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3 **EFFECTS OF ACUTE EXERCISE ON ENDOTHELIAL**  
4 **FUNCTION IN PATIENTS WITH ABDOMINAL AORTIC**  
5 **ANEURYSM**

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33 **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.

64 **NEW AND NOTEWORTHY**

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

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71

72 **KEY WORDS**

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

75

76 **INTRODUCTION**

77 Abdominal aortic aneurysm (AAA) is characterized by the abnormal progressive dilatation of the  
78 abdominal aorta, and is usually diagnosed when maximum abdominal aortic diameter is  $\geq 30$  mm  
79 (106). Screening studies suggest 1-4% of men and 0.5-1% of women aged over 60 years have an  
80 AAA (19, 79). AAA is responsible for ~2% of all deaths (30, 65, 83) and these patients are at  
81 high risk of cardiovascular events, such as myocardial infarction and stroke, and mortality  
82 compared to age-matched healthy adults (13, 14, 66). These patients also have a risk of aortic  
83 rupture due to the weakening of the aortic wall at the site of the aneurysm (25, 63). Currently the  
84 only treatment for the weakened aorta is surgical repair, however there is no treatment-related  
85 survival benefit in patients with small AAA (<55mm) (27). Screening reduces AAA-related  
86 mortality by 50%, yet has no impact on all-cause mortality (29, 105). With AAA there is an  
87 increased prevalence of cardiovascular comorbidities, including ischemic heart disease (~45%),  
88 myocardial infarction (~27%) and stroke (~14%) (13, 14), and the risk of cardiovascular  
89 mortality increases by 3% each year after diagnosis of small AAA (13). Patients with small  
90 AAAs are monitored by regular imaging, but up to 70% progress to a diameter  $\geq 55$ mm  
91 necessitating surgical repair (63), with the associated perioperative mortality and morbidity risk  
92 (52, 89), and cost. Novel therapies are needed which reduce both the risk of cardiovascular  
93 events and the progression of aortic weakening in AAA patients.

94  
95 Alterations in the connective tissue of the aortic wall, including an imbalance between  
96 diminished elastin concentration and collagen proteolysis, is the hallmark of AAA disease. AAA  
97 pathogenesis is not well understood, however endothelial dysfunction is suggested to contribute  
98 to AAA development via increased oxidative stress, inflammation and impaired NO  
99 bioavailability [see recent detailed review (87)]. Thus, treatment that targets endothelial

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

111

112 Brachial FMD improves after regular exercise in patients with known cardiovascular disease and  
113 established endothelial dysfunction, including in individuals with coronary and peripheral artery  
114 disease (21, 70, 108), suggesting that exercise might be a possible treatment option to reverse  
115 endothelial dysfunction in patients with AAA. Vascular improvements with exercise training  
116 depend somewhat on the intensity of exercise (76, 84). An important contribution to the  
117 beneficial effect of exercise on arterial remodelling has been attributed to the repetitive, acute  
118 increases in blood flow and shear stress observed during a single-bout of exercise (36), which  
119 have also been suggested to be beneficial for preventing AAA growth at the site of the aorta (3).

120 In healthy adults, endothelial function is reported to increase after low and moderate-intensity  
121 exercise, but decrease after higher-intensity exercise (10, 15, 24, 49). The effect of exercise on  
122 FMD in individuals with underlying endothelial dysfunction may be augmented (22) compared

