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

Running title: Different vascular response to distinct exercise modality

Authors:

Maxime Boidin[1-3], Robert M Erskine[1,4], Dick HJ Thijssen[1,5], Ellen Adele Dawson[1]

Affiliations:

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

[2]Cardiovascular Prevention and Rehabilitation (EPIC) Center, Montreal Heart Institute, Montreal, Canada

[3]School of Kinesiology and Exercise Science, Faculty of Medicine, Université de Montréal, Montreal, Canada

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

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

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

E.Dawson@ljmu.ac.uk

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

Abstract:

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

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

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

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

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

Key points:

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

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

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

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

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

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

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

Methods

Study design and participants' recruitment

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

Experimental design

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

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

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

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

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

Peak VO_2: Participants completed an increment cycle-exercise (Daum-electronic premium, 8i ergo-bike, Fürth, Germany) test to exhaustion. The protocol began with a power output of 95 W, with an increase of 35 W every 3 minutes until exhaustion thereafter. Subjects maintained a cadence of 80 rpm. This was followed by 15 minutes of unloaded recovery cycling at a self-selected cadence. Oxygen uptake (peak O_2, $mL \cdot min^{-1} \cdot kg^{-1}$), and respiratory exchange ratio (RER) were measured continuously at rest, during exercise, and recovery using a metabolic system (Metamax 3B, MM3B, Cortex, Leipzig, Germany). Heart rate (HR, beats per minute, bpm) was assessed with a Polar FT1 heart rate monitor with a Pro chest strap (Polar Electro Oy, Kempele, Finland). Strong verbal encouragement was given throughout the test. Peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ value during the last 30 sec of the protocol.

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

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

Data analyses

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

Statistical analysis

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

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

Results

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

Brachial artery FMD and acute exercise

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

Discussion

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

Acute effect of exercise on FMD: role of modality

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

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

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

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

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

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

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

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

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

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

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

Competing interests

None to declare.

Data availability statement

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

Author contributions

M.B. drafted the manuscript. All authors contributed to the interpretation of results, and approved the final version of the revised manuscript and agree to be accountable for all aspects of the work. E.D., R.E. and D.T. contributed to the design of the study. E.D., R.E., and D.T. completed data collection and analysis, while E.D., R.E., M.B. and D.T. completed statistical analysis and interpretation. This study was performed at Liverpool John Moores University, with the exercise interventions being conducted at the School of Sport and Exercise Sciences. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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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 ($P=0.06$).