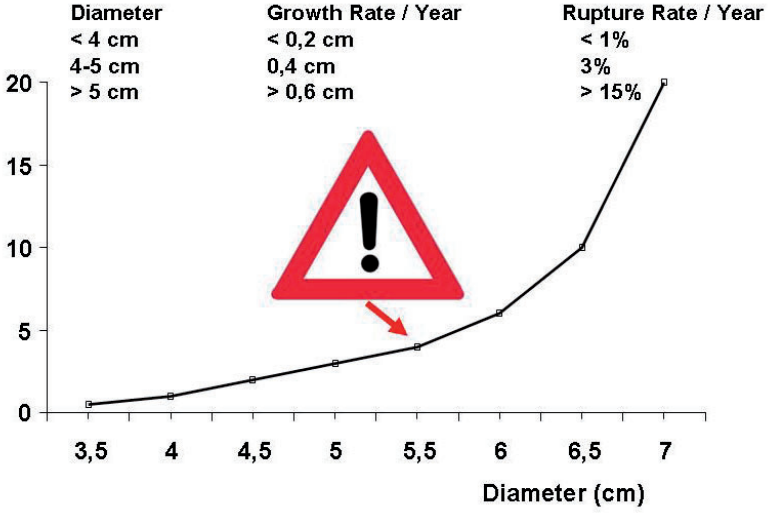

Figure 1: Rupture rate of abominal aortic aneurysms depends on the diameter and the growth rate. Figure modified from [42, 43].

Pathophysiology

The pathophysiology of AAA is not completely understood. There is increasing evidence that AAA is not simply a manifestation of atherosclerosis, but rather a systemic disease with its own genetic and environmental risk factors [9]. The multifactorial pathogenesis of AAA consists of a complex interaction between enzymatic degradation of the aortic vascular wall by matrix metalloproteinases (MMP) with damage of smooth muscle cells, chronic inflammatory processes and oxidative stress. The current understanding of the pathophysiology of AAA has been reviewed recently [9, 11, 14], and is summarized in Figure 2.

Medical treatment of AAA

Statins

Patients with AAA have a markedly increased cardiovascular risk due to atherosclerotic manifestations in other vascular territories. According to data of the UKSAT trial [1] the five-year mortality of patients with small AAA is around 25 %, mainly due to cardiovascular events. A metaanalysis of clinical trials examining the effect of statin treatment in patients with AAA showed that statins slow the progression of atherosclerosis and lower mortality by 43 % over a five-year period [15]. In addition to these clear beneficial effects of statins on the prevention of cardiovascular events, there is some evidence that this class of drugs decreases the growth rate of aneurysms. In the mu-

rine apoE knock-out angiotensin infusion model of AAA treatment with simvastatin significantly decreased aneurysm growth [16]. It has been suggested that statins may slow AAA progression not only due to their cholesterol-lowering effect, but also by their lipid independent pleiotropic effect on vascular inflammation and metalloproteinase expression [17]. Statins have been shown to inhibit expression of proinflammatory molecules, such as C-reactive protein [18]. In addition, pro-MMP-2 and MMP-2 activity was lower in the specimen of aneurysmatic aortic wall from patients that had been treated with atorvastatin compared to patients with no statin treatment before undergoing surgery [19].

Takagi and colleagues have recently published a metaanalysis of the studies investigating the influence of statins on the growth rate of AAAs [20]. The analysis included seven adjusted and four unadjusted observational comparative studies with a total of 4,647 patients and a follow-up period of two months to six years. It demonstrated a significant protective effect of statins on aneurysm growth (standardized mean difference (SMD), –0.420; 95 % confidence interval [CI], –0.651 to –0.189), even though the authors mention some limitations of the analysis such as different definitions and methods of assessment and adjustment of aneurysm progression rates. When the authors separately assessed the protective effect of statin therapy in the seven adjusted high quality studies from their metaanalysis, the protective effect of statin therapy on AAA progression was less prominent but still statistically significant (SMD, –0.367; 95 % CI, –0.566 to –0.168) [20]. The pooled data from all the studies showed a reduction of AAA progression of 0.9 – 1.6 mm per year under statin therapy. Due to the small event rate of aneurysm rupture in these studies, an effect of statins on the rupture rate cannot be confirmed. As statins are indicated in all patients with AAA due to their markedly increased cardiovascular risk, it would be unethical to perform a prospective randomized placebo-controlled study analyzing the effect of statins on aneurysm progression and aneurysm-associated mortality.