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

130

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

145

146 **METHODS**

147 **Participants**

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

160

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

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

170

### 171 **Research Design**

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

187

### 188 **Maximal incremental cycling test for determination of cardiorespiratory fitness**

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



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

200

#### 201 **Experimental exercise and control conditions (visits 2-4)**

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

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

215

### 216 **Measurement of brachial artery FMD**

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

230

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

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

241

### 242 **Statistical analysis**

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

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

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

270  
271 Three-way LMM analysis was also used to detect any differences in heart rate, blood pressure  
272 and perceived exertion in response to the acute protocols between the two groups (AAA and  
273 healthy adults), across time (at 2 and 6 min intervals for HR/RPE and BP, respectively) during  
274 each protocol (control, moderate- and high-intensity exercise). Statistically significant  
275 interactions were further investigated with multiple comparisons using the least significant  
276 difference approach (71, 82). The strength of the association between AAA diameter,  $VO_{2peak}$   
277 and FMD% were assessed using Pearson correlation coefficient. Analyses were conducted using  
278 the Statistical Package for Social Sciences (Version 22; IBM SPSS Inc., Chicago, IL). Statistical  
279 significance was defined at  $P < 0.05$  and exact  $P$  values are cited ( $P$  values of “0.000” are reported  
280 as “<0.001”). Data are presented in the text as mean (95% confidence interval, 95%CI) unless  
281 otherwise stated.

282

283 **Results**284 **Participant characteristics**

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

291

292 **Heart rate, blood pressure and perceived exertion during experimental conditions**

293 There were no significant differences between patients with AAA and healthy adults in heart  
294 rate, blood pressure and RPE throughout each condition ( $P>0.05$ ). Heart rate responses during  
295 exercise were normalised for the peak heart rate obtained during the cardiorespiratory fitness test  
296 in visit 1. Across both groups ( $P=0.213$ ), heart rate was highest during higher-intensity interval  
297 exercise [mean  $68 \%HR_{peak}$  (64 to 71 %)] compared to moderate-intensity continuous exercise  
298 [mean  $62 \%HR_{peak}$  (59 to 64%,  $P<0.01$ )], and lowest during control [mean  $42 \%HR_{peak}$  (95% CI,  
299 39 to 44),  $P<0.01$ ]. The increase in mean arterial pressure during higher-intensity interval  
300 exercise [mean change of 14 mmHg (12 to 17)] was similar during moderate-intensity  
301 continuous exercise [mean change of 14 mmHg (11 to 16),  $P=0.720$ ], whilst increases in mean  
302 arterial pressure responses during both exercise conditions were higher compared to control  
303 [mean change 10 mmHg (8 to 13),  $P<0.05$ ]. RPE was higher during higher-intensity interval

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

306

### 307 **Effect of exercise on endothelial function**

#### 308 *Baseline brachial FMD*

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

319

#### 320 *FMD responses after exercise and control conditions*

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

324

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

327 2). Overall, there were no differences in the magnitude of the FMD response over time between  
328 patients with AAA and the healthy older adults ( $P=0.154$ ). FMD tended to decrease from  
329 baseline after control [at 60-min by 0.43 % (95% CI, -1.10 to 0.96,  $P=0.115$ )], but this was not  
330 significant. FMD increased from baseline by 1.21% (0.69 to 1.73),  $P<0.001$ ) at 10-min after  
331 moderate-intensity continuous exercise, which then returned to near baseline FMD at 60-min.  
332 Conversely, FMD decreased from baseline at 10- and 60-min after higher-intensity interval  
333 exercise, by 0.93% (0.41 to 1.44,  $P<0.001$ ), and 0.51% (0.01 to 1.02,  $P=0.040$ ), respectively.  
334 Thus, the FMD 10-min after the cessation of exercise was significantly higher after moderate-  
335 intensity continuous exercise compared with after control (mean difference in FMD of 1.21 %  
336 (95% CI, 0.63 to 1.75,  $p<0.001$ ) and higher-intensity interval exercise (mean difference of 1.87  
337 % (95% CI, 1.36 to 2.39). At 60-min after exercise, FMD was significantly lower after higher-  
338 intensity interval compared to moderate-intensity continuous exercise (mean difference of 0.60  
339 % [95% CI, 0.06 to 1.13],  $P=0.028$ ). The different responses of FMD% between moderate-  
340 intensity continuous and higher-intensity interval exercise were also observed for absolute FMD  
341 (mm) ( $P=0.024$ ; Table 2).

