Pathogenesis of abdominal aortic aneurysms from the vascular surgeon perspective – knowledge summary

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Abstract

Abdominal aortic aneurysms (AAA) affect 2.4% of the population, with men being five times more likely to be affected than women. The development of AAA is linked to changes in the elastin and vascular wall collagen. The enzymes that damage the cell wall are called metalloproteinases. AAA forms as a result of damage to elastic fibres and the loss of the property of reversible deformation of the aortic wall. The degradation of elastin and other stem proteins in the aortic wall is caused by metalloproteinases and serine proteases, accompanied by cysteine proteases and asparagine proteases. Increased calprotectin levels are observed in AAA patients in comparison to patients with a healthy aorta. A significant role in the pathogenesis of AAA and its rupture is played by inflammatory response cells; proteases of the tissue plasma coagulation and fibrinolysis. Plasminogen activator and plasmin accelerate the degradation of the aortic wall. Microbial involvement of C. pneumoniae, Helicobacter pylori, CMV, and HIV is considered in this inflammatory reaction. The local activation of platelets and the plasma coagulation system leads to the formation of a mural thrombus filling the lumen of the aneurysm. The mural thrombus shows a high tissue factor (TF) activity. The formation of AAA is conditioned by a combination of multiple factors. The factors impacting the formation of AAA discovered so far include genetic factors, sex, age, lifestyle (abuse of alcohol, tobacco misuse, obesity, stress), health conditions (hypertension, high cholesterol level, atherosclerosis), and infectious factors: bacteria, viruses, and other microorganisms.

Keywords: abdominal aortic aneurysm, pathogenesis, pathophysiology, biomechanics, risk factors, review.

Introduction

An abdominal aortic aneurysm (AAA) is a spindle-shaped or saccular dilatation of the abdominal aorta by at least 50% in comparison to the unaffected section. Some determine the size of the AAA on the basis of the ratio of the infrarenal and suprarenal aorta. The diameter of a healthy infrarenal aorta may be 1 cm smaller than the diameter of the suprarenal aorta. The diameter of the aorta can be assessed with an ultrasound scan, CT scan, MRI scan, and aortography. AAA has been defined as the diameter of the infrarenal aorta exceeding the diameter of the suprarenal aorta by more than 3cm or the ratio of suprarenal and infrarenal aortic radii of more than 1.2 [1].

The diameter of the abdominal aorta in people aged 65 and over measures 2.01 cm+/- 0.51. An AAA can have a diameter of 3 to 15cm. AAA affect 2.4% of the population, with men being five times more likely to be affected than women. Statistically, they are most commonly found in the ascending aorta - 12.3%; the aortic arch - 8%; the descending aorta - 26.7%, the abdominal aorta above renal arteries - 23%, and in the abdominal aorta below renal arteries - 30.9%. The prevalence of AAA varies, depending on the adopted definition of aneurysm. According to the Cardiovascular Health Study (CHS), it accounts for 9.5% of cases; according to the Oxford Screening Study OSS, it makes up 6.3% of cases, while according to the British Practitioners Study (BPS), it represents 4% of cases [2].

Pathogenesis of AAA formation

The prevalence of AAA in men is significantly higher than in women. There is a high likelihood of genetic predisposition to AAA. The genome-wide association studies (GWAS) have enabled the identification of additional variants, described as single nucleotide polymorphisms, in people, which may be linked to AAA [3].

Until the end of the 1990s, it was believed that the AAA aetiology was closely linked only with atherosclerosis [4]. Currently, dozens of factors have been identified that may influence the formation of AAA. Factors influencing the formation of AAA include hypertension, smoking, being male, obesity, high cholesterol level, age over 65 years, genetic factors related to collagen and elastase, atherosclerosis as an inflammatory process, bacterial factors, viral factors, and C. pneumoniae [5].

The development of AAA depends on the interaction of factors of aortic dilatation or on the reduction of the capacity to generate tension. Locating areas of increased pressure in relation to wave reflection from the aortic bifurcation is suspected to be responsible for the more frequent occurrences of AAA in infrarenal regions [6,7].

