



LJMU Research Online

Boidin, M, Erskine, RM, Thijssen, DHJ and Dawson, EA

Exercise Modality, But Not Exercise Training, Alters The Acute Effect Of Exercise On Endothelial Function.

<http://researchonline.ljmu.ac.uk/id/eprint/14971/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Boidin, M, Erskine, RM, Thijssen, DHJ and Dawson, EA (2021) Exercise Modality, But Not Exercise Training, Alters The Acute Effect Of Exercise On Endothelial Function. Journal of Applied Physiology (1985). ISSN 8750-7587

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

1 **EXERCISE MODALITY, BUT NOT EXERCISE TRAINING, ALTERS THE ACUTE**
2 **EFFECT OF EXERCISE ON ENDOTHELIAL FUNCTION IN HEALTHY MEN**

3 **Running title:** Different vascular response to distinct exercise modality

4 **Authors:**

5 Maxime Boidin¹⁻³, Robert M Erskine^{1,4}, Dick HJ Thijssen^{1,5}, Ellen Adele Dawson¹

7 **Affiliations:**

8 ¹Research Institute for Sport and Exercise Sciences, Liverpool John Moores University,
9 Liverpool, United-Kingdom

10 ²Cardiovascular Prevention and Rehabilitation (EPIC) Center, Montreal Heart Institute,
11 Montreal, Canada

12 ³School of Kinesiology and Exercise Science, Faculty of Medicine, Université de Montréal,
13 Montreal, Canada

14 ⁴Institute of Sport, Exercise and Health, University College London, UK

15 ⁵Research Institute for Health Sciences, Department of Physiology, Radboud university medical
16 center, Nijmegen, the Netherlands

17
18
19 **Corresponding author:** Dr Ellen Adele Dawson, PhD, Research Institute for Sport and Exercise
20 Science, Liverpool John Moores University, Byrom Street, L3 3AF Liverpool, United Kingdom

21 E.Dawson@ljmu.ac.uk

22 ORCID: <https://orcid.org/0000-0002-5958-267X>

24 **Abstract:**

25 **Purpose.** We used a within-subject cross-over design to examine the impact of exercise modality,
26 i.e. resistance (RT) and endurance (END), on the acute impact of exercise on endothelial function.
27 Secondly, we examined whether a 4-week period of chronic exercise training altered the acute
28 exercise-induced change in endothelial function in healthy individuals.

29 **Methods.** Thirty-four healthy, young men (21±2 years) reported to our laboratory and completed
30 assessment of endothelial function (using the brachial artery flow-mediated dilation test [FMD])
31 before and immediately after a single bout of RT (leg-extension) or END (cycling). Subsequently,
32 participants completed a 4-week period of training (12 sessions), followed by evaluation of the
33 FMD before and after a single bout of exercise. Following a 3-week washout, participants repeated
34 these experiments with the different exercise modality (in a balanced cross-over design).

35 **Results.** An Exercise*Modality-interaction effect was found ($P<0.001$). Post-hoc pairwise
36 analyses revealed a decrease in FMD after END ($P<0.001$), but not after RT ($P=0.06$). Four weeks
37 of exercise training improved resting FMD after END and RT ($P=0.04$), but did not alter the acute
38 effect of exercise on FMD (Exercise*Modality*Training effect: $P=0.63$), an effect independent of
39 the modality of exercise (Exercise*Training interaction: $P=0.46$ and $P=0.11$ in RT and END
40 respectively).

41 **Conclusion.** These distinct changes in FMD following acute exercise may relate to the different
42 prolonged physiological responses induced by endurance *versus* resistance exercise. Specifically,
43 endurance exercise, but not resistance exercise, causes a decrease in brachial artery endothelial
44 function, which was unaffected by 4 weeks of chronic exercise training.

45

46 **Key words.** Vascular function, aerobic exercise, strength training, trainability.

47 **Key points:**

- 48 • We found that resistance and endurance exercise modalities lead to different endothelial
49 function responses after a single bout of exercise.
- 50 • Endothelial function increased after an acute bout of resistance exercise, while it decreased
51 after an acute bout of endurance exercise.
- 52 • Four weeks of chronic exercise training did not affect the acute endothelial function
53 response.
- 54

55 Regular exercise training is associated with strong, independent reductions in risk for future
56 cardiovascular risk in asymptomatic and diseased populations (1). These cardioprotective effects
57 of regular exercise seem, at least partly, to be explained by improvements in cardiovascular risk
58 factors (e.g. hypertension, obesity, cholesterol) (1, 2). In addition, regular exercise training also
59 represents an important stimulus for improved endothelial function and vascular structure (3-7),
60 further contributing to the cardioprotective effects of regular exercise training. Several studies
61 have demonstrated that the acute, exercise-induced alternations in hemodynamic stimuli, e.g.,
62 shear stress and transmural pressure, importantly contribute to the longer-term improvements in
63 vascular function and structure (8-11). Acute change in endothelial function may represent the
64 acute initiation of an adaptive response related to a long-term benefit provided by exercise training
65 on endothelial function (4) and could predict vascular adaptation to training (12). This “hormesis”
66 concept where repeated impairment of endothelial function could lead to long-term vascular
67 adaptation highlights the importance to understand the acute impact of exercise on changes in
68 endothelial function to better understand the effects of (regular) exercise (8, 13).

