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ORIGINAL ARTICLE

The potential of cardiac rehabilitation as a method of suppressing abdominal aortic aneurysm expansion: a pilot study

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Abstract

This study is a prospective evaluation of the effectiveness of cardiac rehabilitation (CR) in terms of clinical outcomes for small abdominal aortic aneurysms (AAA) that were previously reported in a retrospective cohort study. We conducted a prospective non-randomized trial on patients with small AAA ($N=40$; mean age 75.0 ± 6.6 years). Patients were enrolled into one of two groups, rehabilitation (CR) or non-rehabilitation (non-CR) group. Only CR group participated in a supervised-CR program including bicycle ergometer for 150 days. The AAA expansion rate and the risk of AAA repair were compared between two groups. We also researched the relationship between AAA expansion rate and body composition, blood IL-6 and TGFβ1 levels. The CR ($N=15$) and non-CR groups ($N=25$) were comparable in terms their baseline data. The CR group had a significantly smaller change in the maximal AAA size (-1.3 ± 2.4 mm/years) compared to the non-CR group (2.0 ± 3.6 mm/years) ($p<0.01$). The IL-6, and TGFβ1 levels were unrelated to the changes in AAA size. There was mild positive correlation between the change in systolic blood pressure from rest to exercise and the AAA expansion rate ($p=0.06$). The risk of AAA repair after 12 months was lower in the CR group compared to the non-CR group (0% vs. 28%, respectively). CR in patients with small AAA significantly suppressed AAA expansion and resulted in a lowered risk of AAA repair.
Clinical trial Trial name: The study of the profitability and protective effect of cardiac rehabilitation on abdominal aortic aneurysm. Number: UMIN000028237. UTL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R0000323.

Keywords Abdominal aortic aneurysm (AAA) · Rehabilitation · Prevention · Exercise

Introduction

The safety of aerobic exercise under the careful management of blood pressure (BP) for abdominal aortic aneurysms (AAA) is increasingly accepted globally. Recently, Nakayama et al. reported on the protective effect of cardiac rehabilitation (CR) on AAA enlargement [1]. According to the study, the long-term follow-up of patients with small AAA revealed that the expansion rate of AAA was extremely low in patients who had supervised exercise with lower level than anaerobic threshold (AT) level. A prospective study by Jonathan Myers et al. indicated that exercise may limit AAA growth rate, although a statistically significant difference in AAA size was not demonstrated [2]. Therefore, there is a need for further prospective studies to evaluate the protective role of exercise in patients with small AAA.

There are no reports that explore the precise mechanism by which CR may prevent AAA expansion. There are three possible mechanisms for preventing AAA expansion. First, exercise has an anti-inflammatory effect in AAA patients, as reported by several researchers [3–5]. This is attributable to its protective effect, which may be mediated both by a reduction in visceral fat mass and enhancement of immune function [6]. Second, the transforming growth factor (TGF) β1, a co-fibrotic cytokine that plays a key role in preventing AAA expansion [7, 8], may be upregulated by exercise. Third, exercise may stabilize blood pressure (BP). Hypertension is an established risk factor for the onset [9], expansion [10], and rupture [11] of AAA. BP fluctuations may be strongly related to AAA expansion owing to the physical pressure on

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the aortic wall, and when stabilized, may reduce the risk of AAA expansion. Previous retrospective study reported that the change in systolic blood pressure from rest to exercise at modified AT level was related to the AAA expansion rate, unlike the CRP level [1].

Here, we tested the hypothesis that CR prevents against the AAA expansion and postpones the standby time for AAA repair. The underling mechanism was analyzed by the change of body composition and serum cytokine levels.

Methods

Study population

All patients over the age of 45 y with small AAA (defined as the maximal diameter > 30 mm and < 50 mm) attending our hospital from August 2017 to November 2017 were considered for inclusion. Patients with Marfan syndrome, IgG4-related disease, saccular aneurysms, infectious aneurysms, traumatic aneurysms, inflammatory aneurysms, and congenital aneurysms were excluded. Patients who were planned for or underwent AAA repair and transferred to other hospitals were excluded. Of the remaining 61 out of the 356 eligible patients with small AAA, 44 were considered active enough to exercise by their attending doctors and consented to participate in this study. All participants were explained the merits and demerits of CR, and were allowed to choose between the CR and non-CR groups (Fig. 1). After starting cardiac rehabilitation, three patients dropped out of the program from the CR group and one patient from the non-CR group. Finally, there were 15 patients in the CR group and 25 in the non-CR group (Fig. 1). This study was approved by the ethics committee of the hospital (approval ID 10992). All data were collected in the computer of the CR room.