The development of the aneurysm is linked to changes in elastin and collagen in the vessel walls. The damage to the elastic lamina leads to an uncontrolled expansion of the vessel and to the formation of an aneurysm. Compared to the healthy wall of the abdominal aorta, there is a significant loss of elastin in the vessel wall in an aneurysm. Elastin and collagen are the most important structural elastic proteins in the aortic artery wall. The stretchy elastin can double its length and quickly return to its original form. This is how it ensures elasticity of the arteries. The middle layer, which is the thickest part of the aorta wall, has fundamental mechanical significance. It features circularly arranged strands of elastic fibres, which form multiple layers of wave-like lamellae. They form a thick band of elastin. The middle layer also features circularly arranged collagen fibres that run parallel to thin elastin fibres. The wall of the abdominal section of the aorta in humans is 0.7-1.0 mm thick, and its middle layer contains no more than 30 elastic lamellae. The mechanism of elastin degradation in the wall of the aorta remains unexplained. It is certain, however, that it involves proteolytic enzymes and their inhibitors. The enzymes that damage the cell wall are metalloproteinases, which include i.a. elastase, collagenase, gelatinase, and streptokinase. Elastase plays the main role in the formation of AAA [8].

AAA forms as a result of damage to elastic fibres and the loss of the property of reversible deformation of the aortic wall. Elastin and other stem proteins in the aortic wall are degraded by metalloproteinases and serine proteases, accompanied by cysteine proteases and asparagine proteases. Increased activity of enzymes from the group of metalloproteinases degrades elastin, fibrous collagen, and other components of the matrix in the arterial wall not only during the formation of the aneurysm but also during its development [9].

Apart from metalloproteinases 2 and 9, the process of matrix degradation involves urokinase-type plasminogen activator (uPA), tissue plasminogen activator (tPA), and plasmin. Plasmin degrades extracellular proteins and enhances the ability of macrophages to degrade the matrix [10]. Patients with AAA also display an increased level of calprotectin in comparison to patients with a healthy aorta. That level decreases significantly after the removal of AAA [11,12].

In a ruptured AAA one can observe an increase in elastin activity and a disruption in the balance between elastase and alpha 1-antiprotease. Factors contributing to the risk of aneurysm rupture include fast enlargement of the aneurysm by more than 1 cm per year, the presence of bubble-like bulges in its wall, spindle shape, family history, presence of COPD, and hypertension. Haque et al. concluded that factors enabling the prediction of the development of the disease include hypertension, high cholesterol level, age, and smoking of tobacco [7].

Collagenase is also observed in the wall of a rupturing AAA. It has been demonstrated that elastase is responsible for the expansion of the aortic wall, while collagenase is responsible for rupturing of the AAA without prior expansion of the aortic wall. The formation of AAA is caused by an increased proteolytic activity. The wall of the AAA also shows increased activity of cathepsins L, K, and V [13].

In all aortic aneurysms, there is an inflammatory response of varying degrees of intensity. When the inflammatory response is highly intense, such aneurysms are treated as inflammatory aneurysms, which account for 3-12% of all aneurysms. This process involves macrophages and lymphocytes T and B located in the adventitia. They infiltrate the wall of the aneurysm taking advantage of the destructive activity of metalloproteinases to activate proteolysis with cytokines: TNF-alpha, IL1 beta, IL-6, INF-gamma, and IL-8, which disrupt the balance between the synthesis and degradation of matrix proteins. Increased TBF-alpha content has pro-inflammatory properties, it stimulates angiogenesis and the growth and proliferation of endothelial cells [14].

Apart from the growth of endothelial cells, activators of plasminogen and metalloproteinases are released during angiogenesis. They damage the connective tissue and facilitate the migration of cells through the basement membranes of vessels. The rise in the concentration of metalloproteinases on macrophages depends on prostaglandin E2 (PGE2), which is made of arachidonic acid and is to be found in large amounts in the aneurysm tissue [15].

The reduced superoxide dismutase activity in aneurysms facilitates the excessive accumulation of free radicals, which contribute to the formation of the aneurysm too. Studies show that the prevalence of aneurysms in members of the same family is higher than in the general population [16]. As a result of this process, the aneurysm grows slowly by c.a. 4mm per year. The enlargement of the aneurysm is also delayed by the synthesis and remodelling of aortic collagen. Stronger expression of type I and III procollagen genes indicates that repair processes are occurring simultaneously with the destruction of the aneurysm wall [17].

Above all, high blood pressure and reverse flow in the abdominal aorta first damage elastic lamellae made of elastin, which have lower resilience than collagen fibres. Products of the degradation of this elastin cause the destruction of the matrix. There is a mural thrombus in the aneurysm, which obstructs the passage of oxygen and nutrients, impacting negatively on the metabolism of the middle layer [18].

