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Review

The Aging Population and Research into Treatments for Abdominal Aortic Aneurysms

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Abdominal aortic aneurysms (AAAs) usually expand asymptotically until the occurrence of a life-threatening event such as aortic rupture, which is closely associated with high mortality. AAA and aortic dissection are ranked among the top 10 causes of death in Japan. The major risk factors for AAA are age over 65 years, male gender, family history, and smoking. Thus, for prevention, smoking cessation is the most important lifestyle-intervention. For treatment, since AAA generally affects elderly people, less invasive treatment is preferable. However, the only established treatment for AAA is open repair and endovascular repair. This review describes potential medical treatments to slow aneurysm growth or prevent AAA rupture.

Key words: abdominal aortic aneurysms, medical treatment, anti-platelet drugs

Review

Abdominal aortic aneurysm (AAA) is a permanent dilation of the abdominal aorta with an onset of symptoms that is often insidious until the overt manifestation of rupture. The prevalence of AAA increases with age. AAA is uncommon in persons younger than 50 years; however, 12.5% of men and 5.2% of women 74-84 years of age have AAA [1]. It accounts for approximately 11,000 deaths each year in the United States, with mortality rates from ruptured AAAs reaching up to 90% [2]. In 2014, AAA and aortic dissection were the ninth leading cause of death in the Population Survey Report from the Ministry of Health, Labor and Welfare in Japan. The major risk factors for aortic aneurysm are age older than 65 years, male gender, family history, and smoking [3]. In addition to these risk factors, age related-diseases such as

hypertension, ischemic heart diseases, and chronic kidney diseases, but not diabetes mellitus, are also related to the high prevalence of AAA in Japan and Western countries [4].

The management of AAA varies according to AAA size. Open and endovascular surgical repairs are initially indicated in patients with large AAAs (>5.5 cm) to prevent aneurysms from rupturing [3]. Since AAA is common in the elderly, the risks of postoperative complications should be considered. Frailty is also common in elderly people. The prevalence of frailty increases with coexisting cardiovascular diseases [5]. In addition to the classical risk factors for frailty, including age, female gender, cardiac failure, chronic obstructive pulmonary disease, renal impairment, cerebrovascular disease, peripheral artery disease, ischemic heart disease, and diabetes mellitus, a prospective study from over 200 American and Canadian hospitals revealed that evaluation for frailty should be required in the risk assessment of AAA [6]. Endovascular repair is more

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reasonable than open repair in patients with cardiopulmonary or other associated diseases. In particular, endovascular therapy is a useful option in patients who are unable to tolerate open surgery, because it is a minimally invasive therapy. However, endovascular therapy is unsuitable for patients with anatomical problems involving the neck angles and approach. Moreover, graft complications and re-interventions due to various types of end-leaks occur more often in patients with endovascular therapy (9-10%) [7]. Thus, there are both advantages and drawbacks to the current surgical options.

Given the limitations for surgical therapy, several medical options have been studied for the management of small aortic aneurysms, with the goal of slowing aneurysmal growth and preventing rupture. Aneurysmal growth and rupture are considered to be partially due to vascular inflammation, mechanical stress and matrix metalloproteinase activities.

Good management of blood pressure reduces progression and rupture of AAAs. It has been suggested that β blockers could correct excessive extracellular matrix remodeling, in addition to lowering blood pressure [8]. In one clinical study, β blockers were shown to reduce perioperative mortality from AAAs. However, propranolol was reported to have no significant effect in terms of limiting AAA growth in three clinical trials, all of which reported poor patient compliance with treatment [9, 10]. Moreover, angiotensin II has been shown to promote inflammation, matrix remodeling and hypertension, resulting in AAA formation and ruptures in many animal studies. Blocking angiotensin II with angiotensin II receptor blockers and angiotensin converting enzyme inhibitors were expected to have a beneficial effect on AAA growth and rupture. However, clinical trials have failed to show a favorable effect of renin-angiotensin system blockages [11, 12]. Thus, the effect of anti-hypertensive drugs, including β blockers and renin-angiotensin system inhibitors, on AAA enlargement has not been clarified.

Statins attenuated the development and growth of experimental AAA through anti-inflammatory and anti-oxidative stress effects; however, several clinical studies failed to show that they affected AAA enlargement and rupture.

Doxycycline, a broad inhibitor of matrix-metalloproteinase, was successfully demonstrated to slow AAA growth in a small human study [13]. However, it failed to show a significant effect on the AAA growth in phase

II and double-blind control studies [14, 15].

Cyclosporine, an inhibitor of cyclophilin A, was also expected to suppress the development and progression of AAA by inhibiting inflammatory cell recruitment and matrix metalloproteinase activities in animal studies [16]. Short-course administration of cyclosporine A was shown to stabilize the diameter of formed AAA by upregulating TGF- β 1 in animal models; however, the effect and usage of cyclosporin on human AAA and is still under investigation.

Most AAAs contain a large volume of intraluminal thrombus, and the volume of this thrombus has been correlated with AAA growth. Anti-platelet drugs were expected to reduce inflammatory cytokines and matrix-degrading enzymes by reducing thrombus volume. Only a few studies showed significant positive effects of anti-platelet drugs such as aspirin or P2Y12 inhibitors on the development and progression of AAAs, or death from AAAs. Clinical trials examining the efficacy of the anti-platelet agent ticagrelor in limiting AAA growth are currently ongoing. Cilostazol inhibits platelet aggregation by mechanisms different than aspirin or P2Y12 inhibitors. Cilostazol has been reported to have some favorable effects in the field of cerebrovascular diseases through its peritrophic effects [17]. We previously demonstrated the potential ability of cilostazol, a PDE-III inhibitor, on AAA development through its anti-inflammatory effect [18]. Cilostazol is already used in clinical practice for patients with peripheral artery diseases and stroke. Since patients with AAA often have many vascular complications, including coronary artery disease, myocardial infarction, and peripheral artery disease, our findings may suggest a favorable option for AAA treatment.

Development of minimally invasive treatment including drug therapies is very desirable for AAA treatment, especially for elderly people and patients with many complications. Over the last decade, emerging evidence has highlighted several mechanistic insights into AAA growth and rupture using animal models, but translational studies from bench to bedside are still lacking. Further large clinical trials are necessary to explore new promising therapies.

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