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### Article

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# Intra-individual differences in the effect of endurance versus resistance training on vascular function: A cross-over study

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We used a within-subject, cross-over design study to compare the impact of 4-weeks' resistance (RT) versus endurance (END) training on vascular function. We subsequently explored the association of intra-individual effects of RT versus END on vascular function with a single nucleotide polymorphism (SNP) of the *NOS3* gene. Thirty-five healthy males ( $21 \pm 2$  years old) were genotyped for the *NOS3* rs2070744 SNP and completed both training modalities. Participants completed 12 sessions over a 4-week period, either RT (leg-extension) or END (cycling) training in a randomized, balanced cross-over design with a 3-week washout period. Participants performed peak oxygen uptake (peak  $\text{VO}_2$ ) and leg-extension single-repetition maximum (1-RM) testing, and vascular function assessment using flow-mediated dilation (FMD) on 3 separated days pre/post-training. Peak  $\text{VO}_2$  increased after END ( $p < 0.001$ ), while 1-RM increased after RT ( $p < 0.001$ ). FMD improved after 4-weeks' training (time effect:  $p = 0.006$ ), with no difference between exercise modalities (interaction effect:  $p = 0.92$ ). No relation was found between individual changes (delta, pre-post) in FMD to both types of training ( $R^2 = 0.06$ ,  $p = 0.14$ ). Intra-individual changes in FMD following END and RT were associated with the *NOS3* SNP, with TT homozygotes significantly favoring only END ( $p = 0.016$ ) and TC/CC tending to favor RT only ( $p = 0.056$ ). Although both training modes improved vascular function, significant intra-individual variation in the adaptation of FMD was found. The association with *NOS3* genotype suggests a genetic predisposition to FMD adapting to a specific mode of chronic exercise. This study therefore provides novel evidence for personalized exercise training to optimize vascular health.

## KEYWORDS

aerobic training, endothelial function, genetics, response to training, strength training, trainability

## 1 | INTRODUCTION

Regular exercise training or physical activity represents a potent cardioprotective stimulus in the primary and secondary prevention of cardiovascular disease (CVD).<sup>1</sup> In fact, a curvilinear dose-response curve exists between physical activity

and cardiovascular disease, with higher levels of physical activity being related to lower relative risk for CVD.<sup>2,3</sup> To optimize the exercise stimulus, several studies have compared health benefits between resistance training (RT) versus endurance training (END). Studies focusing on clinical endpoints (eg, mortality or morbidity) or classic risk factors (eg,

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blood pressure) reveal no significant difference between both types of exercise.<sup>4–6</sup> In agreement, studies examining vascular function, importantly contributing to cardioprotection of exercise,<sup>7–9</sup> show similarly improved vascular function between RT (n=396, weighted mean differences [WMD]: 2.5%) and END (n = 1,591, WMD: 2.8%).<sup>10</sup> While these data strongly suggest no difference in effect sizes for CVD-relevant outcomes when comparing RT versus END, a key limitation for all these studies is their dependence on between-subject comparisons.

Based on the complex nature of the hemodynamic exercise stimulus, which likely differs within individuals when undertaking RT or END,<sup>11</sup> intra-individual differences should be considered when comparing the impact of both types of exercise training. To support this notion, studies have linked variations within certain genes (ie, polymorphisms) to elite athlete status,<sup>12,13</sup> and human endurance<sup>14</sup> and strength<sup>15</sup> performance. For example, the nitric oxide (NO) synthase 3 (*NOS3*) gene encodes endothelial NO synthase (eNOS).<sup>16</sup> Based on the importance of NO for vascular health,<sup>17</sup> *NOS3* has been extensively screened for polymorphisms. A single nucleotide polymorphism (SNP), with a thymine (T) to cytosine (C) substitution occurring at nucleotide position –786 (rs2070744),<sup>18</sup> has been associated with athletic performance in various athletes.<sup>12,13</sup> These associations are likely linked to the allele-specific effects on gene transcription: the T-allele (TT genotype) is associated with increased *NOS3* gene promoter activity, thus increasing eNOS and NO synthesis, while the C-allele (ie, TC/CC genotypes) is related to attenuated NO production.<sup>19,20</sup> Consequently, this SNP may contribute to intra- and inter-individual differences in the RT- or END-induced change in FMD, a largely NO-mediated vasodilator response.<sup>21</sup> This would support personalizing the type of exercise to maximize health benefits at an individual level, thereby optimizing vascular adaptation and reducing CVD risk.