Significant enzymatic activity is observed in the mural thrombus. It involves proteases (elastase, collagen-like peptidase) and lyposomal enzymes (cathepsins A, D, E), which intensify the degradation of soluble proteins in the aortic wall. This, in turn, contributes to the formation of an aneurysm [19]. The destruction and disintegration of the middle layer occur in the aneurysm. It is accompanied by the reduction in elastin content and its complete disintegration in the adventitia, which proves that the elastolysis of the adventitia is the first part of the process of aneurysm formation.

The most common location of AAA is the abdominal section between the outflow of renal arteries from the aortic bifurcation into iliac arteries. There are no vessels in the middle layer, and the nutrition of this layer takes place by diffusion through the adventitia. In progressive atherosclerosis, the atherosclerotic plaque does not harden but the progressive destruction of the middle layer weakens the aortic wall, which creates conditions for the formation of an aortic aneurysm [20].

Biomechanics of the AAA formation

The biomechanics of the formation and growth of AAA has been known for a long time. Once the thoracic aorta transitions into the abdominal aorta, the number of elastic lamellae decreases significantly, which causes an increase in collagen content in relation to elastin. This makes the wall of the abdominal aorta stiffer and thinner than the wall of the thoracic aorta [21].

The pressure wave of arterial blood flow rebounds from the arteries below the aortic bifurcation into the iliac arteries and overlaps with subsequent incoming waves in the abdominal aorta, which causes pressure in the abdominal aorta and iliac arteries to rise [22]. As a result of this, the tension of the wall increases as the aorta expands, despite unchanging blood pressure, according to Laplace's law: wall tension (T) = mean arterial pressure (P) x aortic radius (R) / divided by the thickness of the aortic wall (W). This law implies that the wall tension increases during the expansion of the aorta even when arterial pressure does not change [23]. Increasing the radius of the lumen of the vessel leads to increased tension of the aortic wall and further dilatation until the AAA eventually ruptures. This causes the shape of the blood vessel to change from cylindrical to spherical, diminishing the forces acting on the aortic wall by half, which may cause the AAA to expand slowly by 4mm per year [24].

The risk of rupture of an aortic aneurysm depends on a number of parameters. The first of these factors is the tension in the aortic wall. An AAA has not been found ruptured when the tension of the wall was lower than 2.80×10^5 N/m^2. When the tension of the wall of an aortic aneurysm is higher than $2.80 \times 10^5 \, N/m^2$, the risk of AAA rupture may increase 8 times [25]. The following formula is used: blood pressure approximated to tension (BPAT) = diameter of the aneurysm/ BMI x average arterial pressure (P). It is a more sensitive indicator of the risk of AAA rupture than the tension of the wall alone. BPAT above 17.9 is a sensitive indicator of an aortic aneurysm rupture risk [26]. Another indicator of the aortic aneurysm rupture risk is the diameter of the L3 circle. When the diameter of the aneurysm/ diameter of the L3 circle is below 1.00, the risk of rupture of the aneurysm is small [27].

Biomechanical rupture of AAA occurs when the mechanism of pressure on the walls exceeds the extensibility of the aneurysm wall. This pressure plays a decisive role in the rupture of the aneurysm and the ability to predict the pressure on the wall may be useful for assessing the risk of rupture. An aneurysm ruptures when the pressure exceeds the ultimate local resistance of the vessel tissue [28,29].

Impact of the coagulation system on AAA

Proteases of the tissue and plasma coagulation and fibrinolysis systems play a significant role in the pathology of aortic aneurysms. Urokinase-type plasminogen activator and aortic wall plasmin play a significant role in the formation,

expansion, and rupture of the aneurysm. The local activation of platelets and the plasma coagulation system leads to the formation of a mural thrombus filling the lumen of the aneurysm. The mural thrombus shows a high tissue factor (TF) activity.

Patients with AAA often experience a chronic, generalised, and asymptomatic activation of blood clotting. Less common is the disseminated intravascular coagulation syndrome with purpura and multiple organ failure.

Plasminogen is synthesised in hepatocytes and granulocytes, and then passes into the blood and intracellular spaces. It is activated by the plasminogen activator. The plasmin formed from plasminogen degrades the proteins in the matrix of intracellular spaces: fibronectin, laminin, and other glycoproteins, causing the activation of many prometalloproteinases: elastase, collagenase, gelatinase, and stromelysin. It has been demonstrated that the wall of an aortic aneurysm displays a higher level of activity of the plasminogen and plasmin activator than a healthy aortic wall [30].