Outcomes

The major endpoints of this study were the changes in AAA size and AAA repair. In our institute, AAA repair was planned according to the 'Guidelines for Diagnosis and Treatment of Aortic Aneurysms and Aortic Dissections' [12]. According to this, repair was considered necessary for AAAs with maximum minor-axis diameter > 50 mm, expansion rate > 5 mm/6 months, or the presence of symptoms such as abdominal pain, lumbago, and back pain. The secondary endpoints were the changes in AAA size, body composition, and serum interleukin-6 (IL-6) and TGFβ1 levels as observed 6 months after registration in both groups. The changes in systolic blood pressure (SBP) from rest to exercise were also investigated in the CR group. The AAA size was finally followed up 12 months after registration in both groups.

Cardiac rehabilitation

A comprehensive CR program was performed in the course of cardiovascular treatment according to the 'Guidelines for Rehabilitation in Patients with Cardiovascular Disease' [13]. The CR group underwent a 150-day rehabilitation program, which was composed of educating life style modification, dietary counselling, reducing stress, and a supervised exercise program consisted of training on bicycle ergometer and low-intensity limb resistance training performed in the hospital at a modified AT level [1], 1–3 times a week. Specifically, after documenting vital signs, a warm-up routine was performed that included stretches for 10 min. The duration of continuous exercise on bicycle ergometer was about 30–40 min and vital signs were checked every 10 min by medical staff in the CR room. Strength exercises, anaerobic exercises, and blood flow moderation exercises were not incorporated into this program.

During the exercise program, patients were supervised by rehabilitation staff comprising of cardiologists, cardiac care nurses, physical therapists (PT), clinical psychologists, and registered dietitians. In view of the hazardous effect of blood pressure elevation during exercise in patients with AAA, the exercise program was not prescribed when the BP at rest was above 130/90 mmHg, and was discontinued if the BP during exercise exceeded 150/100 mmHg.

The measurement of body composition was performed using bio-electrical impedance analysis [14, 15] with 'Inbody270' (Inbody Inc, CA, USA) at 1 week, and at 6 months after registration to calculate total body fat, protein, and water. Serum levels of IL-6 and TGFβ1 were measured at registration and 6 months after. Abdominal echocardiography was performed 6 months and 12 months after registration by vascular surgeons to evaluate maximum minor-axis diameter of AAA as aneurysm size according to previous study [16]. The AAA expansion rate was calculated from the initial to 6 months after registration. The change in BP from rest to exercise was evaluated at 150 days after the introduction of CR to assess stabilization of BP in the CR group alone.

Statistical analyses

Statistical analyses were performed using IBM SPSS statistical software ver. 22 (SPSS, Inc., Chicago, IL, USA). Patient characteristics were compared by χ^2 test for non-continuous variables. After using Kolmogorov–Smirnov test to determine normality, unpaired t test was used to compare normally distributed continuous data and