69

70 Previous work has reported that endothelial function (measured as the flow-mediated dilation,
71 FMD) (14) may decrease immediately after an acute bout of exercise, superseded by a possible
72 over-compensation after 1 to 2 hours after exercise (8, 15). More specifically, several studies (8,
73 12, 16-18), but not all (19, 20) suggest acute endurance (END) exercise leads to a decrease FMD
74 when performed at moderate-to-high intensity. However, conflicting results are reported in
75 relation with acute resistance (RT) exercise (19, 21-23). The conflicting data in the literature with
76 regards to the direction and pattern of these post-exercise changes in FMD may be affected by
77 exercise characteristics (8), including exercise intensity, modality, and duration (8). During END

78 and RT, the physiological stimuli and mechanisms differ markedly. For example, END and RT
79 cause distinct effects in altering blood flow and blood pressure (15, 22, 24). Since these
80 hemodynamic factors impact endothelial function, one may expect distinct effects of different
81 exercise modalities on endothelial function. To date, however, no study has directly compared
82 both modalities within the same individuals.

83
84 The health status and characteristics of the participants (cardiorespiratory fitness, age, and sex)
85 may impact the acute, exercise-induced change in FMD. Despite most studies reporting a decrease
86 FMD after an acute RT bout (15, 21-23, 25), it seems that FMD tends to be unchanged or increased
87 in trained/fit individuals (10, 19, 21-23). Cross-sectional work suggests that endurance-trained
88 individuals show a larger increase of brachial artery diameter but a similar increase in FMD one
89 hour after an acute high-intensity END exercise compared to untrained individuals (26).
90 Intervention studies have demonstrated that chronic END training improves the acute FMD
91 response in metabolic syndrome patients (27), and in animals (28). Similarly, a decrease, increase
92 or no change (21-23, 29) in FMD has been found following acute RT in sedentary individuals,
93 while no change in acute FMD is more common in resistance- or endurance-trained individuals
94 (22).

95
96 Utilising a within-subject cross-over design, to control for between-subject factors influencing
97 exercise-induced responses, our study compared the acute effect of exercise on vascular function
98 between the RT and END modalities in healthy, young men. Secondly, we compared the effect of
99 chronic exercise training on the acute exercise-induced change in FMD between the RT and END
100 modalities. We hypothesised that a single bout of END would lead to an acute decrease in FMD,

101 with no change following acute RT. Furthermore, we hypothesised that chronic exercise training
102 would mitigate the immediate decrease in FMD following an acute bout of END.

103

104 **Methods**

105 **Study design and participants' recruitment**

106 Forty-eight healthy, young, male individuals were recruited from the student population at
107 Liverpool John Moores University via e-mail or poster advertisement. Thirty-four completed all
108 the exercise training and data collection and were included in the final analysis. The study
109 procedures were approved by Liverpool John Moores University Research Ethics Committee
110 (13/APS/032), and adhered to the Declaration of Helsinki. All volunteers gave written informed
111 consent before taking part in the study. Volunteers diagnosed with cardiovascular diseases, who
112 report cardiovascular risk factors or were using any medication that could influence the
113 cardiovascular system, were excluded from the study. Our participants were untrained university
114 students (<2 h a week structured exercise and no history of resistance or endurance training in the
115 six months prior to the study). All patients completed a questionnaire about the habitual physical
116 activity level (PAL) (30) prior to starting the training. The overall PAL was scored using a scale
117 from 1 to 5, where 1 was the least active, 3 was intermediate, and 5 was extremely active. We
118 instructed participants not to change habitual physical activity of the participants during the study.

119

120 **Experimental design**

121 All participants reported once to our laboratory to undergo testing procedures. During the visit, all
122 underwent a resting brachial artery endothelial function before and immediately after an acute RT
123 or END exercise (<5 minutes to get the image). Participants completed 12 sessions over a 4-week

124 period, either RT or END training in a randomised, balanced cross-over design with a wash out
125 period of 3 weeks. Then, the same procedure was performed after the 4-week exercise training
126 programme. It has previously been demonstrated that 2 weeks of detraining reduces
127 cardiopulmonary function and muscular fitness (31) and that vascular function adapts rapidly with
128 detraining (32). For every participant, vascular measurements were taken on the first and final
129 session of the exercise training. The peak $\dot{V}O_2$ assessment was completed within a seven-day
130 period of the first/last training session. All vascular measurements were performed under
131 standardised conditions, in the same respective conditions, and on the right arm (14, 33).

