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REVIEW

Comprehensive Cardiac Rehabilitation as a Therapeutic Strategy for Abdominal Aortic Aneurysm

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Abdominal aortic aneurysms (AAA) are referred to as "time bombs". The only way to prevent AAA rupture is elective repair beforehand using surgical replacement or an endovascular procedure. Non-surgical strategies to prevent AAA expansion are under intense investigation. At each AAA stage, that is, occurrence, expansion, and rupture, the mechanisms and risk factors are different, as discussed in this review. Based on the mechanism and risk factors for AAA expansion, the most effective strategy against AAA expansion need to be identified, but so far none has. Exercise is known to be essential for preventing atherosclerosis related to the coexistence of AAA and CAD, but some doctors are hesitant to prescribe exercise programs to AAA patients given that BP elevation during exercise can cause AAA expansion or rupture. In our retrospective study and prospective study on the safety and effectiveness of exercise for AAA patients, the protective role of mild-moderate exercise against expansion of small AAA was clearly shown. The stability of AAA on exercise might be related to reduced inflammatory activity in the aortic wall, stabilized elevation in BP during exercise, increased aortic blood flow, upregulation of transforming growth factor-β1, moderated BMI and/or fat, or improved endothelial function. Until a revolutionary drug emerges that can regress AAA, cardiac rehabilitation remains the best strategy for preventing AAA expansion and rupture.

Key Words: Abdominal aortic aneurysm; Atherosclerosis; Cardiac rehabilitation; Exercise

Abdominal aortic aneurysms (AAA) are referred to as the "silent killer" or "time bomb"[1] because they grow asymptomatically until they rupture suddenly. The associated mortality rate after AAA rupture is as high as 80%,[2,3] with some patients surviving after successful emergency surgical repair. The only method to prevent AAA rupture is elective repair beforehand using surgical replacement or endovascular procedure. Some medications, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and statins, have been shown to suppress AAA expansion in mouse AAA models.[4–9] Moreover, an inhibitor of c-jun N-terminal kinase led to the successful regression of AAA in animal models.[10] These medications, however, could not suppress AAA expansion in humans. Hence, at present, we have no choice but to observe AAA expansion carefully until the AAA reaches the point where it meets the elective repair criteria. Accordingly, our urgent task is to elucidate the key mechanisms for AAA expansion and identify the potential therapeutic strategies for suppressing AAA expansion.

Mechanisms of AAA Occurrence and Expansion

The expansion of AAA is mediated by multiple factors, which partly differ from those related to the occurrence of AAA and other vascular diseases such as coronary artery disease (CAD), peripheral artery disease (PAD), and carotid stenosis.[11] Among them, inflammatory cells and cytokines play an important role in AAA occurrence and expansion.[12–14] Consistently, inhibition of tumor necrosis factor (TNF)-α, the complement system and peroxisome proliferator-activated receptor γ successfully prevented AAA formation and expansion in mouse AAA models.[15] In contrast, anti-transforming growth factor-β (anti-TGF-β) antibody injection induced AAA rupture in an angiotensin II-stimulated AAA model,[16] indicating that upregulated TGF-β plays a protective role against AAA progression and rupture.[16,17] Taken together, at least in animal models, the mechanism underlying AAA expansion is not similar to that underlying the occurrence of AAA.

Risk Factors for AAA Occurrence, Expansion, and Rupture in Humans

Consistent with the aforedescribed experimental findings, the risk profiles of occurrence, expansion, and rupture of AAA are different from one another in humans.

Except for AAA caused by infection, trauma, or Marfan syndrome, AAA occurrence is more prevalent in aged patients, male subjects, smokers, and those who have chronic obstructive pulmonary disease, hypertension, and low high-density lipoprotein cholesterol.[18] Many cohort studies identified smoking as the strongest risk factor for AAA formation.[19] A cohort study in Sweden suggested that

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a low anti-inflammatory dietary index is a risk factor for AAA occurrence.[20]