This study used a within-subject, cross-over design to compare the impact of 4 weeks of RT versus END on vascular function within healthy individuals. Secondly, we explored whether the *NOS3* (rs2070744) SNP was associated with intra- and inter-individual differences in vascular function changes following different modalities of chronic exercise. We hypothesized that both modalities of exercise

training would lead to a comparable improvement in vascular function at group level, while little relation would be present at an intra-individual level. Moreover, we hypothesized that specific genotypes of the *NOS3* rs2070744 SNP would be associated with the intra- and inter-individual variation in vascular function changes following different modes of exercise training.

## 2 | METHODS

### 2.1 | Study design and participant recruitment

Forty healthy, young, male individuals were recruited from the student population at Liverpool John Moores University via e-mail or poster advertisement. The study procedures were approved by Liverpool John Moores University Research Ethics Committee (approval number: 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.

### 2.2 | Experimental design

Before and after both 4-week exercise training programs, all participants reported to the laboratory on two occasions to undergo testing procedures, separated by at least 24 h between visits. During the first visit, all underwent anthropometric measurements and a maximal cardiopulmonary exercise testing (CPET) with gas exchange analysis. During the second visit, brachial artery vascular function was assessed in all participants. This order was kept the same throughout the entire protocol. Participants completed 12 sessions over a 4-week period, of either RT or END training in a randomized, balanced cross-over design with a washout period of 3 weeks (Figure 1). For every participant, all study testing at baseline, after the first 4 weeks of training, after the 3-week washout period, and at study end were completed within a 7-day period of the first/last training session. All

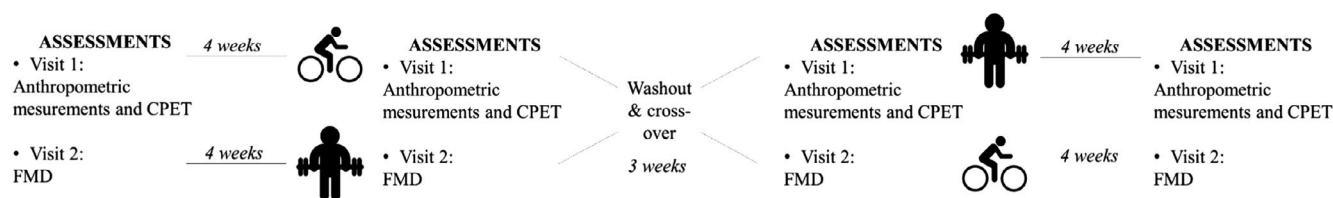


FIGURE 1 Experimental design of the study

vascular measurements were performed under standardized conditions, in the same respective conditions, and on the right arm.<sup>22</sup>

## 2.3 | Measurements

### 2.3.1 | Brachial artery vascular function

Brachial artery vascular function was performed in all participants for measuring the NO released endothelium-dependent vasodilation at baseline and study end in the same time of the day for each participant. 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.<sup>22</sup> To measure brachial artery FMD after a 15-minute resting period in the supine position, the right arm was extended and positioned at an angle of  $\sim 80^\circ$  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.<sup>22</sup> A 10-MHz multifrequency linear probe attached to a high-resolution ultrasound machine (T3000; Terason) 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, while ultrasound parameters were set to optimize the longitudinal, B-mode images of lumen-arterial wall interface. After a 1-minute's baseline recording, the cuff placed around the forearm was inflated to  $\sim 220$  mmHg for 5 min and then deflated for 3 min. Brachial artery diameter was recorded (software: Camtasia, TechSmith) during the 1st min baseline, the last 30-s 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 hyperemia. 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).<sup>22</sup>

Analysis of brachial artery diameters during FMD measurements was performed using custom-designed-edge-detection and wall-tracking software, with an intra-observer coefficient of variation of 6.7%.<sup>23</sup> 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. Automatic analysis of the ROI was performed real time, in synchrony by the software. Critical determinant of FMD response following cuff deflation was 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.