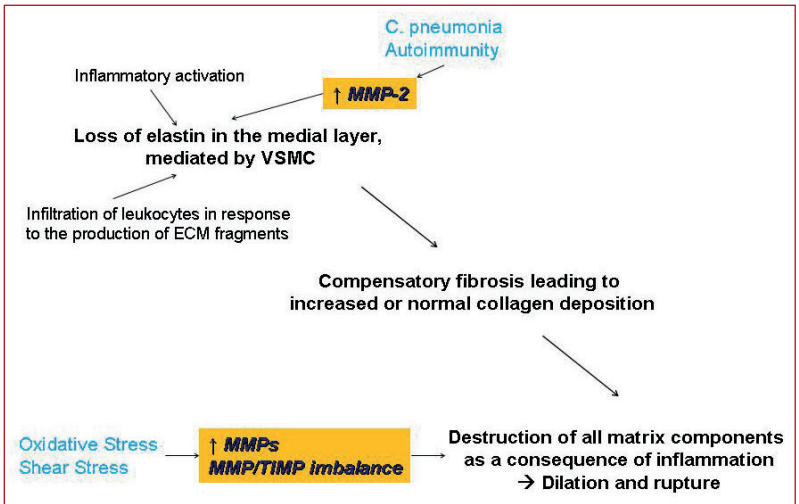

Figure 2: Pathogenesis of abdominal aortic aneurysms: The earliest pathohistological changes in the aneurysmatic aortic wall is a loss of elastin in the medial layer mediated by increased matrix-metalloproteinase 2 (MMP-2) expression of activated vascular smooth muscle cells and propagated by leukocytes that infiltrate the aortic wall in response to the production of extracellular matrix fragments. This may be triggered by autoimmunity. In the intermediate stage of aneurym development compensatory fibrosis leads to increased or normal collagen deposition. As the process proceeds shear stress, oxidative stress and local inflammation results in increased expression of several MMPs and an imbalance between MMPs and their inhibitors leading to the destruction of all matrix components. This finally results in further dilation of the vascular wall and rupture.

Betablockers

Three clinical trials have examined the effect of the betablocker propranolol on AAA growth and have been recently summarized in a Cochrane metaanalysis [21]. Treatment with propranolol (20 – 120 mg, twice a day) had no significant effect on the progression of AAA (1,101 patients, follow up until AAA repair of up to 8 years, MD –0.08 mm; 95 % CI –0.25 to 0.10) but was poorly tolerated with a dropout rate of up to 40 % in the propranolol group. This study suggests that propranolol should not be used for prevention of AAA progression. Other betablockers have not been studied in prospective randomized controlled trials in patients with AAA. In accordance with these negative results, two recent meta-analyses did not find a significant correlation between blood pressure and aneurysm growth [22, 23]. These meta-analyses, however, showed a significant correlation between blood pressure and AAA rupture rate. Therefore, strict blood pressure control is warranted in patients with AAA. With all this said, there is still a valid indication for therapy with beta-

Vasa 2014; 43: 415–421

blockers in patients with AAA due to certain comorbidities, such as e.g. hypertension, coronary heart disease or chronic heart failure.

ACE-inhibitors and AT1 – receptor antagonists

Animal studies have suggested that inhibition of the angiotensin-converting enzyme (ACE) might protect from progression of AAA by down-regulation of the expression of adhesion molecules and proinflammatory cytokines, and by decreasing degradation of extracellular matrix [24]. In addition, the angiotensin II type 1 (AT1)-receptor antagonists telmisartan and irbesartan limited aneurysm enlargement, medial elastolysis, smooth muscle attenuation, macrophage infiltration, adventitial neocapillary formation and the expression of proteinases and proinflammatory mediators in the murine apoE knockout – angiotensin II infusion model of AAA [25], and telmisartan prevented abdominal aortic aneurysm progression independently of blood pressure reduction by inhibiting proteolysis, apoptosis and inflammation in aortic tissue in the rat elastase infusion aneurysm model [26]. Although these experimental data are promising, clinical data regarding the effect of ACE- or AT_1-receptor inhibition on progression of AAA are still controversial. While the initial epidemiological studies have suggested that administration of ACE-inhibitors is associated with a significant reduction in the frequency of AAA rupture (OR 0.82, 95 % CI 0.74-0.90) [27], this observation could not be reproduced in the UK Small Aneurysma Study [28]. Similarly, there is still no proven effect of AT_1 – receptor antagonists on the rate of AAA progression [27, 29]. A clinical trial on the effects of losartan on aortic dilation in individuals with Marfan's syndrome is currently ongoing [30]. Until further data are available these classes of drugs may be used in patients with AAA when indicated for comorbidities but not specifically for the prevention of aneurysm growth or rupture.