Several studies indicated that atherosclerotic conditions do not contribute to the risk of AAA expansion.[21–26] The major risk factors for AAA expansion were the diameter of AAA and smoking, whereas atherosclerosis per se played a minor role in AAA expansion.[21] Diabetes, a strong promoter of atherosclerosis, and PAD, representing the end stage of atherosclerosis, were inversely correlated with AAA expansion rate.[22] We analyzed the clinical characteristics related to AAA expansion in 665 patients, and found an inverse correlation between accelerated AAA expansion rate and the existence of CAD,[23] and subsequent meta-analysis indicated an inverse association of CAD with AAA expansion, although that association did not reach statistical significance.[24] We also identified that high calcification index of the AAA wall, reflecting atherosclerosis stage, is inversely correlated with AAA expansion rate.[25,26] A recent biomechanical analysis showed that elevated peak wall stress (PWS) and peak wall shear stress accelerated AAA expansion, resulting in rupture.[27] Indeed, recent meta-analyses did not identify hypertension as a risk factor for AAA expansion.[28] Large AAA diameter, rapid expansion, smoking, hypertension, female sex, saccular morphology, and elevated PWS are risk factors for AAA rupture.[27,29,30] Here, it is important to be aware that hypertension is a risk factor for AAA rupture,[29,30] but it is not a significant risk factor for AAA expansion.[21–23,28] Therefore, it is understandable that antihypertensive therapy cannot prevent AAA expansion in humans.

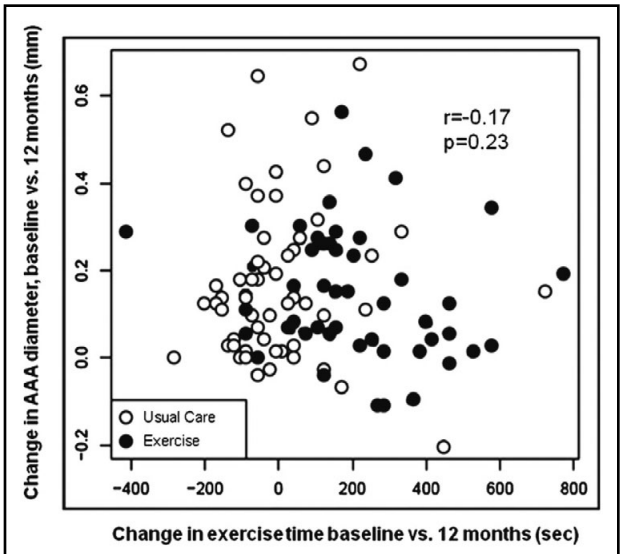

Figure 1. Change in exercise capacity vs. change in abdominal aortic aneurysm (AAA) diameter between baseline and 1-year evaluations. The change in AAA diameter tended to be slightly lower as exercise capacity improved at 1 year. Reproduced with permission from Myers J, et al.[40]

Management of Small AAA

The guidelines for small AAA management recommend avoidance of smoking and competitive sports.[31,32] The guidelines do not recommend anaerobic exercise to AAA patients due to a lack of evidence supporting its benefit. Some doctors are hesitant to prescribe the exercise program to AAA patients for fear that blood pressure (BP) elevation during exercise may cause AAA expansion or rupture. Indeed, in the case report of a 71-year-old man with a 7-cm AAA, high-intensity exercise induced AAA rupture when BP increased from 160/94 mmHg to 200/100 mmHg on an exercise nuclear ventriculogram.[33] Exercise activates the sympathetic nervous system and elevates BP, possibly functioning as a trigger for AAA rupture. Also, an old report indicated that 17% of ruptures occurred while patients were lying in bed, 15% in the sitting position, 54% during mild or moderate load activity, and 13% during high load activity.[34] As for the AAA rupture, the safety margin of exercise intensity is unknown, therefore, it is natural that some doctors are hesitant to prescribe the exercise program to AAA patients for fear of AAA rupture during exercise.