### 2.3.2 | Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed in all participants on an electronically braked cycle ergometer (Daumelectronic premium, 8i ergo-bike). Peak oxygen uptake (peak  $VO_2$ ,  $ml \cdot min^{-1} \cdot kg^{-1}$ ) and respiratory exchange ratio (RER) were measured continuously at rest, during exercise, and recovery using a metabolic system (Metamax 3B, MM3B, Cortex). Measurements also included power output (Watts, W) and heart rate (HR, beats per minute, bpm) with a Polar FT1 heart rate monitor with a Pro chest strap (Polar Electro Oy). The incremental protocol began with a power output of 95 W, followed by an increase of 35 W every 3 min until exhaustion, while maintaining a cadence of 80 rpm. This was followed by 15 min of unloaded recovery cycling at a self-selected cadence. Peak  $VO_2$  was defined as the highest  $VO_2$  value during the last 30 s of the CPET. Strong verbal encouragement was given throughout the test.

## 2.4 | DNA extraction and genotyping

A blood sample was drawn into a 10-ml EDTA vacutainer (BD Vacutainer Systems) from a superficial forearm vein. The whole blood was aliquoted into 2-ml tubes (Eppendorf AG) and stored at  $-80^\circ C$  until subsequent analysis. DNA purification from whole blood samples was performed manually using a QIAamp DNA Blood Mini Kit (Qiagen Ltd.), following the manufacturer's guidelines. DNA samples were then stored at  $4^\circ C$  until subsequent genotyping. Real-time polymerase chain reaction was performed (Rotor-Gene Q, Qiagen) to establish the genotypes of each SNP for each participant. Each 10  $\mu l$  reaction volume contained 5  $\mu l$  Genotyping Master Mix (Applied Biosystems), 3.5  $\mu l$  nuclease-free  $H_2O$  (Qiagen), 0.5  $\mu l$  *NOS3* rs2070744 genotyping assay (Applied Biosystems), plus 1  $\mu l$  DNA sample. Both negative [1  $\mu l$  nuclease-free  $H_2O$  (Qiagen) replaced the DNA template] and positive controls were included in each RT-PCR run, which used the following protocol: denaturation at  $95^\circ C$  for 10 min, followed by 50 cycles of incubation at  $92^\circ C$  for 15 s, then annealing and extension at  $60^\circ C$  for 1 min. Genotypes were determined using Rotor-Gene Q Pure Detection 2.1.0 software (Qiagen). All samples were analyzed in duplicate, and there was 100% agreement between genotype calls for samples from the same participant.

## 2.5 | Exercise training

### 2.5.1 | Resistance training

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). The RT was performed on a leg extension machine (Technogym) by alternating one leg at a time. Prior to the first training session of each week, a one maximal repetition (1-RM) was used to assess the maximal load able to be lifted during one repetition according to guidelines.<sup>24</sup> Each session comprised 4 sets of 10 repetitions at 80% of 1-RM for each leg, with 2 min' recovery between sets. Each week, the training load was adjusted according to the new 1-RM. Before each RT session, a warm-up set of 10 repetitions at 40% of 1-RM was performed. However, the first and last RT sessions were completed on an isokinetic dynamometer (Biodex 3, Medical Systems) to facilitate the measurement of brachial artery vascular function during those sessions. To simulate the RT sessions, participants performed 4 sets of 10 repetitions of maximum isokinetic knee extensor voluntary contractions at an angular velocity of 60 s<sup>-1</sup>.

### 2.5.2 | Endurance training

Endurance training was performed on a cycle ergometer (Lode BV, Groningen, the Netherlands) and comprised 30-min' continuous cycling at 70% maximal HR (HR<sub>max</sub>, assessed during the CPET) for the first 3 sessions. Sessions 4 to 6 comprised 5 repetitions of 1 minute at 90% HR<sub>max</sub> and 5 min at 70% HR<sub>max</sub>. Sessions 7 to 9 comprised 30-min' continuous cycling at 80% HR<sub>max</sub>. Sessions 10 and 11 comprised 5 repetitions of 1 min at 90% HR<sub>max</sub> and 5 minutes at 80% HR<sub>max</sub>. The last session was identical to the first. Before and after each training session, participants performed a 3-min warm-up/cool-down at 60–80 W. Power output and HR were recorded and averaged for each training session.