132
133 *Brachial artery endothelial function* was performed in all participants for measuring the NO-
134 mediated endothelium-dependent vasodilation at the first and final training session. Participants
135 were instructed to abstain from strenuous exercise for 24 h and from caffeine and alcohol ingestion
136 for 18 h, and to fast for 6 h before testing according to expert-consensus guidelines (14). Brachial
137 artery FMD was measured after a 15-minute resting period in the supine position, and the right
138 arm was extended and positioned at an angle of $\sim 80^\circ$ from the torso. Immediately distal to the
139 olecranon process of the right arm, a rapid inflated and deflated pneumatic cuff (D.E. Hokanson,
140 Bellevue, WA) was placed, to provide a stimulus for local ischemia in the forearm (14, 34). A 10-
141 MHz multifrequency linear probe attached to a high-resolution ultrasound machine (T3000;
142 Terason, Burlington, MA) was used to image the brachial artery. The probe was positioned on the
143 distal one-third of the upper arm during the measurements. Once an optimal image was found, the
144 probe was held stable, whilst ultrasound parameters were set to optimise the longitudinal, B-mode
145 images of lumen-arterial wall interface. After a 1-minute baseline, the cuff placed round the
146 forearm was inflated at ~ 220 mmHg for 5 minutes, and then deflated for 3 minutes. Brachial artery

147 diameter was recorded (software: Camtasia, TechSmith, MI, USA) during the first minute
148 baseline, the last 30-second of cuff inflation, and the 3-minute of cuff deflation. Edge-detection
149 methods were used for arterial analysis of FMD and computed by the percentage change from
150 brachial artery baseline diameter to peak diameter induced by reactive hyperaemia. Measurements
151 also included baseline and peak brachial diameters (millimeters, mm), shear rate area under the
152 curve (SR_{auc} , sec), and time to peak (seconds, sec) (14). Images were recorded before and up to 5
153 minute after the acute exercise.

154
155 Blood Pressure (Dinamap 1846 XT (Critikon Corporation, Tampa, FL, USA), Heart rate (HR,
156 beats per minute, bpm) (Polar Electro Oy, Kempele, Finland) and body mass (Seca 877) and height
157 (Seca 217) were measured pre and post-training.

158
159 *Peak $\dot{V}O_2$* : Participants completed an increment cycle-exercise (Daum-electronic premium, 8i
160 ergo-bike, Fürth, Germany) test to exhaustion. The protocol began with a power output of 95 W,
161 with an increase of 35 W every 3 minutes until exhaustion thereafter. Subjects maintained a
162 cadence of 80 rpm. This was followed by 15 minutes of unloaded recovery cycling at a self-
163 selected cadence. Oxygen uptake (peak $\dot{V}O_2$, mL \cdot min⁻¹ \cdot kg⁻¹), and respiratory exchange ratio (RER)
164 were measured continuously at rest, during exercise, and recovery using a metabolic system
165 (Metamax 3B, MM3B, Cortex, Leipzig, Germany). Heart rate (HR, beats per minute, bpm) was
166 assessed with a Polar FT1 heart rate monitor with a Pro chest strap (Polar Electro Oy, Kempele,
167 Finland). Strong verbal encouragement was given throughout the test. Peak $\dot{V}O_2$ was defined as the
168 highest $\dot{V}O_2$ value during the last 30 sec of the protocol.

169

170 *Acute and chronic exercise.* The acute RT session consisted of 4 sets of 10 repetitions of maximal
171 voluntary isokinetic (60 deg/s) unilateral knee extension contractions performed alternately on
172 both legs on an isokinetic dynamometer machine (Biodex 3, Medical Systems, Shirley, USA). We
173 chose leg extension resistance exercise to overload the largest lower-limb muscle group, i.e. the
174 quadriceps femoris, which is also the pre-dominant muscle group involved in cycling (35-37). It
175 was not our intention to match the exercise modalities for time or work, simply to compare the
176 effect of RT *versus* END exercise, both targeting the same muscles but potentially stimulating a
177 different vascular response. The acute END session consisted of a 30-minute continuous exercise
178 at 70% peak HR assessed during the increment cycle-exercise test. All training sessions were
179 supervised by members of the research team and were performed 3 times/week for 4 weeks (a total
180 of 12 sessions). For the RT program, after a warm-up set of 10 repetitions at 40% of one maximal
181 repetition (1-RM) unilateral leg extension, all participants performed 4 sets of 10 repetitions at
182 80% 1-RM with 2 minutes' recovery between sets on a leg extension machine (Technogym SpA,
183 Gambettola, Italy) by alternating one leg at a time. The 1-RM was measured at the beginning of
184 each week to progressively increase the training load. Before and after each END training session,
185 participants performed a 10 min warm up/down, consisting of cycling on a cycle ergometer at 50%
186 maximal heart rate (HR_{max} , assessed during the initial VO_{2max} test). The first week of training
187 (sessions 1, 2 and 3) comprised 30 min moderate intensity continuous cycling at 70% HR_{max} . In
188 the second week (sessions 4, 5 and 6), participants completed five contiguous sets of 5 min
189 moderate intensity exercise (70% of HR_{max}) followed immediately by 1 min higher intensity
190 exercise (90% HR_{max}), with no rest between sets. In the third week (sessions 7, 8 and 9),
191 participants performed 30 min moderate intensity continuous exercise at 80% HR_{max} . In the final
192 week (sessions 10 and 11), participants completed five contiguous sets of 5 min moderate intensity

193 exercise (80% HR_{max}) followed immediately by 1 min at 90% HR_{max}. The 12th and final END
194 session was the same as the first. The intensity of END exercise was based on the results of the
195 CPET.