342

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

348

349 *Blood flow and shear rate responses after exercise and control*

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

359

### 360 **Heart rate and blood pressure responses after exercise**

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

367

### 368 **Discussion**

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



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

377

### 378 **Basal FMD in patients with AAA**

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

384

385 Impaired FMD is independently associated with an increased risk of cardiovascular events and  
386 mortality (37, 48, 54, 92), and may contribute to the high burden of cardiovascular disease and  
387 the observation that ~70% of cardiovascular events and mortality in patients that have small  
388 AAAs is independent of aneurysm-related complications (57, 66, 72). As expected, there was a  
389 higher prevalence of comorbidities amongst the patients with AAA compared to the healthy  
390 adults, such as hypertension and dyslipidaemia, which may have contributed to the impairment  
391 of endothelial function identified (26, 96). Patients with AAA also have a higher prevalence of  
392 comorbidities compared to other surgical populations including cardiac (60-70%), respiratory  
393 (50%), and kidney and metabolic disease (10-12%) , all of which are associated with vascular  
394 dysfunction (28, 44, 68, 77). Poor endothelial function in patients with AAA might contribute to

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

397

398 **Time course of FMD response to exercise**

399 The increase in FMD after moderate-intensity exercise in this study has been observed in some  
400 (10, 20, 49, 80), but not all (22, 114) previous studies of healthy adults and those with  
401 cardiovascular disease. Similarly, the observed decrease in FMD after higher-intensity exercise  
402 has been reported in some (15, 51), but not all (23) studies. Discrepancies between studies may  
403 be related to the timing of measurements after exercise as the FMD response to acute exercise is  
404 suggested to be bi-phasic, with an immediate decrease followed by an increase or return to  
405 baseline FMD after a further period of recovery (1-24h) (24). In this study, we attempted to  
406 capture the bi-phasic response by measuring FMD immediately, and then one hour after exercise.  
407 We found an immediate increase in FMD that then returned to baseline one hour after moderate-  
408 intensity continuous exercise, but an immediate and prolonged decrease in FMD after higher-  
409 intensity interval exercise. These responses are in line with our previous findings in older adults  
410 that have a poor cardiorespiratory fitness (10), and in patients with peripheral arterial disease  
411 (51). It is possible that we may have observed an improvement in FMD with an extended  
412 recovery period after the higher-intensity exercise, as other studies in individuals with  
413 established endothelial dysfunction have demonstrated a delayed increase in FMD 1-4 hours  
414 after exercise (20, 40).

415

416 Our findings of no difference in the FMD response after exercise between AAA and healthy  
417 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  $\beta$ -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-

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

472

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

486

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

510 concerns over the safety of higher-intensity exercise in patients deemed high-risk. Higher  
511 intensity interval exercise is increasingly being prescribed for patients with cardiovascular  
512 disease and other chronic conditions (21, 46, 76, 84, 90, 114), and our study is the first to report  
513 the short-term vascular effects of higher-intensity exercise in patients with AAA. Long-term, a  
514 decrease in FMD of 1% has been associated with a 9-17% increase in cardiovascular event rate  
515 (37, 48). Whether the acute decreases in FMD (of ~1.0% after higher-intensity interval exercise  
516 in this study) are associated with increased risk of acute events, or conversely are important in  
517 triggering the benefits of exercise, is not known (31, 67). The use of higher-intensity exercise in  
518 patients with AAA needs to consider the short-term, potentially harmful, reduction in endothelial  
519 function and the possible benefits of improved cardiorespiratory fitness and endothelial function  
520 in the longer term. A recent hospital-based study using high-intensity exercise in patients with  
521 AAA reported no detrimental effects, although measures of cardiovascular function were not  
522 reported (109).