## 2.6 | Statistical analysis

Data are presented as mean ± standard deviation. The statistical analyses are performed with GraphPad Prism 8.4.1 (GraphPad Software, Inc.). Differences are defined as statistically significant when  $p < 0.05$ . After ensuring a normal distribution, a two-way analysis of variance (ANOVA) was used to compare baseline over the two modalities. A two-way ANOVA with repeated measures (modality x time) was used to compare anthropometric measures, blood pressure and heart rate, and brachial artery function between the two training interventions. The analysis was repeated with the correction for within-subject changes for baseline diameter and SR<sub>auc</sub>.<sup>22</sup> A three-way mixed ANOVA was used to investigate an interaction between exercise modality (RT and END), time (pre- and post-training), and *NOS3* genotype (TT vs. TC+CC). In

the case of a significant three-way interaction, post hoc paired *t* tests were used to determine the effects of each training modality on FMD in each genotype group (using a false discovery rate (FDR) of 10% to control for multiple comparisons).<sup>25</sup> Statistical significance was accepted when  $p < 0.05$ .

## 3 | RESULTS

A total of five participants did not complete both training modalities. Therefore, final analyses were performed on 35 participants (21 ± 2 years old, Table 1). Body mass, BMI, blood pressure, and heart rate did not change after each training intervention (Table 1). We found no evidence for an order effect in the training modalities between groups (interaction effect:  $p > 0.05$  for all variables). Examining the impact of RT, we found an increase in 1-RM from week 1 to 4 ( $p < 0.001$ ), while total workload (load x repetitions x sets) increased by 23% ( $p < 0.001$ , Table 1). When performing END, power output and heart rate increased across exercise training ( $p < 0.001$ ). Importantly, distinct adaptation in peak VO<sub>2</sub> was found between END versus RT (interaction effect:  $p = 0.04$ ), with a significant increase after END, but not after RT (Table 1).

### 3.1 | Impact of RT versus END: effect on vascular function

#### 3.1.1 | Between-group comparison

FMD increased after both 4-week training programs ( $p = 0.006$ ), with no evidence of an interaction effect (Table 2). We found no change in any other brachial artery parameters after 4-weeks' exercise training (all  $p > 0.05$ , Table 2). Correcting FMD for within-subject changes in SR<sub>auc</sub> and baseline diameter did not alter the outcome.

#### 3.1.2 | Within-individual comparison

When presenting the individual change in FMD after RT and END (Figure 2), a characteristic and comparable pattern between both exercise modalities was found with most participants (~65%) demonstrating an increase in FMD after 4-weeks' exercise training. Despite this similarity at group level, matching the individual changes to both types of training showed large variation between individuals (Figure 2C). In fact, there was no correlation between the intra-individual changes in FMD following RT vs. END ( $R^2 = 0.06$ ,  $p = 0.14$ ).



**TABLE 1** Anthropometric measures, resting blood pressure, and heart responses to the training of the participants ( $n = 35$ )

	RT		END		ANOVA		
	Pre	Post	Pre	Post	Exercise	Time	Interaction
Body mass, kg	77.1 ± 10.0	77.0 ± 9.9	76.9 ± 9.6	76.8 ± 10.0	0.93	0.46	0.93
BMI, kg·m <sup>-2</sup>	24.4 ± 3.0	24.3 ± 3.0	24.2 ± 3.0	24.1 ± 3.1	0.87	0.49	>0.99
Systolic blood pressure, mmHg	120 ± 8	125 ± 10	120 ± 7	124 ± 11	0.76	<b>&lt;0.001</b>	0.72
Diastolic blood pressure, mmHg	62 ± 5	62 ± 5	62 ± 6	63 ± 9	0.95	0.48	0.55
Mean arterial pressure, mmHg	84 ± 5	87 ± 5	84 ± 5	87 ± 8	0.88	<b>0.003</b>	0.95
Heart rate, bpm	63 ± 11	67 ± 14	65 ± 15	66 ± 18	0.89	0.18	0.39
RT characteristics							
1-RM, kg	56 ± 14	67 ± 13				<b>&lt;0.001</b>	
Total workload, kg	5,874 ± 1,456	7,208 ± 1,563				<b>&lt;0.001</b>	
END characteristics							
Power output, W			113 ± 23	123 ± 25		<b>0.03</b>	
Heart rate, bpm			135 ± 10	134 ± 8		0.87	
Maximal CPET							
Peak VO <sub>2</sub> , ml·min <sup>-1</sup> ·kg <sup>-1</sup>	47.5 ± 11.0	46.4 ± 10.4	46.5 ± 9.4	49.6 ± 10.4**	0.62	0.13	<b>0.002</b>

Note: Variables are expressed as mean ± SD. Total work load is obtained by computing load x repetitions x sets.

Abbreviations: 1-RM, One maximal repetition; BMI, Body mass index; END, Endurance training; Maximal CPET, Maximal cardiopulmonary exercise testing; Peak VO<sub>2</sub>, Peak oxygen uptake; RT, Resistance training.