196

197 **Data analyses**

198 Analysis of brachial artery diameters during FMD measurements were performed using custom-
199 designed-edge-detection and wall-tracking software with a calculation from ~400 measures within
200 the region of interest at 30Hz, which is largely independent of investigator bias (38), and with an
201 intra-observer coefficient of variation of 6.7% (39). After calibration, regions of interest (ROI)
202 were selected for analysis of diameter (from B-mode image) and blood flow (from blood flow
203 velocity envelope) at 30 Hz (38). Automatic analysis of the ROI was performed real time, in
204 synchrony by the software. Critical determinant of FMD response following cuff deflation were
205 made from the SR_{auc} from cuff deflation until peak dilation. All data were written to a file and used
206 for further analysis in a custom designed analysis package.

207

208 **Statistical analysis**

209 Data were presented as mean \pm standard deviation. The statistical analyses were performed with
210 GraphPad Prism 8.4.3 (GraphPad Software, Inc., La Jolla, California, USA). Differences were
211 defined as statistically significant when $P < 0.05$. After confirming presence of a normal
212 distribution, a three-way analysis of variance (ANOVA) with repeated measures (Modality:
213 resistance-endurance, Training; pre-post training, Exercise: before-after acute exercise) was used
214 to determine whether exercise modality alters the acute change in FMD to a single bout of exercise
215 (Modality*Exercise), and whether this effect is altered by 4-weeks exercise training

216 (Modality*Training*Exercise). In case of a significant interaction-effects, post-hoc pairwise
217 comparisons with Bonferroni correction were used to identify differences. The analysis was
218 repeated using allometric scaling methods with a Generalized Estimating Equation, including
219 baseline artery diameter and shear rate area-under-the-curve (SR_{auc}) as covariates (16, 40).

220

221 **Results**

222 All 34 participants successfully completed the 4-week END and RES exercise training, and were
223 available for the final analysis related to the FMD. Mean age was 21 ± 2 years. There was no
224 difference at baseline between resting haemodynamic and aerobic fitness measures (Table 1). No
225 interaction was found for body composition, blood pressure, or resting and peak heart rate
226 (interaction effect: all $P<0.05$). The PAL-score was 2.7 ± 0.4 points, reflecting that the subjects
227 were intermediately active.

228

229

230 **Brachial artery FMD and acute exercise**

231 A three-way ANOVA showed no Modality*Exercise*Training interaction effect ($P=0.63$), thus
232 four weeks of exercise training did not alter the acute effect of exercise on FMD. However, there
233 was a main effect of exercise modality ($P=0.002$) and, crucially, an interaction effect for the acute
234 change in brachial artery FMD after exercise between both exercise modalities
235 (Exercise*Modality, $P<0.001$). Post-hoc pairwise comparisons on these pooled data showed that
236 FMD significantly decreased after a single bout of END ($P<0.001$), with no change after a bout of
237 RT ($P=0.06$, Figure 1).

238

239 **Discussion**

240 Adopting a within-subject cross-over design, we examined the impact of exercise modality and
241 exercise training on the acute effects of exercise on vascular function in healthy individuals.
242 Firstly, we found that effect of acute exercise on brachial artery FMD was dependent upon exercise
243 modality. Specifically, a single bout of resistance training (RT) was associated with no change in
244 FMD, while endurance exercise (END) led to an immediate drop in FMD following acute exercise.
245 Secondly, whilst 4-week of exercise training improved resting FMD, it did not alter the magnitude
246 or direction of the acute change in FMD after a single bout of END or RT. Taken together, we
247 demonstrated that acute changes of brachial artery endothelial function dependent of the modality
248 of exercise, and that these responses were unaffected by 4-week exercise training.

249

250 *Acute effect of exercise on FMD: role of modality*

251 Previous studies examining the acute impact of exercise on brachial artery FMD have reported
252 conflicting results, which may relate to various between-study factors, including the diversity of
253 exercise modalities. Our within-subject, cross-over design allowed us to truly understand the
254 potential role of exercise modality on the acute change in FMD, and revealed significantly distinct
255 responses between RT and END exercise in healthy individuals. Previous studies specifically
256 focusing on RT found disparate results. Some found an unchanged (21), or an increase (24, 41),
257 or a decrease (15, 22, 25) in FMD after an acute bout of RT in healthy humans. However, FMD
258 tends to be unchanged or increased when the individuals are considered trained or fit (10, 21-23).
259 Studies examining END typically found an increase in FMD following a single bout of low to
260 moderate intensity exercise (10, 42, 43), and a decrease in FMD following high intensity exercise

261 (16, 17). Taken together, this highlights the importance of the role of exercise modality on the
262 acute change in brachial artery FMD.