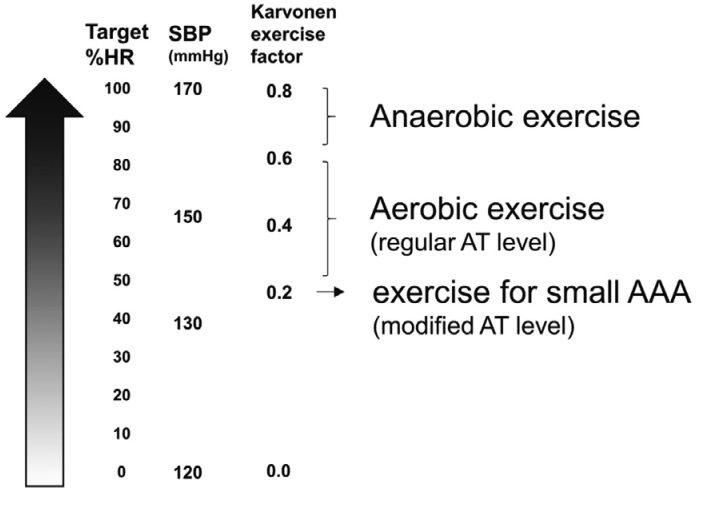

Figure 2. Degree of exercise stress. Exercise at a modified anaerobic threshold (AT) level corresponds to systolic blood pressure (SBP) <150 mmHg. AAA, abdominal aortic aneurysm. Reproduced with permission from Nakayama A, et al.[42]