\*\* $p < 0.01$ : Difference from baseline.

**TABLE 2** Brachial artery function before and after the END and RT modality ( $n = 35$ )

	RT		END		ANOVA		
	Pre	Post	Pre	Post	Exercise	Time	Interaction
Baseline diameter, mm	3.8 ± 0.6	3.9 ± 0.8	3.9 ± 0.5	3.7 ± 0.6	0.81	0.47	0.15
Peak diameter, mm	4.1 ± 0.6	4.2 ± 0.7	4.1 ± 0.5	4.0 ± 0.6	0.71	0.85	0.14
FMD, %	7.1 ± 2.7	8.0 ± 3.3*	6.9 ± 2.5	8.0 ± 3.2*	0.86	0.006	0.92
SR <sub>auc</sub> , s <sup>-1</sup> 10 <sup>3</sup>	23.2 ± 10.8	24.1 ± 11.0	22.5 ± 10.3	21.6 ± 7.8	0.43	0.97	0.42
Time to peak, sec	54 ± 18	61 ± 21	56 ± 17	55 ± 17	0.51	0.25	0.19

Note: Variables are expressed as mean ± SD.

Abbreviations: END, Endurance training; FMD, Flow-mediated dilation; RT, Resistance training; SR<sub>auc</sub>, Shear rate area under the curve.

\* $p < 0.05$ : Difference from baseline.

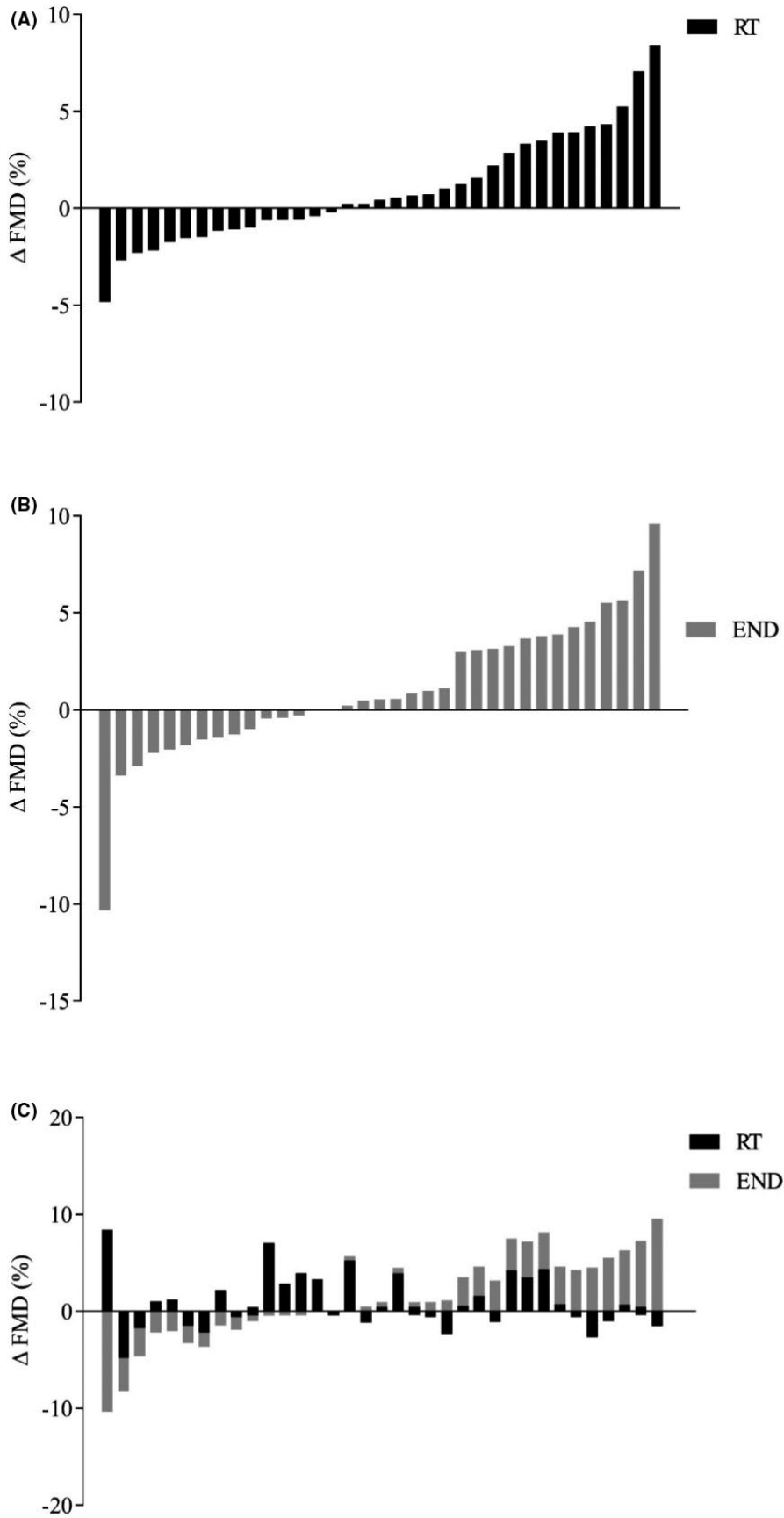
### 3.2 | Impact of RT versus END: role of NOS3 genotype