263
264 The FMD response following acute exercise depends on several factors, including exercise
265 intensity, modality, duration, and also the health status and characteristics of the participants
266 (cardiorespiratory fitness, age, and sex). To better understand the basic physiological principles
267 and role of exercise training, we decided to include an homogenous group. Since many previous
268 studies included healthy men only, we specifically focused on this group of healthy young men (to
269 also allow comparison of our work with previous studies). Our observation of distinct effects of
270 exercise modality on the acute change in FMD raises the question about the potential underlying
271 mechanisms. A likely explanation may be found in the acute, exercise-induced changes in local
272 and systemic hemodynamics and factors influencing vascular health. Whilst shear rate, blood flow
273 and blood pressure acutely increase with both RT (15, 22, 24, 44) and END (10, 12), different
274 patterns are observed between RT and END. This difference is explained by central factors such
275 as cardiac output, mean arterial pressure, sympathetic nervous system and heart rate, and by
276 peripheral factors such as muscle contractions and vascular conductance (3). Change in FMD
277 (post-pre acute END exercise) are correlated with the change in antegrade shear rate during
278 exercise ($r=0.526$, $P=0.01$) (12). Consequently, the reduced FMD observed after the acute END
279 exercise could be explained by an attenuated increase in shear rate or increased
280 oscillatory/retrograde flow, compared to larger increased in blood flow in RT, which is linked to
281 a systolic blood pressure-driven increase in antegrade without changes in retrograde blood flow
282 (and shear rate) (3). Second, oxidative stress, which increases with both END and RT (45) and
283 leads to vascular dysfunction (8, 45, 46), may increase to a greater extent with END (45). Third,

284 baseline artery diameter also plays an important role in the FMD response, with larger arteries
285 demonstrating a lower FMD (47). However, the change in FMD in our study was similar after
286 correction for baseline diameter and, in line with previous work, baseline diameter increased with
287 both RT (25) and END (11, 17, 26, 48), so it cannot fully explain the disparate responses found
288 between RT and END. Importantly, while individual variations in sympathetic activity and
289 thermoregulatory response could explain the between-subjects variability in the exercise-induced
290 changes in antegrade shear rate, the within-subject design of our study ensures that these factors
291 are unlikely to have a significant role (3, 49). Therefore, while the increase in baseline diameter,
292 blood pressure (15), and sympathetic nervous activity (50) impact the FMD response in both RT
293 and END, the imbalance towards a higher oxidative stress (51) in END compared to RT may
294 explain some of the distinct patterns between both exercise modalities.

295

296 *Influence of chronic training on the acute exercise-induced FMD response*

297 First, we found an increase in brachial artery resting FMD after 4-weeks exercise training.
298 Furthermore, we found that chronic exercise training did not alter the magnitude or direction of
299 the acute effect of either RT or END exercise on brachial artery FMD in healthy young men. This
300 observation is in contrast with previous studies in healthy participants, where trained individuals
301 showed a smaller decrease, or no change, or even an increase in FMD following an acute bout of
302 RT compared to untrained individuals (10, 21-23). Consequently, it is possible that the change in
303 the acute response in FMD after the training intervention is dependent on the training status of the
304 individuals (8, 52).

305 Alternatively, it is possible that the duration of exercise training in this study was not sufficient to
306 produce sufficient changes in anti-oxidant status or other protective mechanisms in a group of
307 already healthy individuals. However, we have previously demonstrated that 2-4 weeks is
308 sufficient to induce functional changes in vascular function in healthy individuals (16, 53), and
309 that following longer-duration training, the functional adaptations may be superseded by structural
310 adaptations in healthy individuals (53).

311
312 Our observation that *chronic* exercise training did not alter the *acute* magnitude or direction of the
313 exercise-induced change in FMD raises questions about the potential relevance of the acute change
314 in FMD for long-term adaptation. It has previously been suggested that the decrease in FMD after
315 acute END may represent a ‘stimulus’ for adaptation in vascular function (12, 13). However, the
316 distinct change in FMD immediately after a single bout of END (i.e. decrease) *versus* RT (i.e.
317 increase) strongly argues against this hypothesis, especially since both modalities of exercise were
318 associated with an improvement in resting FMD following a period of 4-weeks’ chronic exercise
319 training. This is further supported by the finding that the acute change in FMD after a single bout
320 of exercise was not altered after a period of chronic exercise training. Some of the differences in
321 the literature may be due to the different training durations and associated time-course of
322 functional and structural adaptations (54). The data from this study suggest that the acute change
323 in FMD after a single bout of exercise (whether END or RT) may not causally link to subsequent
324 chronic adaptation to that same mode of exercise, but given the disparity in the literature further
325 work is needed.

326

327 *Limitations.* Some limitations must be raised. One potential limitation relates to the timing of the
328 post-exercise FMD, especially since some studies reported on a potential biphasic FMD response
329 following the acute exercise.(8) Since different timings are used for the FMD measurements in the
330 other studies, it is hard to make any comparison and interpretation. However, in line with previous
331 work, we examined the immediate change in FMD, and reported distinct responses when
332 comparing between exercise modality, but similarity when evaluating the role of chronic exercise
333 training. We only had measures of endothelial-dependent function and not endothelia-independent
334 function, and cannot therefore fully exclude that the changes are due to the intrinsic contractility
335 of the artery. However, the majority of previous work has reported that the decrease in
336 endothelium-dependent dilation following acute exercise is not accompanied by any change in
337 endothelium-independent dilation (10, 22, 26, 46, 55). Another limitation is that we recruited only
338 healthy young (relatively fit) men, which could limit the extrapolation to clinical populations with
339 risk factors or cardiovascular disease, given that the FMD response depends on fitness, health
340 status (27, 56), and sex (57). It is also worth noting that the chronic exercise training modality was
341 specific to the acute exercise modality. It is possible that endurance training may alter the acute
342 response to resistance exercise and vice versa.