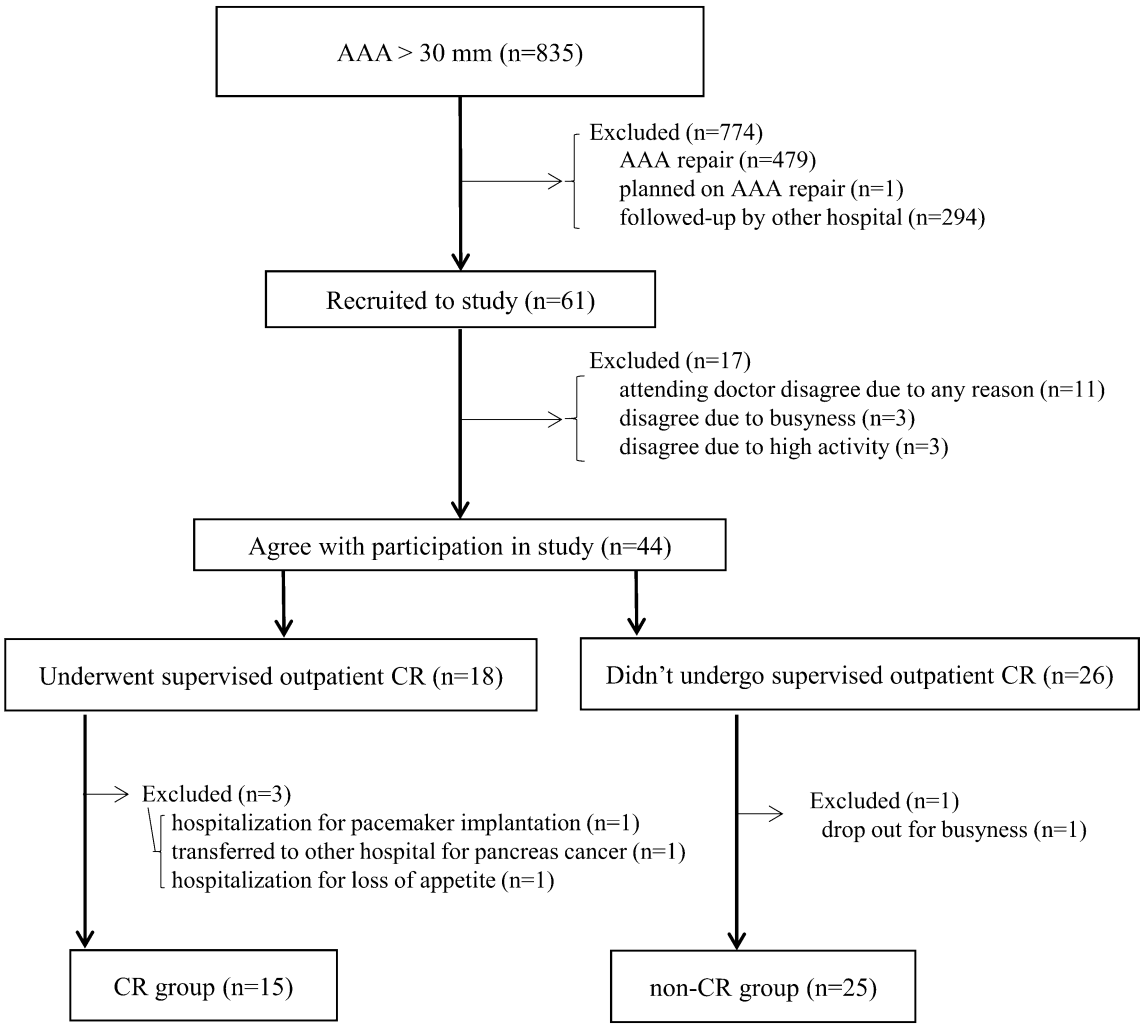

Fig. 1 Flowchart of patient enrollment and reasons for exclusion. Patients with small AAAs (maximal diameter > 30 mm and < 50 mm) were included. Of a total of 356 eligible patients, those who were considered for AAA repair, and those who were not followed-up in our hospital were excluded. Among the remaining 61 patients with small AAAs, 44 agreed to participate in the study. Finally, 15 patients were included in the cardiac rehabilitation (CR) group and 25 patients in the non-CR group

Wilcoxon test for data that were not normally distributed. To evaluate the change at 6-month follow-up, paired *t* tests for AAA size and biomarkers in both groups, or blood pressures in CR group were undergone. After the Kolmogorov–Smirnov Goodness of Fit Test, Pearson *r* correlation was used to measure the degree of relationship between linearly related variables in parametric tests. Spearman rank correlation was used to measure the degree of association between two variables in non-parametric tests.