A total of 14 and 21 participants were *NOS3* TT and TC/CC genotypes, respectively. We compared the effects of different exercise training modalities (RT and END) within and between different *NOS3* genotype groups on changes in FMD over time (Figure 3). The ANOVA revealed a three-way interaction effect ( $p = 0.04$ ) between for FMD (Figure 3). Post hoc paired t tests revealed a significant increase in FMD

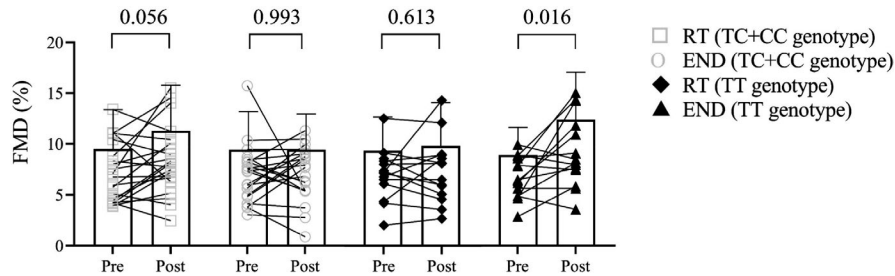
after END only in the TT genotype (time effect:  $p = 0.016$ ), and a strong tendency after RT only in the TC/CC genotype ( $p = 0.056$ ) (Figure 3).

## 4 | DISCUSSION

To the best of our knowledge, this study represents the first cross-over study in humans directly comparing the effects of endurance exercise training versus resistance exercise



**FIGURE 2** Individuals changes in flow-mediated dilation in the END (A), RT (B) modality, and combined (C).  $\Delta$ , Change, post-pre; FMD, Flow-mediated dilation; END, Endurance training; RT, Resistance training



**FIGURE 3** Group and individual flow-mediated dilation responses. FMD, Flow-mediated dilation; RT, Resistance training; END, Endurance training. Interaction-effect:  $P=0.04$ , using a three-way ANOVA with repeated measures (time  $\times$  modality  $\times$  genotypes). P-values represent the paired  $t$ -tests for each modality in each genotype. Error bars represent SD

training on vascular function within the same individuals. It is also the first to explore whether genetic variation can explain any intra- and inter-individual variability in vascular function following different exercise modalities. First, we found that both modalities were effective, with improved muscle strength after RT and increased aerobic fitness following END. This observation highlights the distinct effects of both types of exercise training on fitness-related outcomes. Second, both types of exercise training improved brachial artery function. Although group-based comparisons indicated a comparable effect of both types of exercise training, intra-individual changes in vascular function showed no relationship between both types of training regarding the change in FMD. Third, the strong intra-individual variation in improvement in vascular function to endurance versus resistance training was associated with the *NOS3* rs2070744 SNP. Taken together, our data present evidence for strong intra-individual differences regarding the changes in vascular function following endurance versus resistance training in healthy young men. This suggests a role for personalized prescription of exercise training to maximize the benefits of exercise training at an individual level.

In our cross-over designed study, we observed no differences in the increase in FMD after 4-weeks' RT vs. END, which is in concordance with other studies with a *between* group design.<sup>10</sup> In a previous meta-analysis,<sup>10</sup> 12 weeks' training improved FMD without any difference between both modalities (RT or END), which is in line with our study (albeit using a different study design). Similarly to what we reported with FMD, effects of END and RT do not differ for changes in blood pressure,<sup>6</sup> brain natriuretic peptide (BNP), N-terminal portion BNP,<sup>26</sup> lipid profile,<sup>27</sup> and even morbidity and mortality.<sup>4,5</sup> Taken together, at group level, both RT and END training seem effective types of exercise to improve vascular function.