Antibiotics

C. pneumoniae seropositivity has been associated in epidemiological studies with a faster aneurym expansion rate [31]. In addition, Chlamydia-like particles have been identified in the aneurysmatic aortic wall by immunohistochemistry, electronmicroscopy and PCR [32]. C. pneumonia has been isolated and cultivated from the aneurysmatic aortic wall [33]. As C. pneumonia is detectable in macrophage-like cells in the media and adventitia of aneurysmatic aortas and these bacteria are known to activate macrophages and induce specific T-lymphocytets, it has been hypothesized that they may initiate an immune response, which is then propagated by the host crossreacting determinants leading to clinical disease long after the microorganism has been cleared [14]. Activated macrophages increase MMP-activity, which may contribute to aneurysm development and growth. Several clinical studies have tested whether treatment of chlamydial infection with macrolid antibiotics could prevent AAA progression both by its antibacterial effects as well as by its effects on MMP-expression [34]. A Cochrane analysis [21] was able to show that roxithromycin reduced the expansion rate of AAAs in the group of 176 patients from 2 randomised studies (MD –0.86, 95 % CI –1.57 to –0.14) [35, 36]. The antibiotic therapy with roxithromycin, however, neither influenced frequency of AAA repair nor mortality. Furthermore, a randomized trial by Mosorin and colleagues [37] was able to show a trend towards decreased progression rate of AAAs in patients receiving tetracyclin. This small protective effect, however, needs to be critically weighed against the potential over-use of antibiotics leading to antibiotic resistance in the general population, and currently cannot be recommended.

Emerging medical options

Human AAA tissue has been shown to have high levels of phosphorylated c-Jun N-terminal kinase (JNK). JNK may be a proximal signaling molecule in the pathogenesis of AAA as it modifies gene expression in different cell types that lead to increased expression of extracellular matrix degradating enzymes while decreasing expression of biosynthetic enzymes of the extracellular matrix. Selective inhibition of JNK in mouse models of AAA prevented the development of AAA and also caused regression of established AAA. Therefore JNK may represent a therapeutic target by addressing extracellular matrix metabolism [38, 39].

Another experimental approach more specifically addresses matrix metalloproteinase activity. MMP-9 activity can be decreased by inhibition of the prolyl hydrolxylase domain protein by CoCl2 [40] or by imdapril, which directly binds to the active center of MMP-9 [41]. Both approaches have been shown to retard aneurysm growth in mouse models of AAA. These treatment options will require further preclinical and clinical studies before their potential can be determined.

Conclusions

AAA is a severe systemic cardiovascular disease associated with genetic and environmental risk factors. The presence even of small AAAs not in need of immediate repair should be seen as an indicator of systemic atherosclerosis and very high cardiovascular risk. These patients should

therefore receive optimal medical treatment of their cardiovascular risk factors. Treatment with statins is especially valuable, because they have been shown to not only reduce cardiovascular mortality, but also to prevent AAA growth. Routine use of beta-blockers does not affect the rate of AAA growth but is associated with significant side effects. Therefore there use is restricted to patients with according comorbidities. While ACE inhibitors and AT1–receptor antagonists have a well recognized role in secondary prevention of cardiovascular disease, there is currently no convincing evidence that they can slow AAA progression. Antibiotic therapy with roxithromycin has a small effect on AAA growth, but this effect must be critically balanced against the potential risk of a wide-spread use of antibiotics.

Conflicts of interest

There are no conflicts of interest existing.

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Vasa 2014; 43: 415–421

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