343
344 In conclusion, the cross-over design of our study allowed us to demonstrate that exercise modality
345 determined the direction of the acute, exercise-induced change in brachial artery endothelial
346 function (measured with the FMD) in healthy young men. Specifically, acute endurance exercise
347 caused an immediate decrease in endothelial function, whilst such change was not present
348 following resistance exercise. Although future work is warranted, these distinct changes in FMD
349 following acute exercise may relate to the different physiological responses induced by endurance

350 *versus* resistance exercise. Moreover, we also found that 4 weeks of chronic exercise training did
351 not alter the direction or magnitude of the acute change in brachial artery endothelial function
352 following both modalities of exercise.

353

354

355 **Competing interests**

356 None to declare.

357

358 **Data availability statement**

359 The data that support the findings of this study are available from the corresponding author upon
360 reasonable request.

361

362 **Author contributions**

363 M.B. drafted the manuscript. All authors contributed to the interpretation of results, and approved
364 the final version of the revised manuscript and agree to be accountable for all aspects of the work.

365 E.D., R.E. and D.T. contributed to the design of the study. E.D., R.E., and D.T. completed data

366 collection and analysis, while E.D., R.E., M.B. and D.T. completed statistical analysis and

367 interpretation. This study was performed at Liverpool John Moores University, with the exercise

368 interventions being conducted at the School of Sport and Exercise Sciences. All persons designated

369 as authors qualify for authorship, and all those who qualify for authorship are listed.

References

1. **Booth FW, Chakravarthy MV, and Spangenburg EE.** Exercise and gene expression: physiological regulation of the human genome through physical activity. *J Physiol* 543: 399-411, 2002.
2. **Mora S, Cook N, Buring JE, Ridker PM, and Lee IM.** Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 116: 2110-2118, 2007.
3. **Green DJ, Hopman MT, Padilla J, Laughlin MH, and Thijssen DH.** Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. *Physiol Rev* 97: 495-528, 2017.
4. **Green DJ, Maiorana A, O'Driscoll G, and Taylor R.** Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol* 561: 1-25, 2004.
5. **Green DJ, O'Driscoll G, Joyner MJ, and Cable NT.** Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *Journal of applied physiology* 105: 766-768, 2008.
6. **Green DJ, and Smith KJ.** Effects of Exercise on Vascular Function, Structure, and Health in Humans. *Cold Spring Harb Perspect Med* 8: a029819, 2018.
7. **Green DJ, Walsh JH, Maiorana A, Best MJ, Taylor RR, and O'Driscoll JG.** Exercise-induced improvement in endothelial dysfunction is not mediated by changes in CV risk factors: pooled analysis of diverse patient populations. *American journal of physiology Heart and circulatory physiology* 285: H2679-H2687, 2003.
8. **Dawson EA, Green DJ, Cable NT, and Thijssen DH.** Effects of acute exercise on flow-mediated dilatation in healthy humans. *Journal of applied physiology* 115: 1589-1598, 2013.
9. **Holder SM, Dawson EA, Brislane A, Hisdal J, Green DJ, and Thijssen DH.** Fluctuation in shear rate, with unaltered mean shear rate, improves brachial artery flow-mediated dilation in healthy, young men. *Journal of applied physiology* 126: 1687-1693, 2019.
10. **Tinken TM, Thijssen DH, Hopkins N, Black MA, Dawson EA, Minson CT, Newcomer SC, Laughlin MH, Cable NT, and Green DJ.** Impact of shear rate modulation on vascular function in humans. *Hypertension* 54: 278-285, 2009.
11. **Bailey TG, Birk GK, Cable NT, Atkinson G, Green DJ, Jones H, and Thijssen DH.** Remote ischemic preconditioning prevents reduction in brachial artery flow-mediated dilation after strenuous exercise. *American journal of physiology Heart and circulatory physiology* 303: H533-538, 2012.
12. **Dawson EA, Cable NT, Green DJ, and Thijssen DH.** Do acute effects of exercise on vascular function predict adaptation to training? *European journal of applied physiology* 118: 523-530, 2018.
13. **Padilla J, Simmons GH, Bender SB, Arce-Esquivel AA, Whyte JJ, and Laughlin MH.** Vascular effects of exercise: endothelial adaptations beyond active muscle beds. *Physiology (Bethesda)* 26: 132-145, 2011.
14. **Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Fata F, Greyling A, Zock PL, Taddei S, Deanfield JE, Luscher T, Green DJ, and Ghiadoni L.** Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J* 40: 2534-2547, 2019.
15. **Gonzales JU, Thompson BC, Thistlethwaite JR, and Scheuermann BW.** Association between exercise hemodynamics and changes in local vascular function following acute exercise. *Applied Physiology, Nutrition, and Metabolism* 36: 137-144, 2011.
16. **Birk GK, Dawson EA, Batterham AM, Atkinson G, Cable T, Thijssen DH, and Green DJ.** Effects of exercise intensity on flow mediated dilation in healthy humans. *Int J Sports Med* 34: 409-414, 2013.
17. **Johnson BD, Padilla J, and Wallace JP.** The exercise dose affects oxidative stress and brachial artery flow-mediated dilation in trained men. *Eur J Appl Physiol* 112: 33-42, 2012.
18. **Katayama K, Fujita O, Iemitsu M, Kawano H, Iwamoto E, Saito M, and Ishida K.** The effect of acute exercise in hypoxia on flow-mediated vasodilation. *Eur J Appl Physiol* 113: 349-357, 2013.
19. **Iwamoto E, Bock JM, and Casey DP.** High-Intensity Exercise Enhances Conduit Artery Vascular Function in Older Adults. *Med Sci Sports Exerc* 50: 124-130, 2018.

