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Effects of acute exercise on endothelial function in abdominal aortic aneurysm patients.

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EFFECTS OF ACUTE EXERCISE ON ENDOTHELIAL FUNCTION IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

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SHORT TITLE: Exercise and endothelial function in AAA

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ABSTRACT

Endothelial dysfunction is observed in patients with abdominal aortic aneurysm (AAA), who have increased risk of cardiovascular events and mortality. This study aimed to assess the acute effects of moderate and higher-intensity exercise on endothelial function, as assessed by flow-mediated-dilation (FMD), in AAA patients (n=22; 74±6 y) and healthy adults (n=22; 72±5y). Participants undertook three randomised visits, including moderate-intensity continuous exercise (40% peak power output, PPO), higher-intensity interval exercise (70% PPO), and a no-exercise control. Brachial artery FMD was assessed at baseline, 10- and 60-min after each condition. Baseline FMD was lower in AAA patients compared to healthy adults [by 1.10%, (95% CI, 0.72 to 1.81), P=0.044]. There were no group differences in the FMD responses after each condition (P=0.397). FMD did not change after the control condition, but increased by 1.21% (95% CI, 0.69 to 1.73, P<0.001) 10 min after moderate-intensity continuous exercise in both groups, and returned to baseline levels after 60-min. Conversely, FMD decreased by 0.93% (95% CI, 0.41 to 1.44, P<0.001) 10-min after higher-intensity interval exercise in both groups, and remained decreased after 60 min. This study found that the acute response of endothelial function to exercise is intensity-dependent and similar between AAA patients and healthy adults. This provides evidence that regular exercise may improve vascular function in AAA, as it does in healthy adults. Improved FMD following moderate-intensity exercise may provide short-term benefit. Whether the decrease in FMD following higher-intensity exercise represents additional risk and/or a greater stimulus for vascular adaptation remains to be elucidated.

NEW AND NOTEWORTHY

Abdominal aortic aneurysm (AAA) patients have vascular dysfunction. We observed a short-term increase in vascular function after moderate-intensity exercise. Conversely, higher-intensity exercise induced a prolonged reduction in vascular function which may be associated with both short-term increases in cardiovascular risk, and signalling for longer term vascular adaptation in AAA patients.

KEY WORDS

Abdominal aortic aneurysm; exercise; endothelial function; flow-mediated dilation; cardiovascular risk

INTRODUCTION

Abdominal aortic aneurysm (AAA) is characterized by the abnormal progressive dilatation of the abdominal aorta, and is usually diagnosed when maximum abdominal aortic diameter is ≥30 mm (106). Screening studies suggest 1-4% of men and 0.5-1% of women aged over 60 years have an AAA (19, 79). AAA is responsible for ~2% of all deaths (30, 65, 83) and these patients are at high risk of cardiovascular events, such as myocardial infarction and stroke, and mortality compared to age-matched healthy adults (13, 14, 66). These patients also have a risk of aortic rupture due to the weakening of the aortic wall at the site of the aneurysm (25, 63). Currently the only treatment for the weakened aorta is surgical repair, however there is no treatment-related survival benefit in patients with small AAA (<55mm) (27). Screening reduces AAA-related mortality by 50%, yet has no impact on all-cause mortality (29, 105). With AAA there is an increased prevalence of cardiovascular comorbidities, including ischemic heart disease (~45%), myocardial infarction (~27%) and stroke (~14%) (13, 14), and the risk of cardiovascular mortality increases by 3% each year after diagnosis of small AAA (13). Patients with small AAAs are monitored by regular imaging, but up to 70% progress to a diameter ≥55mm necessitating surgical repair (63), with the associated perioperative mortality and morbidity risk (52, 89), and cost. Novel therapies are needed which reduce both the risk of cardiovascular events and the progression of aortic weakening in AAA patients.

Alterations in the connective tissue of the aortic wall, including an imbalance between diminished elastin concentration and collagen proteolysis, is the hallmark of AAA disease. AAA pathogenesis is not well understood, however endothelial dysfunction is suggested to contribute to AAA development via increased oxidative stress, inflammation and impaired NO bioavailability [see recent detailed review (87)]. Thus, treatment that targets endothelial

dysfunction may benefit patients with AAA. Systemic vascular endothelial dysfunction is observed in patients with AAA and has been implicated in AAA growth. For example, reduced bioavailability and sensitivity to nitric-oxide (NO) has been reported in experimental and human AAA (53, 107). Endothelial function, as assessed by flow-mediated dilation (FMD), has been reported to be reduced in patients with AAA compared to healthy adults which is, in part, NO-mediated (35, 58, 112). Importantly, brachial artery FMD is associated with AAA size, future aneurysm growth, and is improved following surgical repair of AAA (58, 61, 93). FMD is also strongly associated with the general risk of cardiovascular-related events and mortality in healthy individuals and those with cardiovascular disease (37, 59). Thus, improving endothelial function could be a valuable treatment target for reducing cardiovascular risk, and possibly limiting aneurysm growth, in patients with AAA.

Brachial FMD improves after regular exercise in patients with known cardiovascular disease and established endothelial dysfunction, including in individuals with coronary and peripheral artery disease (21, 70, 108), suggesting that exercise might be a possible treatment option to reverse endothelial dysfunction in patients with AAA. Vascular improvements with exercise training depend somewhat on the intensity of exercise (76, 84). An important contribution to the beneficial effect of exercise on arterial remodelling has been attributed to the repetitive, acute increases in blood flow and shear stress observed during a single-bout of exercise (36), which have also been suggested to be beneficial for preventing AAA growth at the site of the aorta (3). In healthy adults, endothelial function is reported to increase after low and moderate-intensity exercise, but decrease after higher-intensity exercise (10, 15, 24, 49). The effect of exercise on FMD in individuals with underlying endothelial dysfunction may be augmented (22) compared

to healthy adults (51). However, the effect of exercise intensity on endothelial function in patients with established cardiovascular disease is less clear, with transient increases (23) and decreases (51, 60, 88, 104) in FMD reported after both moderate and higher-intensity exercise. Whether increased exercise intensity has a negative influence at the site of the aneurysm is unclear. However, aortic wall shear stress has been reported to increase during mild and moderate-intensity exercise. and decreases aortic flow stasis associated with aneurysm progression in patients with AAA (91).

