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Resistance-based interval exercise acutely improves endothelial function in type 2 diabetes

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Abstract

Different modes of exercise, disease, and training status can modify endothelial shear stress and result in distinct effects on endothelial function. To date, no study has examined the influence of type 2 diabetes (T2D) and training status on the acute endothelial response to different modes of interval exercise (INT). We examined the effect of a single session of resistance- and cardio-based INT compared with a time-matched control on endothelial function in 12 age-matched T2D participants, 12 untrained, and 11 trained adults (aged 56 ± 7 yr). Flow-mediated dilation (%FMD) of the brachial artery was assessed at baseline and immediately, 1, and 2 h after an acute bout of cardio interval (C-INT), resistance interval (R-INT), and seated control (CTL); these interventions were randomized and separated by ˃2 days. C-INT involved seven 1-min cycling intervals at 85% of peak power with 1-min recovery between. R-INT involved the same pattern of seven 1-min intervals using leg resistance exercises. Endothelial function (%FMD) was improved after R-INT in all groups (Condition x Time interaction, P ˂ 0.01), an effect that was most robust in T2D where %FMD was higher immediately (+4.0 ± 2.8%), 1 h (+2.5 ± 2.5%), and 2 h (+1.9 ± 1.9%) after R-INT compared with CTL (P ˂ 0.01 for all). C-INT improved %FMD in T2D at 1-h postexercise (+1.6 ± 2.2%, P = 0.03) compared with CTL. In conclusion, R-INT acutely improves endothelial function throughout the 2-h postexercise period in T2D patients. The long-term impact of resistance exercise performed in an interval pattern is warranted.

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Title: **Resistance-Based Interval Exercise Acutely Improves Endothelial Function In Type 2 Diabetes**

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Running head: **Interval Exercise and FMD**

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Abstract

Different modes of exercise, disease and training status can modify endothelial shear stress and result in distinct effects on endothelial function. To date, no study has examined the influence of type 2 diabetes (T2D) and training status on the acute endothelial response to different modes of interval exercise (INT). We examined the effect of a single session of resistance- and cardio-based INT compared to a time-matched control on endothelial function in 12 age-matched T2D participants, 12 untrained and 11 trained adults (aged 56 ± 7 y). Flow-mediated dilation (%FMD) of the brachial artery was assessed at baseline and immediately, 1 and 2 h after an acute bout of cardio interval (C-INT), resistance interval (R-INT) and seated control (CTL); these interventions were randomized and separated by > 2 days. C-INT involved 7 X 1-min cycling intervals at 85% of peak power with 1-min recovery between. R-INT involved the same pattern of 7 X 1-min intervals using leg resistance exercises. Endothelial function (%FMD) was improved after R-INT in all groups (Condition X Time interaction, $p<0.01$), an effect that was most robust in T2D where %FMD was higher immediately (+4.0 ± 2.8%), 1 h (+2.5 ± 2.5%) and 2 h (+1.9 ± 1.9%) after R-INT compared to CTL ($p<0.01$ for all). C-INT improved %FMD in T2D at 1-h post-exercise (+1.6 ± 2.2%, $p=0.03$) compared to CTL. In conclusion, R-INT acutely improves endothelial function throughout the 2 h post-exercise period in T2D patients. The long-term impact of resistance exercise performed in an interval pattern is warranted.

New & Noteworthy (50 words)

This is the first study to demonstrate improved endothelial function after an acute bout of resistance-based interval exercise. Our data indicate a potential therapeutic effect of

resistance interval exercise on endothelial function in older adults with and without type 2 diabetes. The mechanisms underlying these effects warrant further investigation.

Glossary

FMD Flow-mediated dilation
INT Interval exercise
MAP Mean arterial blood pressure
T2D Type 2 diabetes
UN-NG Normoglycemic untrained adults
TR-NG Normoglycemic highly trained adults
AUC Area under the curve
VC Vascular conductance
RPE Rate of perceived exertion

Introduction

The benefits of regular exercise are far more pervasive than the effect on traditional cardiovascular risk factors alone; improvements in endothelial function may explain a large proportion of the risk reduction (27). The endothelium plays a pivotal role regulating the many factors that determine vascular tone, tissue perfusion, coagulation and inflammation (12). Endothelial dysfunction is an early manifestation in many chronic diseases, including diabetes (20), and contributes to the ~2-4 fold greater risk of cardiovascular disease in type 2 diabetes (T2D) (20). Exercise interventions involving aerobic and resistance exercise can improve endothelial function (29, 37), a response largely mediated by acute elevations in blood flow and laminar shear stress during individual exercise bouts (41). The effect of an acute bout of cardio- or resistance-based exercise, performed in an interval pattern, on the endothelium of adults with T2D has not been investigated. It is known that different exercise modes and intensities modify the shear stress stimulus and may result in distinct responses in endothelial function (38, 41) but the impact of exercise mode, in addition to T2D or training status is unclear.