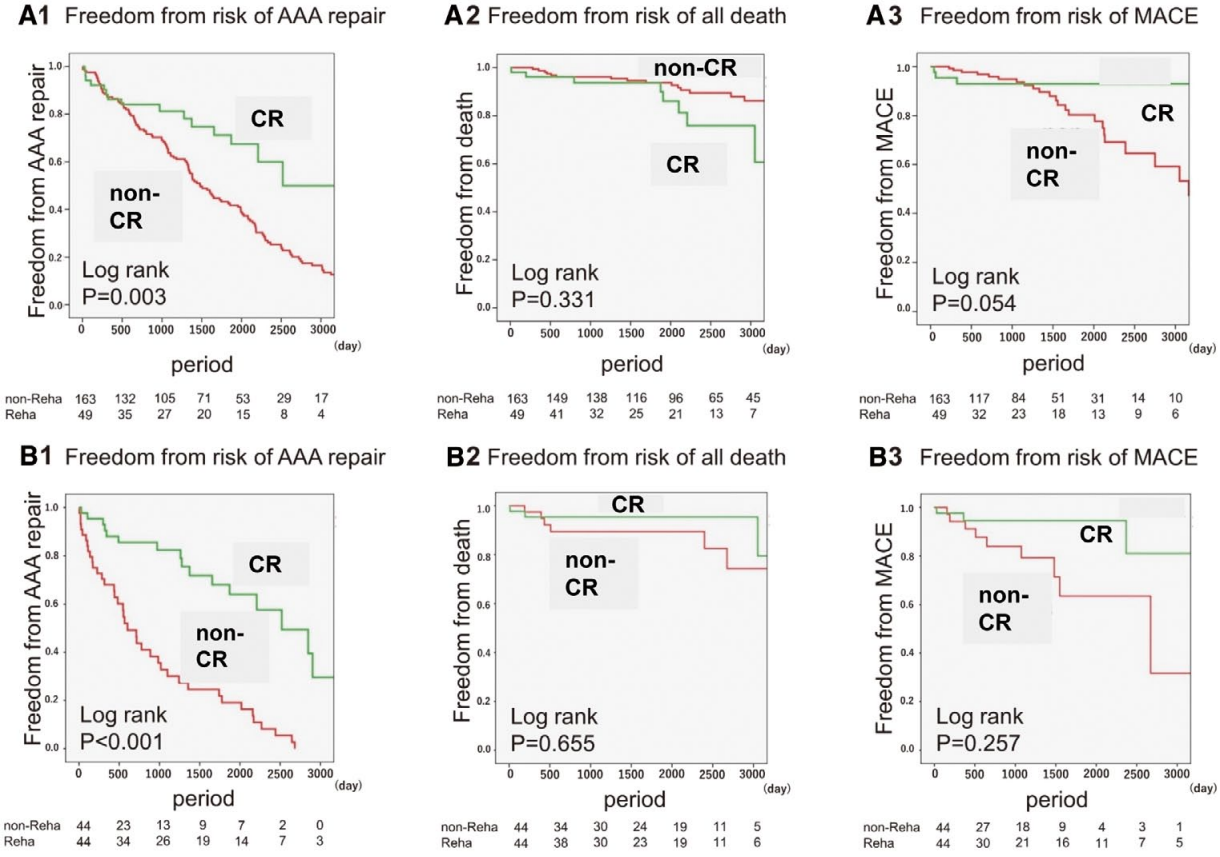

Figure 3. Kaplan-Meier analysis of the risks of abdominal aortic aneurysm (AAA) repair, all-cause death, and major adverse cardiovascular events (MACE) in small AAA patients (**A**) before propensity score matching between the cardiac rehabilitation (CR) group (n=49) and the non-CR group (n=163), and (**B**) after matching, between the CR group (n=44) and the non-CR group (n=44). Reproduced with permission from Nakayama A, et al.[42]

High Frequency of CAD in AAA Patients

In a clinical setting, AAA frequently co-exists with CAD. A recent cohort study reported that 65.3% of AAA patients who underwent elective AAA repair had significant coronary artery stenosis,[35] whereas 51% of AAA patients were found to have CAD in a previous study.[23] Also, 5.4% of CAD patients had AAA in a large cohort study.[36]

CAD patients require cardiac rehabilitation (CR) to improve life expectancy,[37] but when CAD patients have AAA, doctors are hesitant to prescribe CR for fear that BP elevation during exercise may cause AAA expansion or rupture. Here, we should identify the safety zone of exercise intensity for AAA patients, and examine whether CAD patients with AAA could obtain benefit from CR.

Small AAA and Exercise

In 2009, Kothmann et al first studied exercise in AAA patients,[38] but they could not sufficiently analyze the safety or effectiveness of exercise due to the small sample size. Myers et al performed a randomized controlled trial involving AAA patients, showing that peak exercise load in cardiopulmonary exercise test was safe for AAA patients.[39] The sample size, however, was still insufficient to enable generalization of the safety of exercise to all AAA patients. Therefore, the same group conducted a follow-up study in a larger population of AAA patients, and observed that moderate exercise with a target heart rate (HR) 60–80% of the HR reserve was safe.[40] In that study, moderate exercise did not enhance the AAA expansion as compared with AAA patients without exercise (**Figure 1**). Exercise improved peak $\dot{V}O_2$ also in AAA patients.[41] These studies, however, were performed in small groups for short follow-up periods.

We conducted a retrospective study in 1,515 AAA patients in 2 high-volume hospitals from April 2004 to September 2015, using propensity matching analysis.[42] We compared patients with small AAA who underwent CR with those with small AAA who did not undergo CR, and 88 patients remained after propensity score matching. The typical exercise intensity with regular anaerobic threshold (AT) level for cardiovascular patients corresponds to 60–80% of maximum HR (%HR), or 0.4–0.6 of the exercise factor using the Karvonen formula.[43] Considering that elevated BP during exercise could be a risk factor for AAA rupture,[29,30] the exercise intensity corresponded to 0.2 of the exercise factor for the HR reserve using the Karvonen formula, which was designated as exercise with a "modified AT level" in that study (**Figure 2**).[42] This exercise with modified AT level was prescribed to patients with resting

BP <130/90 mmHg, and was discontinued when BP during exercise was >150/100 mmHg.

That study confirmed the apparent positive effects of CR in patients with small AAA.[42] The risk for AAA repair was significantly lower in the CR group (before matching: hazard ratio, 0.43; 95% CI: 0.25–0.72; P=0.001; after matching: hazard ratio, 0.19; 95% CI: 0.07–0.50; P<0.001; **Figure 3**). The AAA expansion rate was slower in the CR group (before matching: CR group vs. non-CR group, 2.3±3.7 vs. 3.8±3.4 mm/year, P=0.008; after matching: CR vs. non-CR group, 2.1±3.0 vs. 4.5±4.0 mm/year, P<0.001). The risks for major adverse cardiovascular events or death were similar between groups. Based on that retrospective study, we concluded that CR with a modified AT level was safe and effective for slowing AAA expansion.[42]

Prevention of AAA Expansion by CR: Possible Mechanisms

The mechanisms by which CR prevents AAA expansion remain to be investigated. We assessed the potential for CR to prevent AAA expansion in a prospective study of 40 patients with small AAA (maximum diameter >30 mm and <50 mm).[44] The risk of AAA repair was significantly lower in the CR group than in the non-CR group (P=0.026; **Figure 4**). The AAA diameter expansion rate was higher in the non-CR group than in the CR group (CR, −1.3±2.4 mm/year; non-CR, 2.0±3.6 mm/year, P<0.01; **Figure 5**).