To date, exercise therapy in patients with AAA has been prescribed using a relatively low- to moderate-intensity continuous exercise (11, 12, 55, 64, 95, 110). Higher-intensity interval exercise enables a greater volume of exercise to be achieved with shorter bouts, and may have additional cardiovascular benefits in clinical groups, including increases in endothelial function, compared to moderate-intensity continuous exercise (76). Higher-intensity interval exercise has been suggested as an alternative method of training for patients with AAA, but has not been thoroughly investigated (109). A better understanding of the acute effect of different exercise intensities on endothelial function in patients with AAA could provide insight in to the potential role of exercise training in reducing cardiovascular risk and for limiting AAA growth in these individuals. We therefore aimed to determine the effect of a single-bout of moderate- and higher-intensity cycling exercise on FMD in patients with AAA and healthy older adults. We hypothesized that exercise intensity would alter the post-exercise FMD response in both groups, and that the overall FMD response to exercise would be augmented in patients with AAA compared to healthy older adults

METHODS

Participants

All study participants (patients with AAA and healthy adults) were included if they were 60-86 years old, able to exercise and did not have medically untreated, or uncontrolled hypertension (defined as an average SBP ≥140 mmHg and/or an average DBP ≥90 mmHg). For all participants, the exclusion criteria included a BMI over 39, reversible or inducible myocardial ischemia during exercise stress testing for which a cardiologist judged they were not suitable for exercise or diagnosed uncontrolled cardiac arrhythmia with recurrent episodes or symptoms on exertion. Further exclusion included documented medical history of the following; chronic heart failure, severe aortic stenosis, ankylosing spondylitis or chronic obstructive pulmonary disease. Participants with documented peripheral neuropathy, venous insufficiency or any concomitant vascular disease (e.g. Raynaud's or vasculitis) were also excluded prior to study entry. Additional to the above study exclusion criteria, healthy control participants were excluded if they had a family history of AAA or known aneurysmal disease.

Twenty-two males with small AAA (30-45 mm maximal diameter) were recruited from public and private vascular units on the Sunshine Coast, Australia. All patients were under current clinical surveillance and AAA size was confirmed with ultrasound by a trained vascular sonographer at study entry. Twenty-two healthy males were recruited as control participants through local advertisement and from a University of the Sunshine Coast Alumni group. During the study, participants continued to take all prescribed medication. All participants provided written informed consent. The study conformed to the Declaration of Helsinki and was approved

by the human research ethics committees of the Prince Charles Hospital, Brisbane (HREC/12/QPCH/13), and the University of the Sunshine Coast.

Research Design

This was a cross-sectional, randomized cross-over study. AAA and healthy participants underwent four visits on separate days to the clinical exercise physiology laboratory at the University of the Sunshine Coast. Participants refrained from alcohol and exercise for 24h and caffeine for 12h before each visit (97). Visit 1 consisted of measurement of height, body mass, and estimation of body composition using bio-impedance scales (BC 545N, Tanita, Australia). Participants then underwent a maximal incremental cycling test for the determination of VO_{2peak} and peak power output (PPO). Experimental visits (2-4) were conducted in a randomised, counter-balanced order and consisted of two separate acute cycling exercise conditions (moderate-intensity continuous vs. higher-intensity intervals) or a no-exercise control condition (Figure 1). Blood pressure and brachial artery FMD were assessed following 20 min of supine rest at baseline, 10-min and 60-min into recovery after exercise or control conditions. Each experimental visit followed an overnight fast with a standardised breakfast (oat biscuits) 3 hours prior. To control for diurnal variation in blood pressure and vascular function each visit was performed at the same time of day (50). Visits were >3 days apart to ensure recovery between them. All visits were conducted in a mean laboratory temperature of 23 ± 0.9 °C.

Maximal incremental cycling test for determination of cardiorespiratory fitness

After pre-exercise measures, the test commenced with a 3-min warm up at 0W on a cycle ergometer (Lode Corival, Groningen, Netherlands). Intensity then increased to 20W for 1 min,

and by a further 10 W/min until volitional cessation. Participants were required to self-select and maintain a pedal cadence between 60 and 90 RPM throughout the test. Expired gases were continuously collected (Parvo Medics, UT, USA) for the determination of oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$), and the respiratory exchange ratio (RER: $\dot{V}CO_2/\dot{V}O_2$), which were averaged every 15 s. Heart rate was measured continuously using 12-lead ECG (Mortara Inc., WI, USA) and was recorded alongside ratings of perceived effort (RPE) in the final 10 s of each stage. VO_{2peak} was determined as the highest 15s average during the final 60 s of peak exercise. Peak power output (PPO) was used to establish cycling intensity during the subsequent experimental visits.

Experimental exercise and control conditions (visits 2-4)

The experimental protocol is summarised in Figure 1. Following pre-exercise measurements of blood pressure and FMD, participants undertook 27 mins of either: 1) moderate-intensity continuous cycling, 2) higher-intensity interval cycling, or 3) seated-rest as a no-exercise control. Both exercise conditions commenced with a 3-min warm-up at 0W, followed by 24 mins of i) moderate-intensity continuous cycling exercise at 40% PPO, or ii) higher-intensity interval cycling exercise incorporating 12 x 60 s bouts at 70% PPO, each separated by 60 s at 10% PPO. The moderate-intensity continuous and higher-intensity interval cycling exercise conditions were matched for total duration and work, for each individual. Heart rate (12-lead ECG) and rating of perceived exertion (RPE) (18) were recorded at 60 s intervals throughout each condition. Blood pressure was monitored and recorded every 6-min using a manual sphygmomanometer. During higher-intensity interval exercise, this was performed during the 60s of the high-intensity

intervals. Immediately following each exercise/control condition, participants returned to the supine position for measurement of blood pressure and FMD at 10 and 60 min post.

Measurement of brachial artery FMD

Brachial blood pressure was obtained from the right arm, ≥5 min prior to each brachial artery FMD measurement, and all FMD measurements were performed in line with recent technical recommendations (17, 39, 97). FMD was performed with participants in the supine position, on the right arm with the cuff placed distal to the olecranon process. A 12-MHz multi-frequency linear array probe, attached to a high-resolution duplex ultrasound machine (T3000; Terason, Burlington, MA), was used to image the brachial artery in the distal third of the upper arm to simultaneously record the longitudinal B-mode image and Doppler blood velocity trace. The Doppler angle of insonation was maintained at 60º. Images were optimised, and the settings (depth, focus position and gain) were maintained between FMD assessments within each test visit, as was the location of the probe which was marked on the skin using sweat-resistant ink. Following a 60-s recording period of diameter and velocity, the cuff was rapidly inflated (220 mmHg) and maintained for 5 mins (D.E. Hokanson, Bellevue, WA). Diameter and velocity recordings resumed 30s prior to rapid cuff deflation (<2s) and continued for 3 mins thereafter.

Analysis of brachial artery diameter was performed using custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias. Recent papers contain detailed descriptions of the analysis approach (17, 97). FMD was calculated as [(peak diameter-baseline diameter) / baseline diameter] and expressed as a percent change in vessel diameter. From synchronised diameter and velocity data, blood flow (the product of lumen cross- sectional

area and Doppler velocity) was calculated at 30 Hz. Shear rate was calculated as 4 times mean blood velocity/vessel diameter (expressed as s^{-1}). The coefficient of variation (CV) for baseline FMD% across the three visits in this study was 12.1±2.7 %, which is similar to those previously reported (10.1-14.7%) (101, 111). Using FMD data from our control condition (baseline and 10 min post control) we established that the within-day CV for FMD% was 9.50±4.37 %.