523

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

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

536

537

538 **Conclusions**

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

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**CONFLICT OF INTEREST: NONE**

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- 911

912 **Table Legend**913 **Table 1. Characteristics of patients with AAA and healthy adults**

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

918

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

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

929

930 **Figure Legend**931 **Figure 1. Study protocol for patients with AAA and healthy adults.**

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

935

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

938

939

940 **Figure 3. Mean (black circles) and individual (lines)  $\Delta$ FMD (%) from baseline at 10 and 60 min**  
 941 **after control, moderate- and higher-intensity exercise in healthy adults (left panels) and patients**  
 942 **with AAA (right panels).**

943 Data are displayed as mean±95% CI. Significant intensity effect ( $p<0.001$ ), time effect ( $p=0.028$ ), intensity x time  
 944 interaction ( $p=0.033$ ). No group effect ( $p=0.128$ ), or group x intensity x time interaction ( $p=0.522$ ). \*significantly  
 945 different to baseline <sup>#</sup>significantly different to moderate-intensity exercise <sup>‡</sup>significantly different to control  
 946 <sup>β</sup>significantly different to 10-min post. AAA, abdominal aortic aneurysm; FMD, flow-mediated dilation.

947

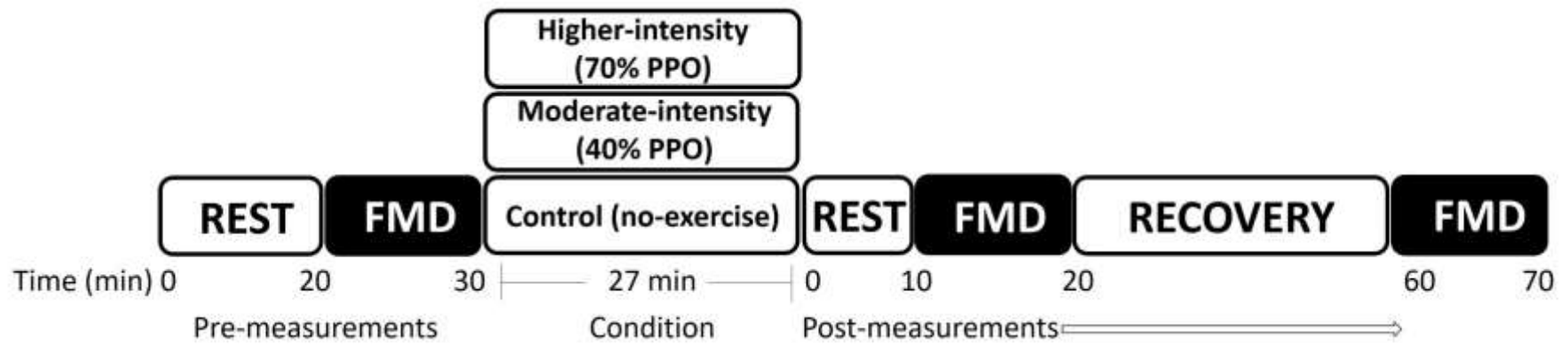


Figure 1.