There are several hypotheses regarding the preventive role of CR against AAA expansion (**Figure 6**).[45] Briefly, the stability of AAA could be related to reduced inflammatory activity in the aortic wall, stabilized elevation of BP during exercise, increased aortic blood flow, upregulation of TGF-β1, moderated body mass index (BMI) and/or fat, or improved endothelial function.

Inhibition of Aortic Wall Inflammation

Inflammatory activity in the aortic wall is thought to be a trigger for AAA formation and expansion.[12–14] Atherosclerosis-driven changes in the aortic wall underlie the pathogenesis of AAA, and inflammatory mechanisms contribute to aortic wall weakening. The inflammatory cytokine TNF-α plays a role in the pathogenic mechanisms of AAA, and oral intake of a TNF-α antagonist, infliximab,

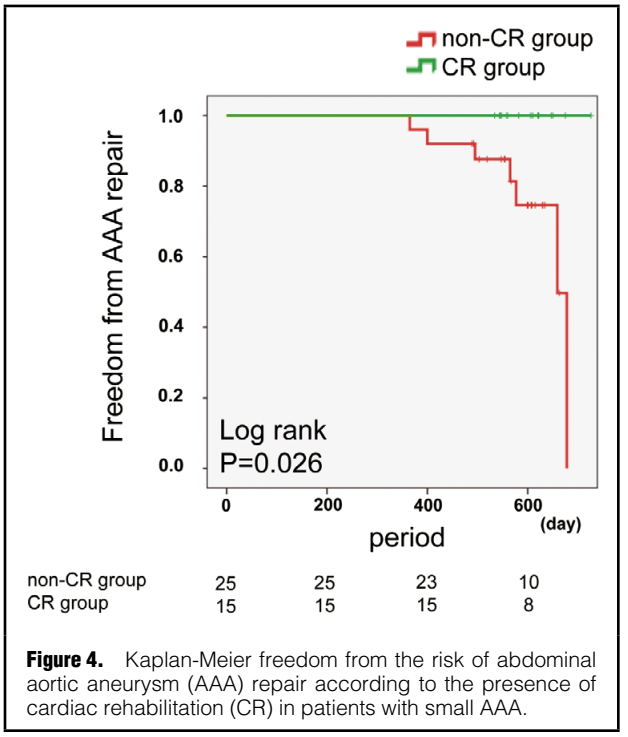

Figure 4. Kaplan-Meier freedom from the risk of abdominal aortic aneurysm (AAA) repair according to the presence of cardiac rehabilitation (CR) in patients with small AAA.