Results

There was no difference in the baseline patient data between the two groups (Table 1). The initial size of AAA was similar in both groups (CR group 36 ± 6 mm; non-CR group 37 ± 6 mm; $p = 0.75$). Although the AAA diameters at 6 and 12 months were similar in both groups, the AAA expansion rate in the non-CR group was significantly greater compared to the CR group (CR group, − 1.3 ± 2.4 mm/years; non-CR group 2.0 ± 3.6 mm/years; $p < 0.01$) (Table 2). In the body composition tests, the changes in body weight, total body protein, total body fat, and total body water were similar in both groups. Also, the changes in CRP and IL-6 levels were similar in the two groups. As for the changes of the biomarkers between baseline and 6-month follow-up**,** after 6 months, the TGFβ1 levels elevated in CR group (initial 9 ± 11 ng/ml; after 6 months 25 ± 21 ng/ml; $p = 0.03$), otherwise the TGFβ1 levels did not change in non-CR group (initial 12 ± 12 ng/ml; after 6 months 21 ± 21 ng/ml; $p = 0.14$). The IL-6 levels were similar between before and after CR.

Table 1 Patient background

	CR ($n=15$)	Non-CR ($n=25$)	p
Age (years)	77.2 ± 3.5	74.1 ± 6.4	0.15
Male, *n* (%)	13 (87)	22 (88)	0.63
BMI (kg/m^2)	23.4 ± 3.5	22.5 ± 4.3	0.46
Hypertension, *n* (%)	11 (73)	12 (48)	0.11
Dyslipidemia, *n* (%)	5 (33)	11 (44)	0.37
Diabetes, *n* (%)	3 (20)	5 (20)	0.66
Current smoking, *n* (%)	2 (13)	1 (4)	0.31
Ex-smoking, *n* (%)	3 (20)	8 (32)	0.33
Hemodialysis, *n* (%)	2 (13)	0 (0)	0.14
Family history of AAA, *n* (%)	0 (0)	1 (4)	0.63
CAD[a], *n* (%)	8 (53)	9 (36)	0.23
CVD[a], *n* (%)	1 (7)	1 (4)	0.62
COPD[a], *n* (%)	1 (7)	1 (4)	0.62
PAD[a], *n* (%)	0 (0)	0 (0)	–
CKD, *n* (%)	5 (33)	4 (16)	0.20
Single antiplatelet drug, *n* (%)	3 (20)	3 (12)	0.49
Dual antiplatelet drugs, *n* (%)	4 (27)	3 (12)	0.24
β, αβ-Blocker, *n* (%)	6 (40)	4 (16)	0.10
ACE inhibitor/ARB, *n* (%)	5 (33)	12 (48)	0.28
Calcium channel blocker, *n* (%)	7 (47)	9 (36)	0.37
Statin, *n* (%)	7 (47)	7 (28)	0.92
Creatinine (mg/dl)[a]			
Initial	1.1 ± 0.5	0.9 ± 0.3	0.34
After 6 M	1.2 ± 0.6	0.9 ± 0.5	0.10
After 12 M	1.2 ± 0.8	0.8 ± 0.7	0.11
hsCRP (mg/dl)			
Initial	0.19 ± 0.27	0.30 ± 0.46	0.50
After 6 M	0.22 ± 0.29	0.28 ± 0.45	0.65
After 12 M	0.20 ± 0.27	0.28 ± 0.46	0.54
HbA1c (%)			
Initial	6.1 ± 1.1	6.2 ± 0.1	0.90
After 6 M	5.9 ± 0.7	6.2 ± 0.7	0.20
After 12 M	6.0 ± 0.6	6.2 ± 0.7	0.36
T-chol (mg/dl)			
Initial	185 ± 30	177 ± 17	0.55
After 6 M	168 ± 34	175 ± 19	0.41
After 12 M	168 ± 46	163 ± 23	0.65
LDL-chol (mg/dl)			
Initial	99 ± 22	100 ± 22	0.91
After 6 M	96 ± 22	79 ± 44	0.17
After 12 M	96 ± 23	91 ± 23	0.43
HDL-chol (mg/dl)			
Initial	57 ± 19	54 ± 22	0.80
After 6 M	56 ± 15	67 ± 18	0.05
After 12 M	59 ± 20	65 ± 9	0.20
TG (mg/dl)			
Initial	142 ± 106	170 ± 101	0.61
After 6 M	109 ± 34	91 ± 41	0.16
After 12 M	120 ± 50	107 ± 55	0.46