The degradation of structural proteins by plasmin and metalloproteinases causes the mechanical resistance of the aortic wall to diminish locally. The activation of platelets and blood coagulation factors in patients with an aortic aneurysm may be limited or generalised. Local and generalised activation of the coagulation system that occurs in cases of aneurysm may be latent or manifest clinically. 0.5 to 1% of patients with AAA experience a generalised hypercoagulability, which is described as disseminated intravascular coagulation (DIC).

The endothelium damaged at the site of aneurysmal dilatation loses its anti-coagulation properties and acquires prothrombotic properties. In most cases, the formation of a clot or bleeding is determined by the imbalance between clotting and fibrinolysis processes. The main role in the formation of the clot in the vessel is played by platelets. Membrane receptors of platelets in the aortic wall, which determine their adhesion and aggregation, are exposed under conditions of rapid blood flow. Homocysteine may influence AAA pathogenesis by intensifying proteolysis and impairing the coagulation/fibrinolysis system [31].

The forming fibrin fibres reinforce the platelet plug. The plasmin generated in the clot acts on the already-formed fibrin. Due to the local activation of blood clotting, the aortic aneurysm is filled with the mural thrombus. As a rule, the mural thrombus does not contain clotting and fibrinolysis inhibitors. High levels of tissue factor (TF) activity and the absence of anti-thrombin substances promote the enlargement of the mural thrombus in the lumen of the aneurysm. The growth of the thrombus is limited by the significant content of plasminogen and the absence of antiplasmin. Thanks to the coagulation-fibrinolytic balance, the thrombus in the lumen of the aneurysm does not grow excessively; it restricts the flow of blood only partially and does not cause aortic obstruction. The mural thrombus reduces the impact of hemodynamic forces on the aneurysm wall and improves blood flow conditions through the aneurysmal dilatation, which may slow down its further enlargement. The detachment of thrombus fragments may lead to the formation of peripheral embolisms [32].

Infectious factors in the course of AAA

AAA involves a chronic inflammatory process, in which the key role is played by inflammatory reaction cells producing proteases and plasminogen activator, which accelerate the degradation of the aortic wall. Microbial involvement of C. pneumoniae, Helicobacter pylori, CMV, and HIV is considered in this inflammatory reaction [33]. From 80% to 90% of patients with AAA experience a chronic infection with C. pneumoniae, which may serve as a confirmation of the thesis that it plays a role in the pathogenesis of the condition [34].

Infectious factors contribute to the development of a generalised and localised inflammation of the endothelium, which leads to atherosclerosis complications, thrombosis, and AAA formation. Studies conducted in Denmark as early as 1998 showed a significant correlation between the presence of class IgA C. pneumoniae antibodies and the enlargement of AAA. The link between the infection with C. pneumoniae and atherosclerotic changes was first demonstrated in 1992 in a South African population on the basis of studies conducted with PCR methods; immunocytochemistry, immunocytofluorescence, and in situ hybridization [35]. These methods detected C. pneumoniae on average in 60% of patients with dissecting AAA. A hypothesis was formulated that macrophages carry these microorganisms from the lungs to arteries. They engulf damaged infected smooth muscle cells containing C. pneumoniae. Studies have shown that C. pneumoniae may replicate in the endothelial cells, smooth muscles, and macrophages [36].

According to claims made by Koch and to the current state of knowledge, neither atherosclerosis nor AAA can be regarded as infectious diseases. C. pneumoniae is not always present in the pathological aneurysm tissue. It has to be remembered that according to Koch, ulcer disease is not an infectious disease either, as Helicobacter is not always found in the pathological gastric tissue. In leprosy and syphilis, Koch's claims are also not fulfilled. The presence of bacteria in the vessel wall may be the consequence of phagocytosis by macrophages from a different anatomical region of the organism and accidental migration to atherosclerotic plaques as part of filtration, or to endothelial cells and smooth muscle. A significantly higher frequency of occurrence of C. pneumoniae in patients with AAA was demonstrated with the use of PCR technique, immunoblotting, and with the use of electron microscope [37,38]. Hence the suggestion that the damage of atherosclerotic plaques by C. pneumoniae contributes to atherosclerosis and, indirectly, to the development of AAA.

Summary

The formation of AAA is conditioned by a combination of multiple factors. The impact of genetic factors, environmental factors such as sex, age, smoking, obesity, health conditions (hypertension, high cholesterol level, atherosclerosis), and infectious factors (bacteria, viruses, and other microorganisms) has been identified so far.

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