Despite both exercise modalities inducing comparable changes in FMD after 4 weeks of training, the response to both modes of training varied markedly within individuals. In fact, the change in FMD after the RT intervention was not

correlated with the change in FMD after END. In line with previous work,<sup>28</sup> including data from our group, large heterogeneity is present between individuals regarding the change in FMD to exercise training. For example, a grouped analysis of multiple exercise studies reported that 76% of the individuals (total  $n=182$ ) showed improvement while 24% showed a decrease in FMD with an identical supervised endurance-type exercise training program.<sup>29</sup> This pattern of large heterogeneity was consistent between both types of training in our study, but large improvements to END did not relate to enhanced FMD after RT.<sup>29</sup> This observation fits with a cross-over study in 91 sedentary individuals ( $42 \pm 5$  years), that reported large inter-individual differences in the improvement of peak  $\text{VO}_2$  after RT or END.<sup>30</sup> Another recent cross-over design study, comparing 3-month RT or END between twin individuals, also showed that responsiveness to training strongly varies between modalities of exercise.<sup>31</sup> It is also possible that some individuals require a greater degree dose of exercise to elicit changes.<sup>32</sup> These outcomes reinforce the presence of within-subject differences in response to different types of exercise training, which suggests a role for personalized exercise training.

FMD was similarly improved after both interventions in our study, but probably through different mechanisms. Endurance exercise is associated with a prolonged increase in blood flow to active tissues.<sup>11</sup> This results in an increase in shear stress on the vessels, a key stimulus for acute and chronic vascular adaptations.<sup>9</sup> Consequently, FMD is most likely improved by repeated episodic increases in shear stress in END, which lead to increased production of eNOS, increased anti-oxidant, and reduced markers of oxidative stress.<sup>9</sup> This in turn leads to an increased NO bioavailability, resulting in improved vasodilation in response to shear stimulus.<sup>9</sup> In fact, exercise-induced changes in shear stress provide the principal physiological stimulus to FMD adaptation.<sup>9</sup> In contrast, resistance exercise is associated with transient increases in blood pressure and local ischemia.<sup>33</sup> Therefore, transmural pressure may be a relevant physiological stimulus for adaptation in FMD in response to RT.<sup>34</sup>



Alternatively, fluctuations in shear stress, a stimulus that seems to be present with RT, were recently found to be a potential hemodynamic stimulus for adaptation in FMD.<sup>35</sup> At the very least, these observations suggest that distinct hemodynamic stimuli may underlie some of the different adaptations in FMD within individuals after both types of exercise training.<sup>9</sup> Further work is required to better understand the direct evidence of distinct adaptations within individuals to the different types of training. In addition, further work is required to see whether this relationship holds true for other markers of cardiovascular health. This is required to facilitate personalized exercise training to optimize the beneficial effects and to offer protection from disease.

Differences in genetic profile may represent another potential mechanism underpinning the intra-individual responses to different types of exercise training. This concept of genetic variation being associated with trainability has been extensively studied in relation to peak  $\text{VO}_2$ , potentially explaining up to ~50% variability in the change in peak  $\text{VO}_2$  after endurance training.<sup>36</sup> The other half includes environment factors such as training principles.<sup>31,36</sup> Interestingly, we found a three-way interaction effect for the *NOS3* rs2070744 SNP, with improvements in FMD following END but not RT in *NOS3* TT homozygotes only. In contrast, there was a strong tendency for an improvement in FMD after RT but not END in C-allele carriers (*ie*, individuals of *NOS3* TC or CC genotype). This interaction may be linked to reduced promoter activity of the *NOS3* C-allele,<sup>37</sup> due to its greater affinity for replication protein A1 (RPA1),<sup>37</sup> which inhibits *NOS3* transcription, thus limiting NO production.<sup>20</sup> As well as potentially regulating RPA1 binding, vascular shear stress (caused by END) increases *NOS3* promoter activity by causing NF- $\kappa$ B subunits p50 and p65 to bind to a shear-responsive element upstream of the *NOS3* transcription start site.<sup>38</sup> This may explain the increase in FMD in our TT homozygotes (but not TC/CC genotypes) after END. However, it is less clear why FMD tended to increase after RT only in C-allele carriers. One explanation could be linked to transmural pressure, which (rather than shear stress) is thought to regulate FMD during RT,<sup>34</sup> and may activate *NOS3* transcription independently of shear stress. Further, transmural pressure in place of shear stress may lead to a reduction in RPA1 binding, thus potentially enabling our TC/CC homozygotes to increase *NOS3* transcription (and therefore FMD) as much as our TT homozygotes following RT despite our C-allele carriers' apparent genetic disadvantage. Therefore, although the precise mechanism(s) for a *NOS3* rs2070744 genotype regulation of FMD in response to exercise modality remain(s) to be elucidated, our novel data provide evidence that they exist.