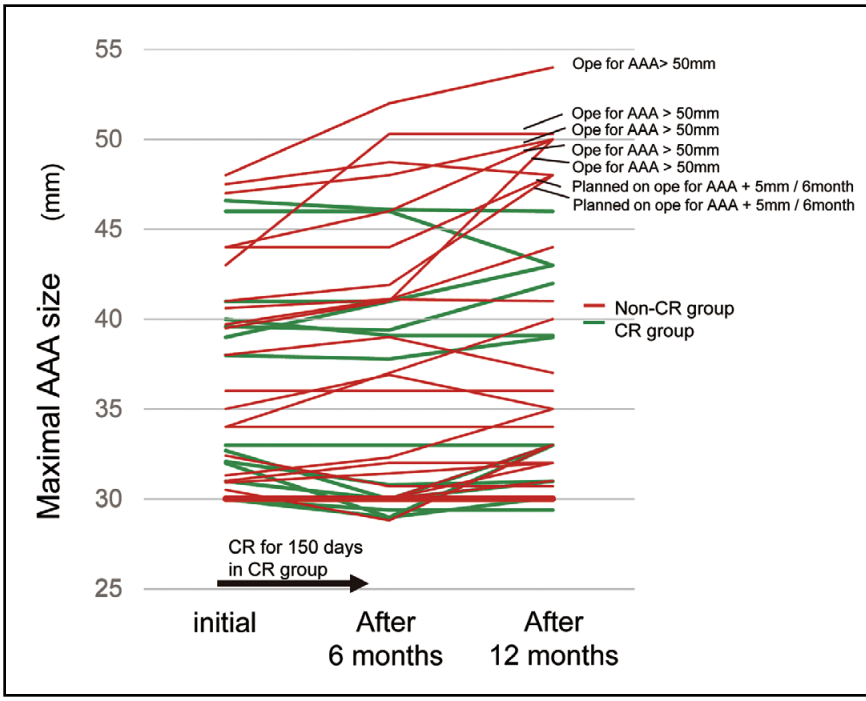

Figure 5. Change in maximum abdominal aortic aneurysm (AAA) size after registration, according to the presence of cardiac rehabilitation (CR). The reason for AAA repair is based on the criteria of diameter and expansion rate. Ope, operation. Reproduced with permission from Nakayama A, et al.[44]

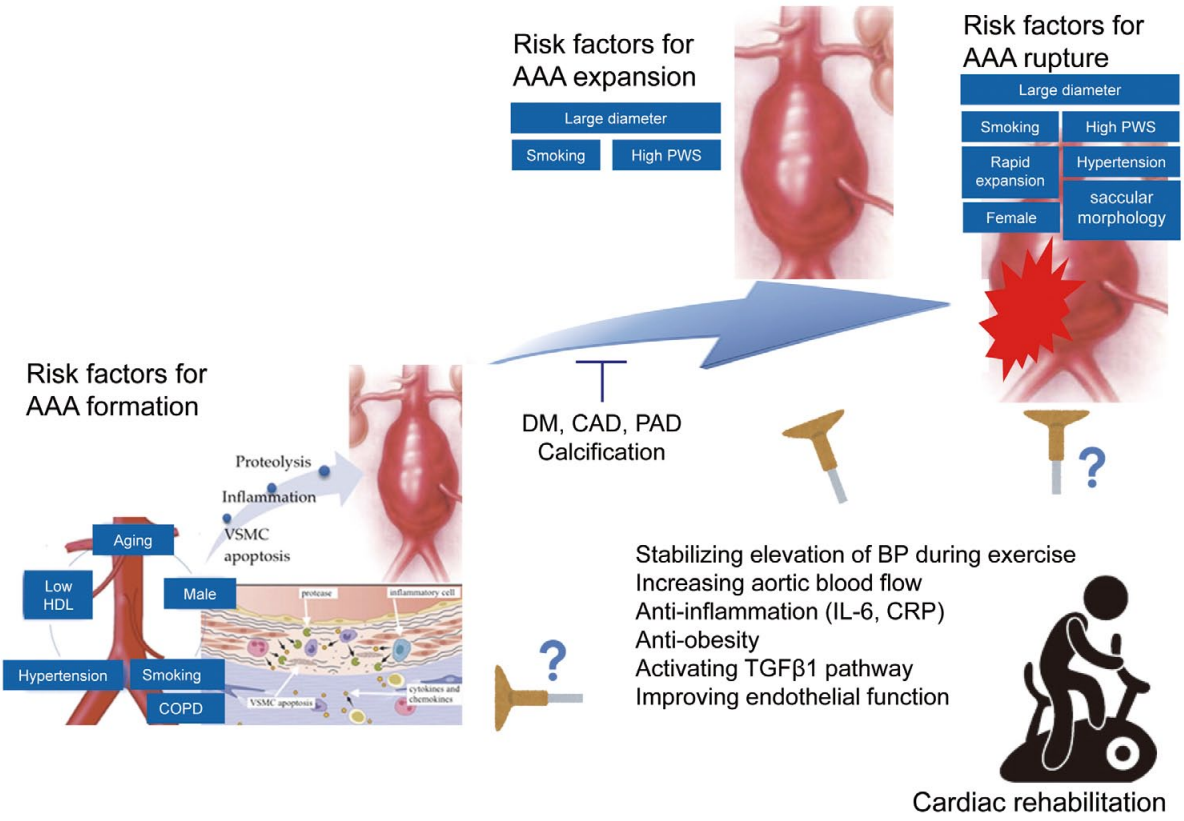

Figure 6. Schematic diagram of the effect of cardiac rehabilitation on the formation, expansion, and rupture of abdominal aortic aneurysms (AAA). BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; IL-6, interleukin-6; PAD, peripheral artery disease; PWS, peak wall stress; TGF-β1, transforming growth factor-β1; VSMC, vascular smooth muscle cell. Reproduced with permission from Carino D, et al.[45]