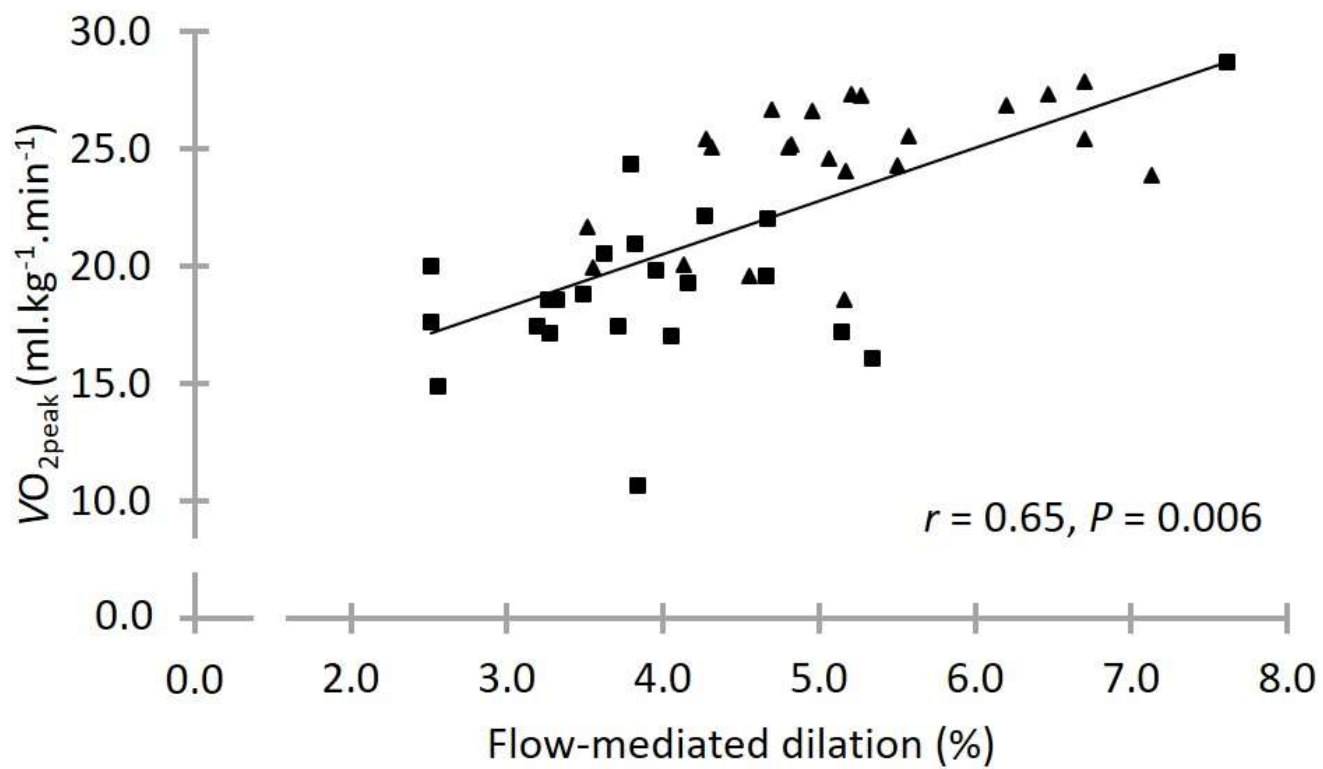
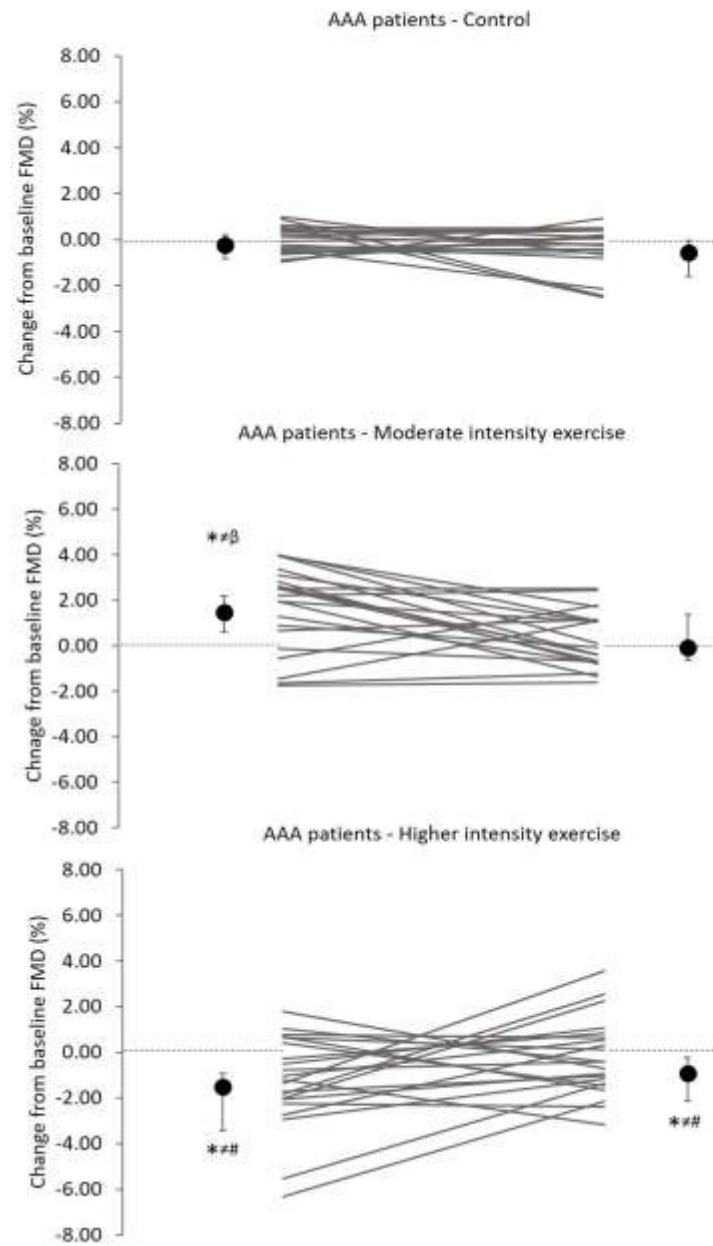