Table 1 (continued)

BMI body mass index, *CAD* coronary artery disease, *AAA* abdominal aortic aneurysm, *CVD* cerebrovascular disorder, *COPD* chronic obstructive pulmonary disease, *PAD* peripheral arterial disease, *CKD* chronic kidney disease, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *hsCRP* high-sensitivity C-reactive protein, *HBA1c* hemoglobin A1c, *T-chol* total cholesterol, *LDL-chol* low-density lipoprotein-cholesterol, *HDL-chol* high-density lipoprotein-cholesterol, *TG* triglyceride, *M* months

[a]The CAD, CVD, COPD, and PAD were detected by interview and medical record

The follow-up period was 12 months after registration in both groups. Figure 2 shows the changes in the AAA maximal diameter from initial to 1 year after registration. In the non-CR group, 7 patients were undergone AAA repair. None of the patients in the CR group were considered for AAA repair as they did not meet the size criterion. The analysis of the risk for AAA repair after 12 months clearly revealed the lower rate of AAA repair in the CR group ($n=0$ out of 15, 0%) compared to the non-CR group ($n=7$ out of 25, 28%).

By correlation analysis, the change in AAA size was positively related to initial AAA size, initial body mass index, and initial total body fat ($r=0.43$, $p<0.001$; $r=0.37$, $p=0.03$; $r=0.35$, $p=0.04$, respectively) (Fig. 3). There was no association among total body protein, total body water, hsCRP, IL-6, and TGFβ1 and AAA expansion. The change in body composition including ΔBody fat mass, ΔIL-6, and ΔTGFβ1 was not correlated with AAA expansion rate. In CR group, BP did not change between before and after CR program (Table 3), but the change in SBP during exercise indicated a mild relation to AAA expansion rate ($r=0.34$, $p=0.06$). There were no missing data in this study.

Discussion

This prospective study demonstrated the protective effect of CR on AAA expansion, and longer surgical wait times of patients in the CR group, compared to patients in the non-CR group.

The management of small AAA before surgery is described in the AHA/ACC, ESC, and the Japan Circulation Society (JCS) guidelines [12, 17, 18]. According to these guidelines, patients with AAA should avoid heavy weight lifting or competitive athletics involving isometric exercise as they may trigger aneurysmal rupture. On the other hand, aerobic exercise may effectively control blood pressure, cholesterol, and associated aortic wall stress in patients with small AAA. Several studies established the safety of CR in AAA patients [19, 20], and identified a protective effect of CR on AAA expansion [1].

Our study is the first prospective study to demonstrate that CR protects against AAA expansion. The initial AAA

Table 2 The AAA diameter, AAA expansion rate, inflammatory cytokines, and body composition

		CR (n=15)	non-CR (n=25)	P
AAA diameter (mm)	initial	36 ± 6	37 ± 6	0.75
	after 6M	35 ± 6	38 ± 7 *	0.33
	after 12M	36 ± 6	39 ± 8	0.21
ΔAAA diameter (mm)	from initial to 6M	-0.6 ± 1.2	1.0 ± 1.8	<0.01
Expansion rate (mm/yr)	from initial to 6M	-1.3 ± 2.4	2.0 ± 3.6	<0.01
hs CRP (mg/dl)	initial	0.19 ± 0.27	0.30 ± 0.46	0.50
	after 6M	0.22 ± 0.29	0.28 ± 0.45	0.68
Δhs CRP	from initial to 6M	0.03 ± 0.15	-0.02 ± 0.15	0.42
IL-6 (pg/ml)	initial	3.9 ± 2.7	4.2 ± 3.1	0.74
	after 6M	4.3 ± 3.7	4.4 ± 5.5	0.93
ΔIL-6	from initial to 6M	-0.2 ± 1.4	-0.4 ± 1.7	0.76
TGFβ1 (ng/ml)	initial	9 ± 11 *	12 ± 12	0.46
	after 6M	25 ± 21	21 ± 21	0.59
ΔTGFβ1	from initial to 6M	14 ± 21	7 ± 23	0.39
Weight (kg)	initial	61 ± 11	64 ± 12	0.46
	after 6M	61 ± 11	63 ± 12	0.53
ΔWeight	from initial to 6M	0.2 ± 1.4	-0.2 ± 1.9	0.50
Protein (kg)	initial	8.7 ± 1.3	9.1 ± 1.8	0.46
	after 6M	8.8 ± 1.3	9.1 ± 1.7	0.51
ΔProtein	from initial to 6M	0.04 ± 0.30	-0.01 ± 0.42	0.71
Body Fat Mass (kg)	initial	16 ± 6	17 ± 6	0.65
	after 6M	16 ± 6	17 ± 6	0.71
ΔBody Fat Mass	from initial to 6M	-0.1 ± 1.4	-0.2 ± 2.3	0.84
Body water (kg)	initial	34 ± 7	33 ± 5	0.51
	after 6M	34 ± 6	34 ± 5	0.56
ΔBody water	from initial to 6M	0.0 ± 1.6	0.2 ± 1.0	0.69