Statistical analysis

Continuous data were normally distributed as assessed by Shapiro-Wilks test. A students t-test was used to assess differences in baseline continuous data between patients with AAA and healthy adults. Pearson's Chi Squared test was used to assess differences in categorical data between patients with AAA and healthy adults. A three-way (group*condition*time) linear mixed model (LMM) analysis was used to analyse changes in FMD parameters [brachial diameter, peak diameter and FMD (mm), FMD (%), time to peak, shear rate area-under-the-curve (SRauc), blood flow,] and blood pressure between the two groups (AAA and healthy), across "time" (baseline, 10- and 60-min post) during each condition (control, moderate- and higher-intensity exercise). This LMM analysis allows for random factor subjects and fixed factors of group, condition and time. Absolute FMD (mm) was analysed using a LMM analysis. In line with recent recommendations (9), and to account for the influence of baseline artery diameter on FMD% (5, 7, 8) FMD% was assessed using allometric scaling of logarithmically transformed absolute diameter change (difference between peak artery diameter and baseline diameter in mm). Logarithmically transformed baseline diameter and shear rate were also included as covariates specific to each FMD% test. For each group, condition and time-point, the logged absolute diameter changes were back-transformed and interpreted in the conventional

manner to obtain allometrically scaled FMD (percent diameter change) for comparative purposes in line with recent recommendations (4, 10, 86, 102). All other FMD parameters were not logged for LMM analysis.

To further explore the magnitude and direction of change in FMD% following exercise and control, we used a three-way (group*condition*time) LMM to analyse delta changes from baseline in FMD% (again, with baseline diameter and shear rate specific to each time-point included as covariates). Based on our previous study in healthy older adults (10), we aimed to detect a minimum absolute difference of 1.5% FMD (representing the difference between the change in FMD after moderate and higher-intensity exercise). We required 19 participants per group to detect this difference within and between each group, assuming a 3% standard deviation of the change, and an alpha level of 0.05with a statistical power of 80% (10).

Three-way LMM analysis was also used to detect any differences in heart rate, blood pressure and perceived exertion in response to the acute protocols between the two groups (AAA and healthy adults), across time (at 2 and 6 min intervals for HR/RPE and BP, respectively) during each protocol (control, moderate- and high-intensity exercise). Statistically significant interactions were further investigated with multiple comparisons using the least significant difference approach (71, 82). The strength of the association between AAA diameter, VO_{2peak} and FMD% were assessed using Pearson correlation coefficient. Analyses were conducted using the Statistical Package for Social Sciences (Version 22; IBM SPSS Inc., Chicago, IL). Statistical significance was defined at $P<0.05$ and exact P values are cited (P values of "0.000" are reported as "<0.001"). Data are presented in the text as mean (95% confidence interval, 95%CI) unless otherwise stated.

Results

Participant characteristics

Participant characteristics are presented in Table 1. Mean age was similar in AAA and healthy adults (P=0.200). Mean resting blood pressure was similar in patients with AAA and healthy adults. Cardiorespiratory fitness, measured as VO_{2peak}, was significantly lower in patients with AAA compared to healthy adults [mean difference 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (3.4 to 7.3), P<0.001]. Heart rate at peak exercise during the cardiorespiratory fitness test was significantly lower in patients with AAA compared to healthy adults [mean difference of 22 bpm (1 to 31), P<0.001].

Heart rate, blood pressure and perceived exertion during experimental conditions

There were no significant differences between patients with AAA and healthy adults in heart rate, blood pressure and RPE throughout each condition (P>0.05). Heart rate responses during exercise were normalised for the peak heart rate obtained during the cardiorespiratory fitness test in visit 1. Across both groups (P=0.213), heart rate was highest during higher-intensity interval exercise [mean 68 $\%HR_{peak}$ (64 to 71 %)] compared to moderate-intensity continuous exercise [mean 62 $\%HR_{peak}$ (59 to 64%, P<0.01)], and lowest during control [mean 42 $\%HR_{peak}$ (95% CI, 39 to 44), P<0.01]. The increase in mean arterial pressure during higher-intensity interval exercise [mean change of 14 mmHg (12 to 17)] was similar during moderate-intensity continuous exercise [mean change of 14 mmHg (11 to 16), P=0.720], whilst increases in mean arterial pressure responses during both exercise conditions were higher compared to control [mean change 10 mmHg (8 to 13), P<0.05]. RPE was higher during higher-intensity interval

exercise [mean RPE 4 AU (3 to 4)] compared to during moderate-intensity continuous exercise [mean RPE 3 AU (2 to 3, P <0.001)].

Effect of exercise on endothelial function

Baseline brachial FMD

Brachial FMD was 1.10% (0.72 to 1.81; P=0.044) lower in patients with AAA compared to healthy adults. No differences in baseline brachial artery diameter were observed between groups (P=0.604). SR_{AUC} after cuff deflation was higher in healthy adults compared to patients with AAA [mean difference of 5.7 $10^3 \cdot s^{-1}$ (95% CI, 2.4 to 9.1), P=0.001]. Time to peak diameter was longer in patients with AAA compared to healthy adults [mean difference 14 s (95% CI, 1 to 27), P=0.044]. Baseline FMD and VO_{2peak} were moderately correlated in the combined group of participants (r=0.655, P = 0.006; Figure 2). In patients with AAA, there was a modest, but non-significant inverse correlation between maximum AAA diameter and VO_{2peak} (r=-0.356, P=0.103). There was no significant correlation between maximum AAA diameter and baseline FMD (r=-0.041, P=0.429).

FMD responses after exercise and control conditions

Baseline and recovery (10 and 60 min post) brachial FMD% and associated variables are shown in Table 2. The (delta) changes in FMD% from baseline to recovery (10- and 60-min post condition) are shown in Figure 3.