20. **Dawson EA, Whyte GP, Black MA, Jones H, Hopkins N, Oxborough D, Gaze D, Shave RE, Wilson M, George KP, and Green DJ.** Changes in vascular and cardiac function after prolonged strenuous exercise in humans. *Journal of applied physiology* 105: 1562-1568, 2008.
21. **Jurva JW, Phillips SA, Syed AQ, Syed AY, Pitt S, Weaver A, and Gutterman DD.** The effect of exertional hypertension evoked by weight lifting on vascular endothelial function. *Journal of the American College of Cardiology* 48: 588-589, 2006.
22. **Phillips SA, Das E, Wang J, Pritchard K, and Gutterman DD.** Resistance and aerobic exercise protects against acute endothelial impairment induced by a single exposure to hypertension during exertion. *Journal of applied physiology* 110: 1013-1020, 2011.
23. **Varady KA, Bhutani S, Church EC, and Phillips SA.** Adipokine responses to acute resistance exercise in trained and untrained men. *Med Sci Sports Exerc* 42: 456-462, 2010.
24. **Atkinson CL, Carter HH, Dawson EA, Naylor LH, Thijssen DH, and Green DJ.** Impact of handgrip exercise intensity on brachial artery flow-mediated dilation. *Eur J Appl Physiol* 115: 1705-1713, 2015.
25. **Gori T, Grotti S, Dragoni S, Lisi M, Di Stolfo G, Sonnati S, Fineschi M, and Parker JD.** Assessment of vascular function: flow-mediated constriction complements the information of flow-mediated dilatation. *Heart* 96: 141-147, 2010.
26. **Rognmo O, Bjornstad TH, Kahrs C, Tjonna AE, Bye A, Haram PM, Stolen T, Slordahl SA, and Wisloff U.** Endothelial function in highly endurance-trained men: effects of acute exercise. *J Strength Cond Res* 22: 535-542, 2008.
27. **Tjonna AE, Rognmo O, Bye A, Stolen TO, and Wisloff U.** Time course of endothelial adaptation after acute and chronic exercise in patients with metabolic syndrome. *J Strength Cond Res* 25: 2552-2558, 2011.
28. **Haram PM, Adams V, Kemi OJ, Brubakk AO, Hambrecht R, Ellingsen O, and Wisloff U.** Time-course of endothelial adaptation following acute and regular exercise. *Eur J Cardiovasc Prev Rehabil* 13: 585-591, 2006.
29. **Boeno FP, Farinha JB, Ramis TR, Macedo RCO, Rodrigues-Krause J, do Nascimento Queiroz J, Lopez P, Pinto RS, and Reischak-Oliveira A.** Effects of a Single Session of High- and Moderate-Intensity Resistance Exercise on Endothelial Function of Middle-Aged Sedentary Men. *Front Physiol* 10: 777, 2019.
30. **Baecke JA, Burema J, and Frijters JE.** A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 36: 936-942, 1982.
31. **Maeda S, Miyauchi T, Kakiyama T, Sugawara J, Iemitsu M, Irukayama-Tomobe Y, Murakami H, Kumagai Y, Kuno S, and Matsuda M.** Effects of exercise training of 8 weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. *Life Sci* 69: 1005-1016, 2001.
32. **Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, and Green DJ.** Impact of inactivity and exercise on the vasculature in humans. *Eur J Appl Physiol* 108: 845-875, 2010.
33. **Jones H, Green DJ, George K, and Atkinson G.** Intermittent exercise abolishes the diurnal variation in endothelial-dependent flow-mediated dilation in humans. *American journal of physiology Regulatory, integrative and comparative physiology* 298: R427-432, 2010.
34. **Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R, and International Brachial Artery Reactivity Task F.** Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *Journal of the American College of Cardiology* 39: 257-265, 2002.
35. **Endo MY, Kobayakawa M, Kinugasa R, Kuno S, Akima H, Rossiter HB, Miura A, and Fukuba Y.** Thigh muscle activation distribution and pulmonary VO₂ kinetics during moderate, heavy, and very heavy intensity cycling exercise in humans. *American journal of physiology Regulatory, integrative and comparative physiology* 293: R812-820, 2007.
36. **Reid MB.** Nitric oxide, reactive oxygen species, and skeletal muscle contraction. *Med Sci Sports Exerc* 33: 371-376, 2001.