The AAA diameters at initial and 6 (6 M) and 12 months (12 M) after registration were compared between the Reha group and the non-Reha group. Expansion rate was calculated as the change of AAA diameter per year (mm/year). *The change was significant ($p < 0.05$) between initial level and the level after 6 months by paired *t* test

size, BMI, and total body fat were related to AAA expansion rate. The association between BMI or fat and AAA growth has been well discussed [21]. A recent meta-analysis demonstrated a trend toward a positive, though statistically non-significant, association between BMI and the presence of AAA [22]. Otherwise, the RESCAN meta-analysis [23] demonstrated a negative association between BMI and AAA rupture, but their study included only 80 AAA ruptures in only five studies. Takagi et al. concluded that BMI is not associated with AAA growth by meta-analysis. As those researchers mentioned, the evidence had been very limited and the mechanism of AAA growth influenced by fat is still unclear. In our study, the AAA expansion rate was related to the change of BMI or body fat; therefore, we recognized BMI and total body fat as risks for AAA expansion. But we could not regard them as target modification factors to protect against AAA expansion, because the ΔBMI or ΔBody fat mass was not correlated with AAA expansion.

The inflammatory activity on aortic wall is thought to accelerate AAA formation [24]. The atherosclerosis-driven changes in the aortic wall underlie AAA pathology, and inflammatory mechanisms contribute the aortic wall weakening. Anti-inflammatory therapy, which is the treatment with an anti-IL-1β, was reported to prevent the AAA formation using AAA mice model [25]. Therefore, our first hypothesis of protective mechanism against aortic wall expansion was the CR-induced anti-inflammation theory [26]. However, contrary to our expectations, AAA expansion did not correlate with changes in body protein, body fat, body water, inflammatory biomarkers, and co-fibrotic cytokines. BP-restricted exercise in AAA patients may not result in a statistically significant increase in body protein or reduction in body fat. Further, these mild changes also may not stimulate an anti-inflammatory effect on AAAs. Although an experimental model of AAA demonstrated that TGFβ1 upregulation inhibited aneurysm progression [27], the role of TGFβ1 signaling in AAA is controversial [28, 29]. In our study, although TGFβ1 level was elevated in the CR group, this change did not relate to the AAA expansion rate. However, the increase of TGFβ1 in