inhibited AAA formation in mice.[13] Treatment with an anti-interleukin-1β (anti-IL-1β) antibody also suppressed angiotensin II-induced aortic inflammation and AAA formation in mice.[14] In our analysis, however, the inflammatory cytokines high-sensitivity C-reactive protein and IL-6 were not suppressed by CR, and they were not related to the AAA expansion rate.[44] Additional research on inflammatory cytokines, including interferon-γ, TNF-α, IL-1, and IL-8, is needed to confirm the anti-inflammatory effect on the relationship between CR and AAA expansion.

Stabilization of BP Elevation During Exercise

By exercise training, both systolic and diastolic BP were lowered,[46] and BP elevation during exercise was stabilized.[47] The BP-lowering effects of CR can be explained by a reduction in total peripheral resistance[48] or improvement in autonomic function[49] following exercise training. Both our studies suggested that stabilization of changes in BP from rest to modified AT level after the CR program were correlated with the lower AAA expansion rate.[42,44] Although hypertension per se was not a risk factor for AAA expansion, daily BP fluctuations may contribute to the risk of AAA expansion and CR could limit this BP fluctuation.

Increased Aortic Blood Flow

Increased aortic blood flow is reported to attenuate AAA expansion via wall shear or strain-related reductions in oxidative stress.[50] Moderate exercise can increase aortic blood flow,[51] but it is unknown whether this increased blood flow could slow AAA expansion in humans.

Upregulation of TGF-β1

Activated TGF-β1 is well-reported in patients and in animal models of AAA. Several studies reported TGF-β1 activity as the cause of AAA formation, but downregulation of TGF-β induced AAA rupture in an angiotensin II-stimulated AAA model,[16] and TGF-β1 upregulation slowed AAA expansion.[17] TGF-β1 might be activated by inflammation or atherosclerosis, exerting a protective effect against AAA expansion. In our prospective study, TGF-β1 activation was higher in the CR group, but the change in TGF-β1 level was not related to AAA expansion rate.[44] There are few reports regarding TGF-β1 after exercise training in humans, and our prospective study first reported elevation in serum TGF-β1 after CR.[44] We expect that the activation of TGF-β1 might be a key mechanism for suppressed AAA expansion by CR. The role of activated TGF-β1 signaling after CR remains to be investigated, and more studies with larger populations are needed to clarify its protective role

in AAA expansion.

Lowering BMI and/or Body Fat

One of the causes of AAA formation is atherosclerosis. In that sense, a high BMI or excess fat were thought to be a trigger of AAA formation. A recent meta-analysis demonstrated a trend toward a positive, although not statistically significant, association between BMI and AAA formation.[52] In contrast, a meta-analysis on the association between BMI and AAA rupture demonstrated that a lower BMI was related to AAA rupture.[53] In our study, the changes in BMI or body fat mass during 6 months were not correlated with AAA expansion rate.[44] Therefore, we cannot regard BMI and body fat mass as target modification factors to protect against AAA expansion.

Improved Endothelial Function

Endothelial cells have been reported to play an important role in AAA expansion through increased oxidative stress.[54] A meta-analysis showed that physical exercise has beneficial effects on endothelial function, measured as flow-mediated dilation, which could regulate vascular tone and circulatory homeostasis.[55] Additional research is needed to understand the relationship between CR, endothelial function and AAA expansion.

Conclusions

Considering the hypotheses discussed here, stabilization of the elevation of BP during exercise plays an important role in protecting against rapid AAA expansion. Our goal is to regress the small AAA to avoid surgical repair, but medication for small AAA lacks sufficient evidence in humans. Anti-TNF-α and TGF-β1 activation are expected to be good candidates for treatment to protect against AAA expansion. Until a revolutionary drug has been developed that can regress AAA, CR remains the best therapeutic strategy for preventing AAA expansion and rupture (**Figure 6**).

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Disclosure

I.K. is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

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