Brachial FMD increased after moderate-intensity continuous exercise, but decreased after higher-intensity interval exercise in both patients with AAA and healthy adults (Figure 3, Table

2). Overall, there were no differences in the magnitude of the FMD response over time between patients with AAA and the healthy older adults (P=0.154). FMD tended to decrease from baseline after control [at 60-min by 0.43 % (95% CI, -1.10 to 0.96, P=0.115)], but this was not significant. FMD increased from baseline by 1.21% (0.69 to 1.73), P<0.001) at 10-min after moderate-intensity continuous exercise, which then returned to near baseline FMD at 60-min. Conversely, FMD decreased from baseline at 10- and 60-min after higher-intensity interval exercise, by 0.93% (0.41 to 1.44, P<0.001), and 0.51% (0.01 to 1.02, P=0.040)], respectively. Thus, the FMD 10-min after the cessation of exercise was significantly higher after moderate-intensity continuous exercise compared with after control (mean difference in FMD of 1.21 % (95% CI, 0.63 to 1.75, p<0.001) and higher-intensity interval exercise (mean difference of 1.87 % (95% CI, 1.36 to 2.39). At 60-min after exercise, FMD was significantly lower after higher-intensity interval compared to moderate-intensity continuous exercise (mean difference of 0.60 % [95% CI, 0.06 to 1.13], P=0.028). The different responses of FMD% between moderate-intensity continuous and higher-intensity interval exercise were also observed for absolute FMD (mm) (P=0.024; Table 2).

To account for differences in FMD% at baseline between AAA and healthy adults, we calculated the delta change in FMD% after exercise and control (Figure 3). Outcomes of this analysis were consistent with the analysis based on absolute FMD% in Table 2, and we found an intensity*time interaction on delta FMD% (p=0.033), but no differences between groups in the delta FMD % responses after each condition (p=0.522).

Blood flow and shear rate responses after exercise and control

Brachial blood flow and shear rate responses are displayed in Table 2. Resting blood flow was significantly elevated 10 min following both exercise conditions compared to control ($P<0.01$), and was greater following higher-intensity compared with moderate-intensity exercise [mean difference of 0.38 $mL.s^{-1}$ (95% CI, -0.08 to 0.68), $P=0.014$] (Table 2). Overall, shear rate was higher in healthy older adults compared to patients with AAA (mean difference of 4.78 s^{-1} (95% CI, 2.21 to 7.35), $P=0.002$), but was similarly altered by exercise in AAA and healthy adults ($P=0.760$). Shear rate was elevated 10 min after both exercise protocols compared with control (Table 2, $P=0.005$), and was similar after higher-intensity interval compared to moderate-intensity continuous exercise [mean difference of 1.14 10^3 s^{-1} (95% CI, -1.22 to 3.16), $P=0.342$].

Heart rate and blood pressure responses after exercise

There was a condition*time interaction for HR, SBP and MAP ($P<0.001$, see Table 2) where the mean changes in HR (increase), SBP and MAP (decrease) were larger after exercise compared to those observed after control. Moreover, no group differences were observed for the HR ($P=0.885$) and blood pressure ($P=0.553$) responses following each condition. Overall, MAP decreased by 3 mmHg (95% CI, 1 to 5, $P<0.004$) and 4 mmHg (95% CI, 2 to 6, $P<0.001$) 60-min after moderate- and high-intensity exercise, respectively, compared to control.

Discussion

To our knowledge, this is the first study to assess the response of endothelial function during early recovery from different exercise intensities in patients with AAA. The main finding of this study was that the response of FMD to a single bout of cycling exercise was similar in patients with AAA compared to healthy adults of the same age and sex. For both groups, we observed an

immediate increase in FMD following moderate-intensity continuous exercise, which returned to near-baseline levels after one hour of recovery. In contrast, FMD decreased immediately following higher-intensity interval exercise and remained decreased after one hour in both groups.

Basal FMD in patients with AAA

In this study, we observed reduced basal FMD in patients with AAA compared to healthy adults, which is consistent with previous reports (61, 94). Previous studies assessing FMD in AAA fail to report cardiorespiratory fitness levels, which may also contribute to differences in FMD%. Poor fitness has previously been shown to be associated with impaired FMD (62), and we observed a significant relationship between resting FMD and VO_{2peak} in this study.

Impaired FMD is independently associated with an increased risk of cardiovascular events and mortality (37, 48, 54, 92), and may contribute to the high burden of cardiovascular disease and the observation that ~70% of cardiovascular events and mortality in patients that have small AAAs is independent of aneurysm-related complications (57, 66, 72). As expected, there was a higher prevalence of comorbidities amongst the patients with AAA compared to the healthy adults, such as hypertension and dyslipidaemia, which may have contributed to the impairment of endothelial function identified (26, 96). Patients with AAA also have a higher prevalence of comorbidities compared to other surgical populations including cardiac (60-70%), respiratory (50%), and kidney and metabolic disease (10-12%) , all of which are associated with vascular dysfunction (28, 44, 68, 77). Poor endothelial function in patients with AAA might contribute to

their elevated cardiovascular risk, and is likely to be exacerbated by the presence of comorbidities, which reinforces the potential of FMD as a treatment target for this population.

Time course of FMD response to exercise

The increase in FMD after moderate-intensity exercise in this study has been observed in some (10, 20, 49, 80), but not all (22, 114) previous studies of healthy adults and those with cardiovascular disease. Similarly, the observed decrease in FMD after higher-intensity exercise has been reported in some (15, 51), but not all (23) studies. Discrepancies between studies may be related to the timing of measurements after exercise as the FMD response to acute exercise is suggested to be bi-phasic, with an immediate decrease followed by an increase or return to baseline FMD after a further period of recovery (1-24h) (24). In this study, we attempted to capture the bi-phasic response by measuring FMD immediately, and then one hour after exercise. We found an immediate increase in FMD that then returned to baseline one hour after moderate-intensity continuous exercise, but an immediate and prolonged decrease in FMD after higher-intensity interval exercise. These responses are in line with our previous findings in older adults that have a poor cardiorespiratory fitness (10), and in patients with peripheral arterial disease (51). It is possible that we may have observed an improvement in FMD with an extended recovery period after the higher-intensity exercise, as other studies in individuals with established endothelial dysfunction have demonstrated a delayed increase in FMD 1-4 hours after exercise (20, 40).

Our findings of no difference in the FMD response after exercise between AAA and healthy adults in this study were somewhat unexpected. It has previously been suggested that a

418 "basement effect" exists in older adults with poor endothelial function, where there is an
419 incapacity for a decrease in FMD after exercise (78). In patients with coronary artery disease
420 who exhibit severe endothelial dysfunction an increase, not a decrease, was observed in FMD
421 after exercise, yet no direct comparisons were made to healthy adults of similar age (22). In this
422 study, both the patients with AAA and the healthy older adults exhibited a degree of endothelial
423 dysfunction at rest compared with values reported in healthy younger adults (16), potentially due
424 to older age (99). Despite differences in fitness between groups in this study and its relationship
425 with endothelial function, the fitness of both groups was "poor" based on normative values for
426 healthy older adults (1). Further, despite observing no differences in the FMD response between
427 normotensive and controlled hypertensive individuals in this study (data not shown), we cannot
428 rule out the potential confounding influence of other known comorbidities and antihypertensive-,
429 statin- and β-blocker medication on the FMD responses. Nonetheless, cardiovascular risk factors
430 such as hypertension and known cardiovascular disease, including coronary heart disease, stroke
431 and previous myocardial infarction are highly prevalent in patients with small AAA (13, 14) and
432 as such our findings are likely to be generalizable to this patient group. Including a comparative
433 group with known cardiovascular risk factors and disease may allow for the influence of AAA to
434 be separated from the influence of other cardiovascular comorbidities. The similar responses in
435 FMD after exercise in both groups in this study suggests the exercise stimulus per se affects the
436 endothelium in older-aged individuals in a similar way, irrespective of the resting level of
437 endothelial function, disease status, medication use or known cardiovascular risk factors.
438
439 Shear rate was lower throughout all conditions and time-points in patients with AAA compared
440 with healthy older adults. Shear stress is proposed as the primary stimulus for FMD (75, 97), and