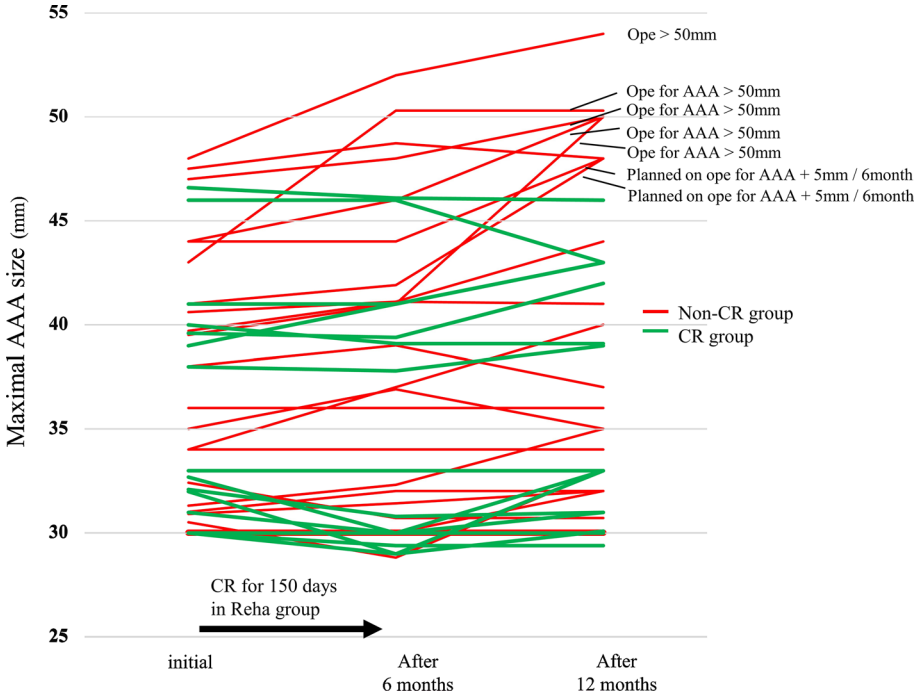

Fig. 2 Changes in maximal AAA size. Patients in the CR group are represented by green lines and those in the non-CR group by red lines. The reason for AAA repair is based on the criterion of diameter and expansion rate

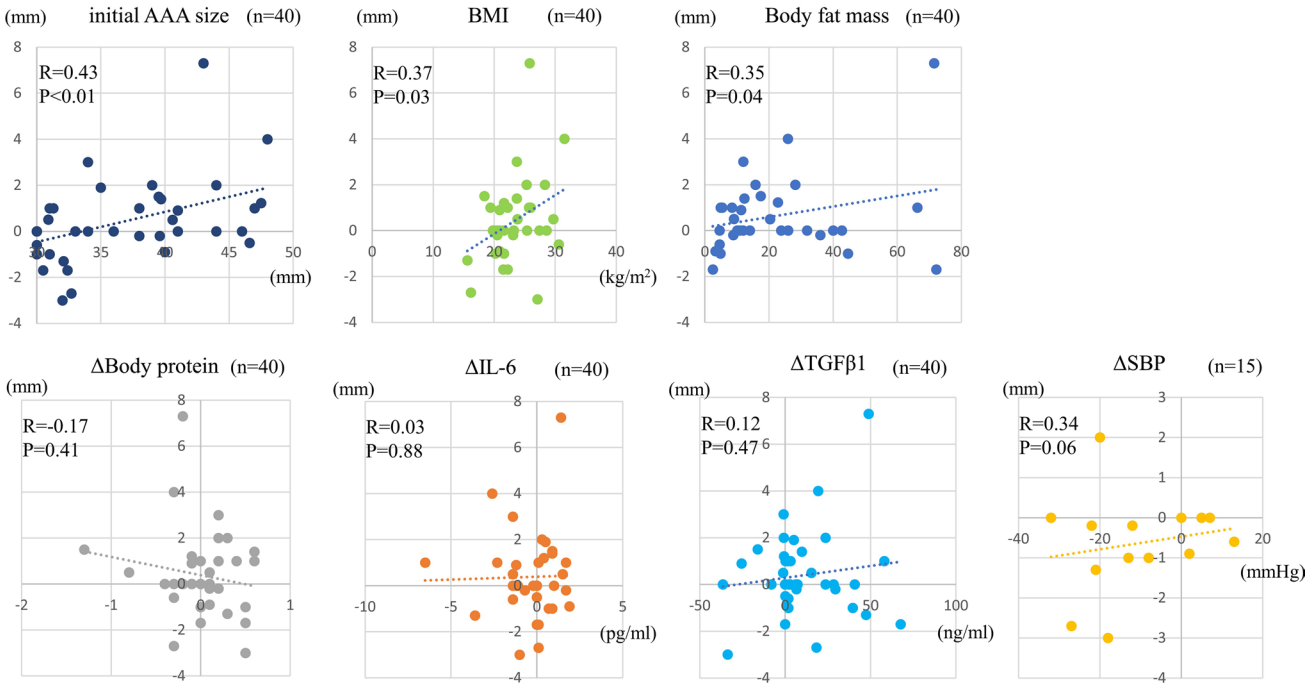

Fig. 3 Association between biomarkers and change in AAA size. After the CR program, the AAA expansion rate tended towards correlation with the change in SBP during exercise. *AAA* abdominal aortic aneurysm, *SBP* systolic blood pressure, *CR* cardiac rehabilitation, *BMI* body mass index, *IL-6* interleukin-6, *TGFβ1* transforming growth factor β1