37. **Ericson M.** On the biomechanics of cycling. A study of joint and muscle load during exercise on the bicycle ergometer. *Scand J Rehabil Med Suppl* 16: 1-43, 1986.
38. **Black MA, Cable NT, Thijssen DH, and Green DJ.** Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension* 51: 203-210, 2008.
39. **Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, Puddey IB, Beilin LJ, Burke V, Mori TA, and Green D.** Improved analysis of brachial artery ultrasound using a novel edge-detection software system. *Journal of applied physiology* 91: 929-937, 2001.
40. **Atkinson G, Batterham AM, Thijssen DH, and Green DJ.** A new approach to improve the specificity of flow-mediated dilation for indicating endothelial function in cardiovascular research. *J Hypertens* 31: 287-291, 2013.
41. **Morishima T, Iemitsu M, and Ochi E.** Short-term cycling restores endothelial dysfunction after resistance exercise. *Scand J Med Sci Sports* 29: 1115-1120, 2019.
42. **Padilla J, Harris RA, Fly AD, Rink LD, and Wallace JP.** The effect of acute exercise on endothelial function following a high-fat meal. *Eur J Appl Physiol* 98: 256-262, 2006.
43. **Johnson BD, Mather KJ, Newcomer SC, Mickleborough TD, and Wallace JP.** Brachial artery flow-mediated dilation following exercise with augmented oscillatory and retrograde shear rate. *Cardiovasc Ultrasound* 10: 34, 2012.
44. **Atkinson CL, Carter HH, Naylor LH, Dawson EA, Marusic P, Hering D, Schlaich MP, Thijssen DH, and Green DJ.** Opposing effects of shear-mediated dilation and myogenic constriction on artery diameter in response to handgrip exercise in humans. *Journal of applied physiology* 119: 858-864, 2015.
45. **Finaud J, Lac G, and Filaire EJSm.** Oxidative stress. 36: 327-358, 2006.
46. **Llewellyn T, Chaffin M, Berg K, and Meendering JJAP.** The relationship between shear rate and flow-mediated dilation is altered by acute exercise. 205: 394-402, 2012.
47. **Thijssen DH, van Bommel MM, Bullens LM, Dawson EA, Hopkins ND, Tinken TM, Black MA, Hopman MT, Cable NT, and Green DJ.** The impact of baseline diameter on flow-mediated dilation differs in young and older humans. *American journal of physiology Heart and circulatory physiology* 295: H1594-1598, 2008.
48. **Thijssen DH, de Groot P, Kooijman M, Smits P, and Hopman MT.** Sympathetic nervous system contributes to the age-related impairment of flow-mediated dilation of the superficial femoral artery. *American journal of physiology Heart and circulatory physiology* 291: H3122-3129, 2006.
49. **Benda NM, Seeger JP, van Lier DP, Bellersen L, van Dijk AP, Hopman MT, and Thijssen DH.** Heart failure patients demonstrate impaired changes in brachial artery blood flow and shear rate pattern during moderate-intensity cycle exercise. *Exp Physiol* 100: 463-474, 2015.
50. **Padilla J, Harris RA, and Wallace JPJCu.** Can the measurement of brachial artery flow-mediated dilation be applied to the acute exercise model? 5: 1-7, 2007.
51. **Johnson BD, Padilla J, and Wallace JPJEjoap.** The exercise dose affects oxidative stress and brachial artery flow-mediated dilation in trained men. 112: 33-42, 2012.
52. **Tjonna AE, Lee SJ, Rognmo O, Stolen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slordahl SA, Kemi OJ, Najjar SM, and Wisloff U.** Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 118: 346-354, 2008.
53. **Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, and Green DJ.** Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension* 55: 312-318, 2010.
54. **Tinken TM, Thijssen DH, Black MA, Cable NT, and Green DJ.** Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol* 586: 5003-5012, 2008.
55. **Silvestro A, Scopacasa F, Oliva G, de Cristofaro T, Iuliano L, and Brevetti G.** Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. *Atherosclerosis* 165: 277-283, 2002.

56. **Bailey TG, Perissiou M, Windsor M, Russell F, Golledge J, Green DJ, and Askew CDJJoAP.** Cardiorespiratory fitness modulates the acute flow-mediated dilation response following high-intensity but not moderate-intensity exercise in elderly men. *122*: 1238-1248, 2017.
57. **Yoo JK, Pinto MM, Kim HK, Hwang CL, Lim J, Handberg EM, and Christou DD.** Sex impacts the flow-mediated dilation response to acute aerobic exercise in older adults. *Exp Gerontol* 91: 57-63, 2017.

Tables and figures

Table 1. Baseline and post-training characteristics of the young healthy individuals (n=34).

Table 2. Brachial artery function before and after the END and RT modality (n=34).

Figure 1. FMD before and after acute and chronic intervention in RT and END.

FMD: Flow-mediated dilation; RT: Resistance training; END: Endurance training.

Post-hoc pairwise comparisons on the Exercise*Modality interaction showed that FMD significantly decreased after a single bout of END ($P<0.001$), with no change after a bout of RT ($P=0.06$).