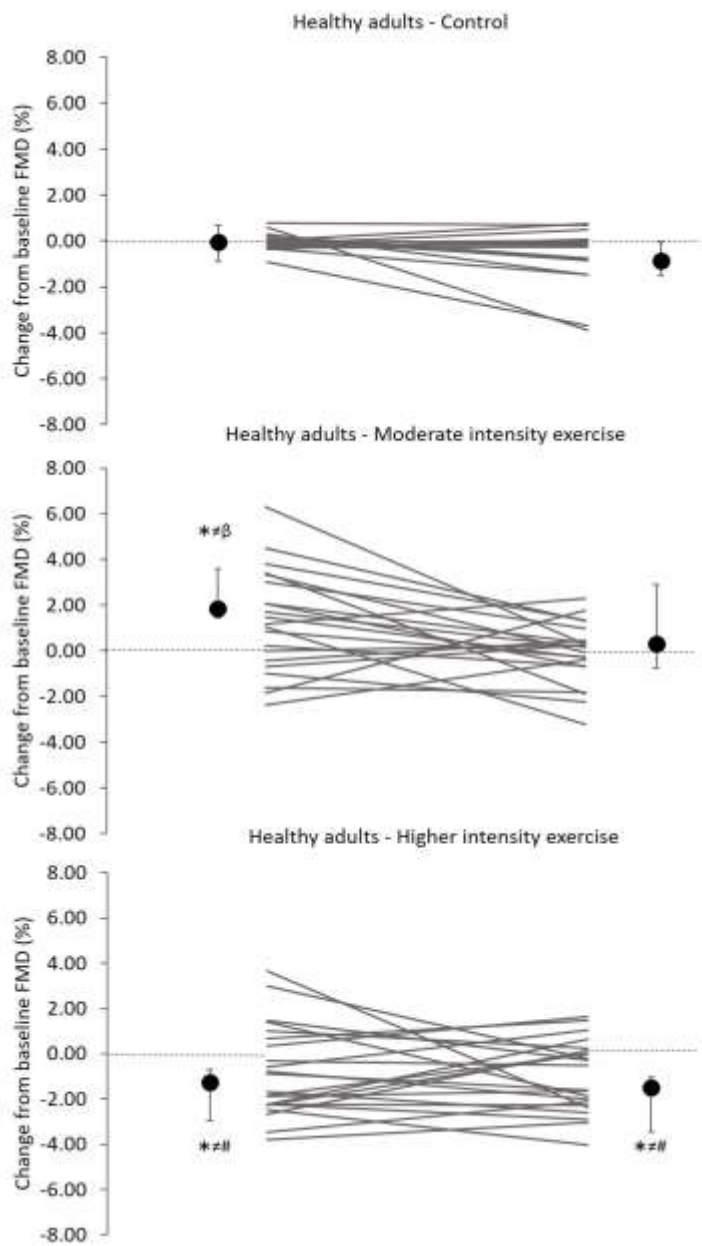