Our study has several strengths which include the cross-over design, the relation between the chronic training effects

on vascular function, the individual responses between the two different training modalities, and the exploratory association between the individual response and *NOS3* genotype. However, one important limitation relates to the difficulty to 'match' the workload or intensity between different types of exercise training. In line with this limitation, it is difficult to understand, relate, and match the hemodynamic responses as an eliciting stimulus for improvements in both types of training, given that hemodynamic response is intensity-dependant.<sup>9</sup> Moreover, we used a single joint movement resistance training exercise which is not representative of most resistance training paradigms. Although we consider that our sample was relatively large for a cross-over exercise intervention study, it may be considered small for a genetic study and independent groups should attempt to replicate our findings with larger cohorts. There is an inherent biological variation in vascular responses which may explain some of the differences between exercise modalities. However, previous work has shown that the FMD response to acute exercise is reproducible<sup>39</sup> and adherence to guidelines strongly improves reproducibility.<sup>40</sup> Nonetheless, our significant and highly novel findings may have elucidated a genetic predisposition to greater vascular adaptation to one exercise modality over another. Future studies should investigate the mechanisms linking *NOS3* rs2070744 genotype to exercise modality-specific FMD adaptation with a larger sample size. It is worth noting that in addition to genes, there are numerous other factors that can influence the response to exercise training including nutrition and sleep. Moreover, longer duration training programs and greater exercise intensity may have resulted in larger changes in many of the outcome variables. Finally, our study focused on young, healthy men only and cannot be generalized to other populations. It is possible that, as the subjects were healthy, this limited the capacity to further improve vascular function as there may be a 'ceiling effect' with lower pre-training FMD% predictive of exercise training induced changes.<sup>29</sup> Future work should look at the role of fitness, gender, aging, ethnicity, and different disease groups on these responses. However, given that many of these factors can influence genotype frequency distribution mixing, these in one study will greatly increase the noise and there is an argument for homogeneous groups in the initial studies exploring these relationships. However, the differences between both types of training should be considered when understanding the different impacts of exercise on FMD.

In conclusion, resistance and endurance training had a similar impact on vascular function when examined at a group level in healthy, young males. However, large inter- and intra-individualities were present when examining the impact of both endurance and resistance training on vascular function. In other words, individuals appear

to respond differently according to the training modality. Interestingly, these intra-individual differences in the adaptation of vascular function to endurance and resistance training seem in part to be explained through variation in the *NOS3* gene. Specifically, *NOS3* (rs2070744) TT homozygotes improved their vascular function only after endurance training, while TC/CC homozygotes showed a strong tendency to improve FMD only after resistance training. Taken together, this study highlights a potential role for personalize exercise training for the optimization of vascular health.

## 5 | PERSPECTIVES

Our results indicate that, even if vascular function improves similarly after a short-term resistance or endurance training intervention, considerable intra-individual variability occurs (ie, some people improve following one type of training but not the other), and this seems to be linked to genetic make-up (specifically variation in the *NOS3* gene). The cross-over design of our study, therefore, reinforces the implications of our findings, namely that exercise should be personalized to optimize vascular health. Considering that vascular function is a precursor of the atherosclerotic process, and that exercise training improves vascular function, personalization of exercise is also an important parameter to consider for clinical populations. Shear stress and transmural pressure are the two main mechanisms responsible for the vascular adaptation to exercise training, and future studies are needed to further understand how these vascular stimuli cause changes in vascular function after resistance versus endurance training.

### CONFLICT OF INTEREST

None to declare.

### 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 B.S. completed data collection, while E.D., R.E., B.S., and M.B. completed data analysis. 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.

### DATA AVAILABILITY STATEMENT

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

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