CR group might have some contributions to the protective effect of AAA expansion, because the biomarkers, hsCRP, IL-6, and TGFβ1 in serum may reflect the circulating cytokines in the systemic circulation, and they may not be well representative of focal inflammation in the AAA. Therefore, the AAA is difficult to be detected by circulating biomarkers, and evaluation of focal inflammatory change may be needed [30].

Table 3 The change of blood pressure at exercise in CR group

CR group ($n=15$)	Initial	After 6 months	p for paired t
Rest SBP (mmHg)	133 ± 26	130 ± 24	0.47
SBP at exercise (mmHg)	122 ± 24	119 ± 14	0.51
ΔSBP from rest to exercise (mmHg)	− 11 ± 22	− 10 ± 18	0.99
Rest DBP (mmHg)	71 ± 18	70 ± 11	0.81
DBP at exercise (mmHg)	68 ± 13	68 ± 12	0.93
ΔDBP from rest to exercise (mmHg)	− 3 ± 14	− 2 ± 11	0.77

The AAA diameters at initial and 6 M after registration were compared between the Reha group and the non-Reha group

SBP systolic blood pressure, *DBP* diastolic blood pressure

The change of SBP from rest to exercise at exercise tended towards an association with AAA expansion in our study. As mentioned previously [1], exercise training results in lowering BP [20, 31] and stabilizes BP elevation during exercise [32]. The BP lowering effect can be explained by the reduction in total peripheral resistance [33] or improvement in autonomic function [34] following exercise training. We must argue more about BP fluctuation of small AAA patients to prevent the AAA expansion. Although the direct effect of exercise was not obvious in this study, the effects of comprehensive CR, including life style modification, dietary counselling, and mental stability in patients with small AAA, may have contributed towards preventing AAA expansion. Participating in CR may have helped patients with AAA learn to effectively control their BP. Our study supports the recommendation that patients with small AAA should participate in supervised CR and improve their lifestyle to prevent AAA expansion.

Additionally, endothelial cells were said to play an important role on AAA expansion due to increased oxidative stress [35]. Meta-analysis showed physical exercise exerts beneficial effects on endothelial function by measuring the flow-mediated dilation (FMD) which is a physiologically important stimulus regulating vascular tone and homeostasis of the circulation [36]. Though we could not research FMD in this study, exercise might suppress AAA expansion by improved endothelial function.

A few patients in CR group had a slight regression of AAA in our study. Myers et al. also showed the cases of decreased AAA size after exercise program [2]. Furthermore, a successful endovascular stent grafting led the shrinkage of AAA diameter in some patients [37], and Yoshimura et al. showed the potential of AAA regression therapy using c-Jun N-terminal kinase inhibitor by AAA mice model [38]. Considering those reports, the regression therapy of AAA may not be impossible in the future.

Limitations

The small sample size of our study is a large limitation in confirming our findings. A large population trial is warrant to conclude the underling mechanism of protective effect on AAA of CR.

Because patient with rapid AAA expansion was planned surgery repair and excluded from this study, we believe the AAA expansion rate before registration was not high. Owing to the risk of exercise in patients with AAA, and the ethical concerns therein, we excluded patients with AAA diameter > 50 mm. For the same reasons, we also avoided a randomized control trial. Therefore, patients who participated in CR group might be motivated to improve their disease compared to patients in non-CR group. However, the similarity in the background characteristics of the two groups may strengthen the value of our observations regarding the utility of CR. Most patients lived in Tokyo and had easy access to medical service of our hospital. No patient in non-CR group had exercise habits in this study.

Conclusion

A modified cardiac rehabilitation program was found to be safe in patients with small AAA. It protected patients against AAA expansion and delayed the need for AAA repair.

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Compliance with ethical standards

Conflict of interest There are no financial disclosures.

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