Figure 2.



<b>Table 1.</b>	<b>AAA patients (n=22)</b>	<b>Healthy adults (n=22)</b>	<b>P value</b>
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 <sup>-2</sup>	27.9±3.9	26.1±3.5	0.100
<b>Clinical information</b>			
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
<b>Medication</b>			
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
<b>Hemodynamic variables</b>			
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
<b>Peak Cardiorespiratory fitness</b>			
Absolute VO <sub>2</sub> , L.min <sup>-1</sup>	1.58±0.36	1.94±0.35	0.002
Relative VO <sub>2</sub> , mL.kg <sup>-1</sup> .min <sup>-1</sup>	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
<b>Flow-mediated dilation</b>	<i>Healthy adults</i>								
Artery diameter, mm	4.75±0.50	4.67±0.56	4.63±0.53*	4.78±0.56	4.74±0.54 <sup>#</sup>	4.75±0.52	4.85±0.50	4.90±0.53 <sup>*#α</sup>	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 <sup>*#α</sup>	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01
Rest blood flow, mL.s <sup>-1</sup>	1.25±0.70	1.12±0.54	0.98±0.67*	1.34±0.61	1.69±1.02 <sup>*#</sup>	0.97±0.67*	1.44±0.68	2.16±1.43 <sup>*#</sup>	0.99±0.56*
Peak blood flow, mL.s <sup>-1</sup>	5.25±1.95	4.88±2.36	4.23±2.36*	4.92±2.14	5.42±2.14 <sup>*#</sup>	5.03±2.70	5.28±3.02	6.45±2.46 <sup>*#α</sup>	5.35±2.84 <sup>#</sup>
SR <sub>AUC</sub> , 10 <sup>3</sup> s <sup>-1</sup>	14.03±5.42	13.85±8.58	13.37±7.31*	14.32±8.38	16.90±8.22 <sup>*#</sup>	13.98±7.84	16.20±7.32	17.55±7.94 <sup>*#α</sup>	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 <sup>#</sup>
FMD, %	5.06±1.50	5.12±1.10	4.75±1.10	5.20±1.58	6.14±1.94 <sup>*#α</sup>	5.30±1.30	4.96±1.09	3.84±1.95 <sup>*#α</sup>	4.00±1.43 <sup>*α</sup>
<b>Heart rate and blood pressure</b>									
Heart rate, bpm	59±10	56±9	54±7	58±8	71±15 <sup>*#</sup>	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
<b>Flow-mediated dilation</b>	<i>Abdominal aortic aneurysm patients</i>								
Artery diameter, mm	4.90±0.38	4.90±0.40	4.80±0.44*	4.81±0.52	4.77±0.53 <sup>#</sup>	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 <sup>*#α</sup>	0.02±0.01	0.02±0.01	0.01±0.01*	0.02±0.01
Rest blood flow, mL.s <sup>-1</sup>	1.14±0.78	0.85±0.57	0.60±0.47*	0.95±0.60	1.44±1.01 <sup>*#α</sup>	0.88±0.92	1.10±0.63	1.69±1.38*	1.14±0.85 <sup>#</sup>
Peak blood flow, mL.s <sup>-1</sup>	4.28±1.89	3.78±1.49	2.76±1.36*	3.77±1.74	4.89±2.26 <sup>*#</sup>	4.19±1.78 <sup>#</sup>	3.94±1.92	4.73±1.57*	4.45±2.23 <sup>#</sup>
SR <sub>AUC</sub> , 10 <sup>3</sup> s <sup>-1</sup>	10.26±6.17	9.33±5.50	7.26±3.89*	9.83±5.70	12.46±7.58 <sup>*#</sup>	10.72±6.77 <sup>#</sup>	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 <sup>*α</sup>	56±28
FMD, %	3.94±1.29	4.01±1.51	3.73±1.71	3.73±1.06	4.97±1.49 <sup>*#</sup>	4.28±1.69	4.02±1.39	3.00±1.39 <sup>*α</sup>	3.91±1.67 <sup>*α</sup>
<b>Heart rate and blood pressure</b>									
Heart rate, bpm	59±9	56±8	56±10	60±9	68±11 <sup>*#</sup>	58±8	59±9	69±11 <sup>*#</sup>	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