441 may therefore have contributed to the lower FMD in patients with AAA. Whilst simple
442 normalization of FMD to shear rate is sometimes utilised (74), we found no linear relationship
443 between FMD and shear rate (P=0.271, r= 0.21), and therefore used a recommended statistical
444 model that controlled for shear rate and baseline diameter (6, 9). Given we observed no group
445 differences in brachial artery diameter, the lower shear rate is likely a consequence of the
446 decreased reactive hyperaemia in patients with AAA in this study, which may be indicative of
447 microvascular impairment. As peak reactive hyperaemia is also predictive of future
448 cardiovascular events in vascular patients (45), further studies investigating microvascular
449 function in patient with AAA are warranted.
450
451 As we did not directly assess all the mechanisms responsible for exercise-intensity dependent
452 changes in FMD, we can only speculate on the possible causes, which are suggested to include
453 changes in blood pressure, shear stress, reactive oxygen species and sympathetic nervous activity
454 (24). Blood pressure did not differ significantly during and after moderate- and higher-intensity
455 exercise, and is therefore unlikely to explain the observed differences in FMD responses. NO
456 bioavailability has been shown to be impaired in patients with AAA (53, 87), and therefore
457 altered NO bioavailability after moderate-intensity exercise may explain the increase in FMD.
458 Blood flow patterns during exercise, including increased antegrade flow and shear stress,
459 enhances NO availability and increases FMD (98, 101, 103). Conversely increases in exercise
460 intensity and oscillatory shear and/or retrograde flow increase reactive oxygen species, including
461 superoxide anions (32, 47), which are capable of scavenging NO. This is suggested to reduce
462 FMD in atherosclerotic-prone arteries (85), which may include and be acutely detrimental to the
463 aorta, however this is unknown. The observed decrease in brachial FMD following higher-

intensity interval-based exercise in this study may be attributed to repeated and abrupt increases in brachial artery oscillatory flow (101) observed at the onset of cycling exercise (34), whereas continuous rhythmic exercise elevates antegrade blood flow and increases FMD (100, 103). There is also evidence to suggest that FMD may not be solely NO-mediated (69, 73, 112), and hence other factors should also be considered. Reductions in FMD after higher-intensity, but not moderate-intensity exercise, may be due to a dose-dependent increase in oxidative stress (32), endothelin-1 expression (42), or increased sympathetic nervous activity (41), that negatively impacts endothelial function.

If the changes in brachial artery FMD responses to exercise mirror changes in the aorta, it is possible that different exercise intensities may have differing effects on aortic remodelling, and potentially AAA growth and rupture risk. This, however, remains to be investigated. Interestingly, aortic blood flow increases during steady-state moderate-intensity cycling exercise in patients with AAA, enhances wall shear stress and decreases platelet aggregation which has been suggested to be conducive to preventing AAA progression (43). Whether this proposed benefit remains during higher-intensity interval exercise warrants investigation, although exercise-induced increases in shear stress may enhance eNOS expression and vascular repair mechanisms (81), including the mobilisation of endothelial progenitor cells (113). We did not measure the effect of exercise on aortic endothelial function in this study, however it has recently been reported that brachial artery FMD is improved following surgical repair of AAA (58), suggesting a direct association between aortic and systemic endothelial health in patients with AAA.

487 **FMD responses and potential adaptations with exercise training**

488 The rationale for assessing the time-course of responses in endothelial function after a single
489 bout of exercise relates to the potential impact of repeated bouts on vascular adaptation with
490 exercise training (38). FMD is improved following exercise training in sedentary elderly
491 individuals (56), and the similar acute FMD responses between patients with AAA and healthy
492 adults in this study suggest a capacity for vascular adaptation in AAA patients. Importantly,
493 FMD may be further improved after higher-intensity compared to moderate-intensity exercise
494 training in older adults and in individuals with cardiovascular disease (33, 76, 84). Whether the
495 difference in the acute FMD responses between moderate- and higher-intensity exercise is
496 important for future vascular adaptation in patients with AAA is currently unknown. A reduction
497 in FMD for 60 minutes after higher-intensity interval exercise observed in this study may be
498 linked to vascular remodelling after a period of exercise training (67). Myers et al (2014)
499 reported no significant effect on AAA size after a two year exercise therapy intervention, despite
500 a tendency for a slower aneurysm growth rate after exercise training compared to usual care (64).
501 That study only used low-to-moderate intensity exercise, and this raises the possibility that any
502 potential benefit of exercise on vascular function and AAA growth may be dependent on higher-
503 intensity exercise that promotes a greater perturbation in arterial haemodynamics and endothelial
504 function.

505

506 **Exercise and CV risk in patients with AAA**

507 While the absolute risk of exercise is low, acute cardiovascular events induced by a single-bout
508 of exercise are more common in the elderly and those with atherosclerotic disease (2). Exercise
509 studies in patients with AAA to date have adopted a conservative approach, potentially due to

concerns over the safety of higher-intensity exercise in patients deemed high-risk. Higher intensity interval exercise is increasingly being prescribed for patients with cardiovascular disease and other chronic conditions (21, 46, 76, 84, 90, 114), and our study is the first to report the short-term vascular effects of higher-intensity exercise in patients with AAA. Long-term, a decrease in FMD of 1% has been associated with a 9-17% increase in cardiovascular event rate (37, 48). Whether the acute decreases in FMD (of ~1.0% after higher-intensity interval exercise in this study) are associated with increased risk of acute events, or conversely are important in triggering the benefits of exercise, is not known (31, 67). The use of higher-intensity exercise in patients with AAA needs to consider the short-term, potentially harmful, reduction in endothelial function and the possible benefits of improved cardiorespiratory fitness and endothelial function in the longer term. A recent hospital-based study using high-intensity exercise in patients with AAA reported no detrimental effects, although measures of cardiovascular function were not reported (109).

This study has some limitations that should be noted. Since AAA is asymptomatic it is possible that some of the healthy controls could have had an AAA, although given the low prevalence of AAA, this is unlikely. We only recruited men and therefore the findings may not be generalised to women with AAA. We cannot rule out the potential influence of cardiovascular risk reducing medication on the current findings, including antihypertensive and statin therapy, and further research is needed to understand the direct impact of medication use on the FMD response to exercise in patients with cardiovascular disease. Nonetheless, this is the first study to investigate the acute effects of different exercise-intensities on endothelial function in patients with AAA compared to healthy adults. Further studies are required to more fully explore the interaction

between exercise intensity, endothelial function and cardiovascular risk in patients with AAA. Investigations of the longer-term benefits of higher-intensity exercise training in patients with an AAA are warranted.

Conclusions

The present study suggests that the acute FMD responses to exercise in patients with AAA are similar to healthy adults of similar age. We show that FMD transiently improves after moderate-intensity continuous exercise whereas decreases in FMD are observed for up to one hour after higher-intensity interval exercise. Future studies on the effects of exercise training will be important to better understand the role of transient changes in endothelial function with acute exercise on AAA growth and cardiovascular risk.

CONFLICT OF INTEREST: NONE

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Table Legend

Table 1. Characteristics of patients with AAA and healthy adults

Data are displayed as mean±SD or number (%). BMI, body mass index; AAA, abdominal aortic aneurysm; MI, myocardial infarction; CABG, coronary artery bypass graft; ARB, Angiotensin II receptor blockers; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO_2, oxygen uptake; RER, respiratory exchange ratio.

Table 2. Flow-mediated dilation and hemodynamic indices at rest and following acute exercise in healthy adults and patients with AAA

Data are displayed as mean±SD. Absolute FMD (mm) was not logged for analysis. For conventional presentation of FMD%, absolute FMD data was logged for LMM analysis, back-transformed and interpreted as % change. For clarity, post-hoc p values are reported in the text only. For FMD% significant group ($p=0.044$), time ($p<0.001$), and intensity effects ($p<0.001$), and an intensity x time interaction ($p<0.001$) were observed. There were no group x time ($p=0.154$) or group x intensity x time ($p=0.697$) interactions. *significantly different to baseline $^{\#}$significantly different to seated rest (control condition) $^{\alpha}$significantly different between moderate- and high-intensity exercise. FMD, flow-mediated dilation; SRauc, shear rate area-under-the-curve; TTP, time to peak diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Figure Legend

Figure 1. Study protocol for patients with AAA and healthy adults.

Rest, supine position; FMD, flow-mediated dilation; Condition, control (no exercise seated rest), moderate-intensity continuous cycling (40% peak power-output), higher-intensity interval cycling (12x1 min at 70% peak power-output, separated by 1 min 10% peak power-output); Rest/Recovery, supine position

Figure 2. Relationship between VO_{2peak} ($ml.kg^{-1}.min^{-1}$) and basal flow-mediated dilation including both abdominal aortic aneurysm patients (squares) and healthy older adults (triangles).

Figure 3. Mean (black circles) and individual (lines) ΔFMD (%) from baseline at 10 and 60 min after control, moderate- and higher-intensity exercise in healthy adults (left panels) and patients with AAA (right panels).

Data are displayed as mean±95% CI. Significant intensity effect ($p<0.001$), time effect ($p=0.028$), intensity x time interaction ($p=0.033$). No group effect ($p=0.128$), or group x intensity x time interaction ($p=0.522$). *significantly different to baseline $^{\#}$significantly different to moderate-intensity exercise $^{\neq}$significantly different to control $^{\beta}$significantly different to 10-min post. AAA, abdominal aortic aneurysm; FMD, flow-mediated dilation.

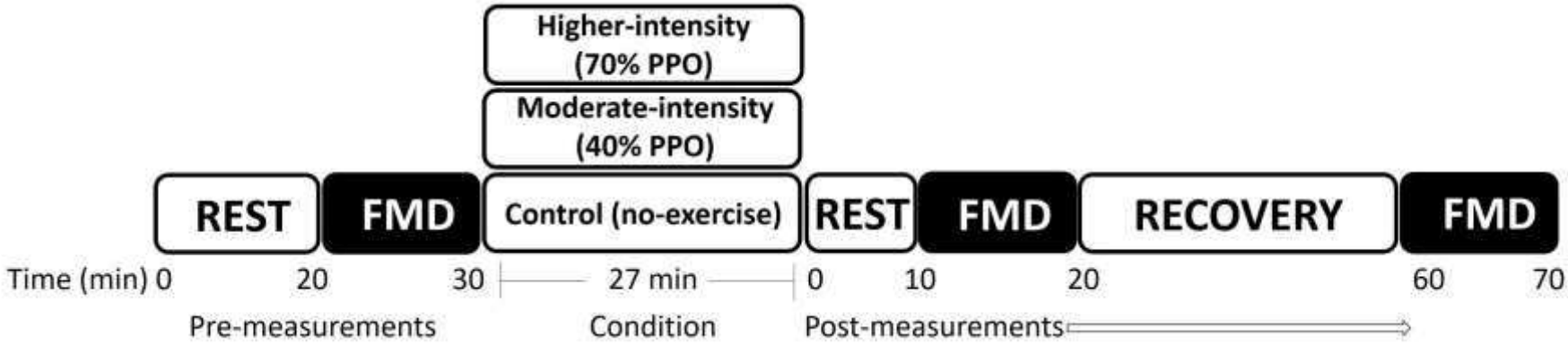
Higher-intensity
(70% PPO)
Moderate-intensity
(40% PPO)
REST
FMD
Control (no-exercise)
REST
FMD
RECOVERY
FMD
Time (min) 0
20
30
27 min
0
10
20
60
70
Pre-measurements
Condition
Post-measurements

Figure 1.

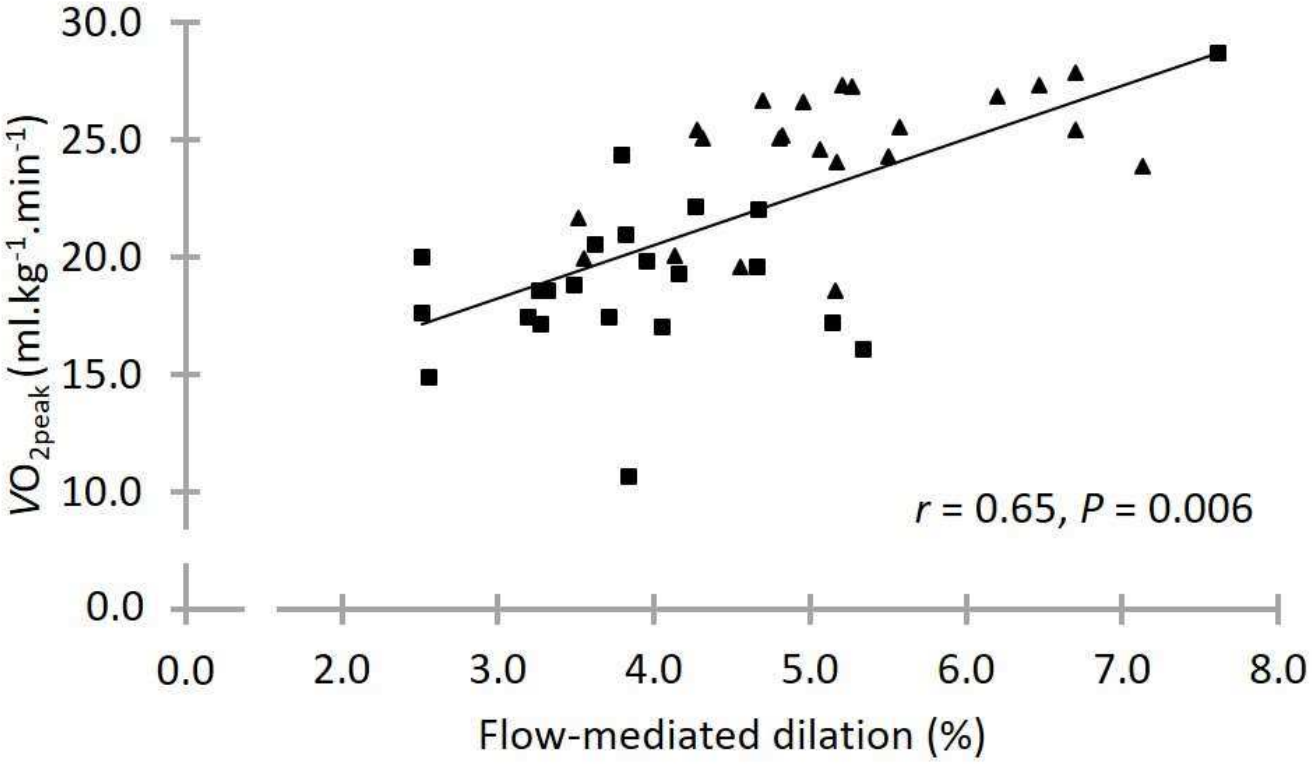
30.0
25.0
20.0
15.0
10.0
0.0
VO_{2peak} (ml.kg^{-1}.min^{-1})
r = 0.65, P = 0.006
0.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Flow-mediated dilation (%)

Figure 2.

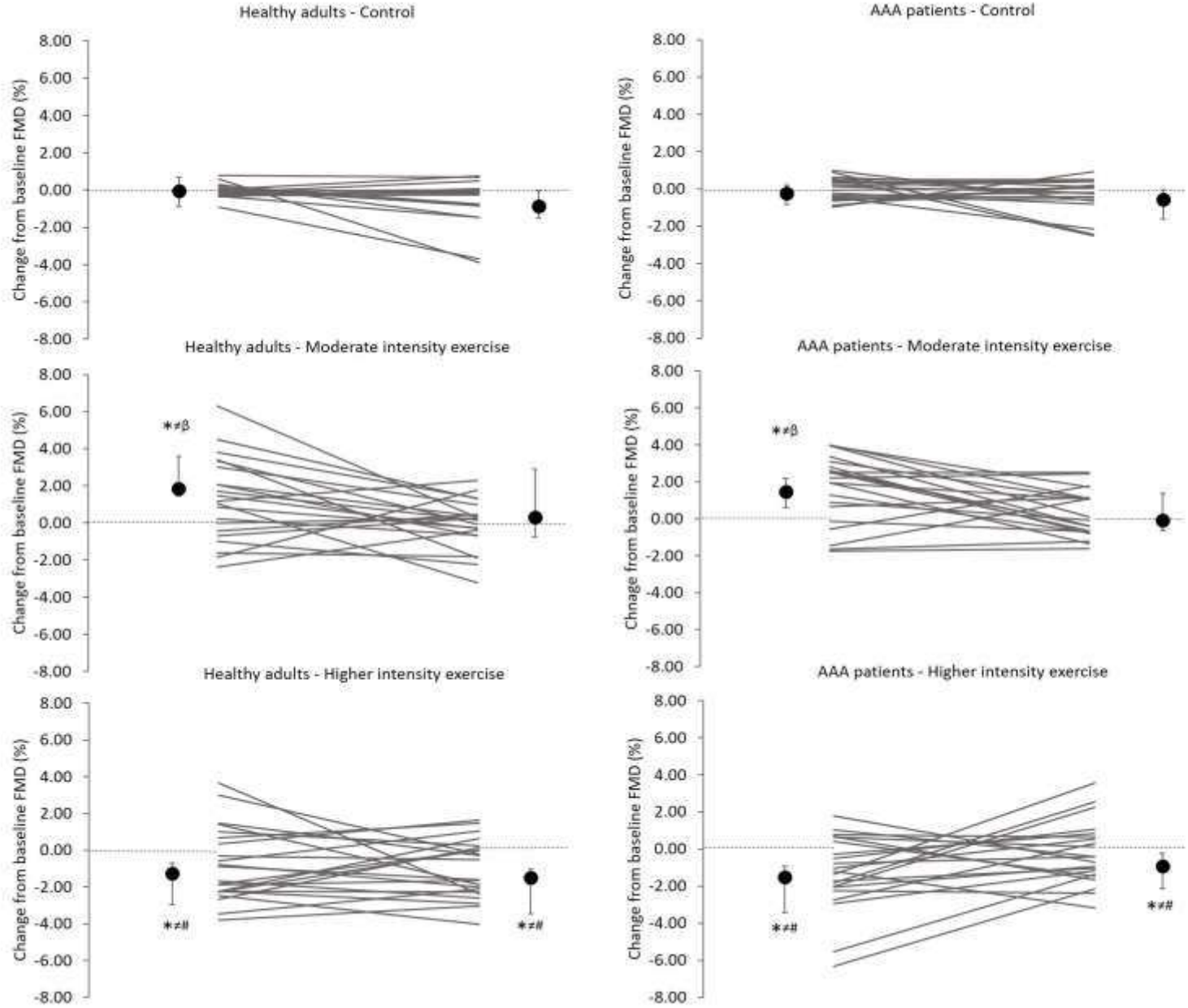
Healthy adults - Control
AAA patients - Control
Healthy adults - Moderate intensity exercise
AAA patients - Moderate intensity exercise
Healthy adults - Higher intensity exercise
AAA patients - Higher intensity exercise
Change from baseline FMD (%)
Chnage from baseline FMD (%)
8.00
6.00
4.00
2.00
0.00
-2.00
-4.00
-6.00
-8.00
*≠β
*≠#

Table 1.	**AAA patients (n=22)**	**Healthy adults (n=22)**	**P value**
Age, years	74±6	72±6	0.200
Male, %	100	100	-
Height, m	1.73±0.07	1.75±0.07	0.463
Weight, kg	83.8±15.7	79.1±11.3	0.264
BMI, $kg.m^{-2}$	27.9±3.9	26.1±3.5	0.100
Clinical information			
Maximum AAA diameter (mm)	36±5	-	-
Hypertension, N (%)	15 (68)	5 (22)	0.006
Dyslipidaemia, N (%)	18 (82)	8 (36)	0.005
Diabetes	2 (9)	0 (0)	0.478
Smoking, current N (%)	2 (9)	1 (5)	0.697
Smoking, previous N (%)	12 (55)	11 (50)	0.701
Previous stroke, N (%)	2 (9)	0 (0)	0.488
Previous MI, N (%)	6 (27)	1 (5)	0.021
Previous CABG, N (%)	11 (50)	1 (5)	0.002
Medication			
ARB/ACE inhibitors, N (%)	9 (40)	4 (18)	0.140
Anti-platelet, N (%)	13 (60)	2 (9)	0.003
Beta-blockers, N (%)	9 (40)	2 (9)	0.034
Calcium channel blockers, N (%)	4 (18)	1 (5)	0.345
Statins, N (%)	20 (90)	9 (40)	0.001
Hemodynamic variables			
Resting heart rate, bpm	59±8	57±8	0.354
Brachial SBP, mmHg	129±13	124±11	0.206
Brachial DBP, mmHg	73±7	73±9	0.970
Peak Cardiorespiratory fitness			
Absolute $\dot{V}O_2$, $L.min^{-1}$	1.58±0.36	1.94±0.35	0.002
Relative $\dot{V}O_2$, $mL.kg^{-1}.min^{-1}$	19.03±3.54	24.47±2.78	<0.001
Peak heart rate, bpm	126±15	148±16	<0.001
Age-predicted peak heart rate, %	86±10	97±11	<0.001
Peak RER, AU	1.17±0.10	1.19±0.11	0.575
Peak Power, Watts	120±20	150±30	<0.001

Table 2

	Control (No Exercise)			Moderate-intensity continuous exercise			Higher-intensity interval exercise		
	Baseline	**Post, 10 min**	**Post, 60 min**	**Baseline**	**Post, 10 min**	**Post, 60 min**	**Baseline**	**Post, 10 min**	**Post, 60 min**
Flow-mediated dilation					**Healthy adults**				
Artery diameter, mm	4.75±0.50	4.67±0.56	4.63±0.53*	4.78±0.56	4.74±0.54$^{\#}$	4.75±0.52	4.85±0.50	4.90±0.53*$^{\#\,\alpha}$	4.87±0.55
FMD, mm	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01	0.03±0.01*$^{\#\alpha}$	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01
Rest blood flow, mL.s^{-1}	1.25±0.70	1.12±0.54	0.98±0.67*	1.34±0.61	1.69±1.02*$^{\#}$	0.97±0.67*	1.44±0.68	2.16±1.43*$^{\#}$	0.99±0.56*
Peak blood flow, mL.s^{-1}	5.25±1.95	4.88±2.36	4.23±2.36*	4.92±2.14	5.42±2.14*$^{\#}$	5.03±2.70	5.28±3.02	6.45±2.46*$^{\#\,\alpha}$	5.35±2.84$^{\#}$
SR_{AUC}, 10^3 s^{-1}	14.03±5.42	13.85±8.58	13.37±7.31*	14.32±8.38	16.90±8.22*$^{\#}$	13.98±7.84	16.20±7.32	17.55±7.94*$^{\#\,\alpha}$	14.61±6.50*
TTP diameter, s	64±23	58±24	70±31	62±31	66±25	63±30	65±32	69±28	63±22$^{\#}$
FMD, %	5.06±1.50	5.12±1.10	4.75±1.10	5.20±1.58	6.14±1.94*$^{\#\,\alpha}$	5.30±1.30	4.96±1.09	3.84±1.95*$^{\#\,\alpha}$	4.00±1.43*$^{\,\alpha}$
Heart rate and blood pressure									
Heart rate, bpm	59±10	56±9	54±7	58±8	71±15*$^{\#}$	59±9	58±7	68±10*	58±6
Systolic BP, mmHg	123±15	130±15*	128±15*	126±13	132±13*	127±15	123±11	130±13*	123±11
Diastolic BP, mmHg	72±10	76±10	74±10	74.10±	76±8	75±11	73±9	76±9	75±10
MAP, mmHg	87±11	91±11*	90±11*	89±10	93±9*	86±10	87±9	92±11*	88±9
Flow-mediated dilation					**Abdominal aortic aneurysm patients**				
Artery diameter, mm	4.90±0.38	4.90±0.40	4.80±0.44*	4.81±0.52	4.77±0.53$^{\#}$	4.76±0.54	4.94±0.50	4.95±0.46	4.93±0.43
FMD, mm	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01	0.03±0.01*$^{\#\,\alpha}$	0.02±0.01	0.02±0.01	0.01±0.01*	0.02±0.01
Rest blood flow, mL.s^{-1}	1.14±0.78	0.85±0.57	0.60±0.47*	0.95±0.60	1.44±1.01*$^{\#\,\alpha}$	0.88±0.92	1.10±0.63	1.69±1.38*	1.14±0.85$^{\#}$
Peak blood flow, mL.s^{-1}	4.28±1.89	3.78±1.49	2.76±1.36*	3.77±1.74	4.89±2.26*$^{\#}$	4.19±1.78$^{\#}$	3.94±1.92	4.73±1.57*	4.45±2.23$^{\#}$
SR_{AUC}, 10^3 s^{-1}	10.26±6.17	9.33±5.50	7.26±3.89*	9.83±5.70	12.46±7.58*$^{\#}$	10.72±6.77$^{\#}$	9.86±5.90	13.50±5.95*	11.01±4.35*
TTP diameter, s	56±29	53±23	54±26	55±31	56±26	61±24	59±36	70±27*$^{\,\alpha}$	56±28
FMD, %	3.94±1.29	4.01±1.51	3.73±1.71	3.73±1.06	4.97±1.49*$^{\#}$	4.28±1.69	4.02±1.39	3.00±1.39*$^{\,\alpha}$	3.91±1.67*$^{\,\alpha}$
Heart rate and blood pressure									
Heart rate, bpm	59±9	56±8	56±10	60±9	68±11*$^{\#}$	58±8	59±9	69±11*$^{\#}$	60±8
Systolic BP, mmHg	127±11	136±14*	135±18*	130±15	133±16*	130±15	129±15	133±14*	127±13
Diastolic BP, mmHg	72±6	76±7	75±9	74±9	74±8	73±8	73±8	69±8	73±8
MAP, mmHg	88±7	93±9*	94±12*	90±9	92±9*	89±10	89±9	90±10*	89±9