There is continued widespread interest in interval exercise (INT) because it has been shown to improve cardiometabolic health with relatively minimal time-commitment (16) (4, 46). INT alternates high and low intensity exercise periods, often in a 1:1 work:rest ratio (14, 46). This pattern of exercise may be attractive and makes vigorous exercise attainable for most individuals because it incorporates built in rest/recovery periods (14). A single session of INT has been shown to improve endothelial function in coronary artery disease patients (aged ~66 y) (10) and lower 24 h glucose in T2D (15). Resistance

exercise may be more effective than cardio for improving vascular function and remodeling (35, 37, 44), although this is not a universal finding (32). Resistance and cardio exercise can be effectively performed as INT; for example, in insulin resistant individuals combined resistance- and cardio-based interval exercise was just as effective as cardio-based INT for improving glucose control (13). It is possible that the addition of resistance exercise to the oscillatory pattern of high- and low-intensity INT exercise may offer a prophylactic effect on the vasculature (47). Despite this, no study has investigated the effects of leg resistance INT alone and most of the literature has investigated the endothelial responses after cardio-based continuous exercise [reviewed in: (11)].

In addition to exercise parameters, inconsistent findings surrounding acute exercise and endothelial function [reviewed in: (11)] may be due to vascular risk factors (e.g., T2D) and/or training status. For example, Hallmark et al. (21) found that while high-intensity exercise improved endothelial function in lean adults, there was no effect in obese adults (21). Similarly, in inactive overweight men endothelial function was decreased after exercise, independent of exercise intensity, compared to an increase in active overweight men (22). These studies suggest that presence of vascular risk factors and/or habitual activity levels may modulate the impact of acute exercise on endothelial function.

Given the clinical and functional importance of changes in endothelial function, we sought to examine the effect of two common exercise modes performed as INT in age matched T2D, untrained, and highly-trained normoglycemic adults. The primary purpose was to examine the effects of cardio- and resistance-INT on endothelial function

measured by flow-mediated dilation. The secondary aim was to examine the influence of INT mode on shear stress, blood flow and blood pressure. We tested the hypothesis that both acute cardio- and resistance-INT would lead to improvements in endothelial function compared to a time-matched control.

Methods

Study overview and pre-screening

A randomized crossover design was used to compare the vascular response to cardio-INT (C-INT) and resistance-INT (R-INT) relative to a time-matched control condition (CTL) in age-matched T2D, normoglycemic adults who met current physical activity guidelines but were not participating in a structured exercise training program (UN-NG), and highly-trained normoglycemic adults (TR-NG). The study protocol was approved by the University of British Columbia Clinical Research Ethics Board and all participants provided written informed consent. Prior to participation T2D participants were screened using a 12-lead ECG exercise stress test and cleared for vigorous exercise by a cardiologist. All participants then completed a maximal exercise test on a cycle ergometer to determine cardiorespiratory fitness ($\dot{V}O_{2\ peak}$). The T2D patients had been familiarized with six sessions of exercise (two R-INT and four C-INT sessions involving 4-6 X 1-min intervals at a rating of perceived exertion [RPE] corresponding to ~5 on the CR-10 scale (6)) across two weeks in order to introduce them to INT and build up to the exercise protocols for testing days. Baseline investigations were performed after 48 h of rest from a previous exercise session to avoid the acute effects of exercise on baseline

147 values. UN-NG and TR-NG maintained their typical physical activity habits throughout
148 the study but similar to T2D participants refrained from exercise for 48 h prior to testing
149 sessions. UN-NG and TR-NG were screened using a Physical Activity Readiness
150 Questionnaire-Plus (PAR-Q+) and a health-screening questionnaire that included a Godin
151 Leisure Time Physical Activity Questionnaire. TR-NG were defined by completing >7
152 hours of endurance training per week and were in the >80th percentile for age- and
153 gender-adjusted $\dot{V}O_{2\ peak}$ based on data from the NHANES and Aerobics Centre
154 Longitudinal Study (5, 7, 31) (range 37-63 mL/kg/min). UN-NG self-reported performing
155 213 ± 145 min/wk of light and/or 115 ± 145 min/wk of moderate physical activity (42)
156 and had a $\dot{V}O_{2\ peak}$ in the 20-50th percentile (range 20-35 mL/kg/min).
157
158 *Participants*
159 Thirty-five participants (40% male, 60% female, average age 56 ± 7 y, range 40-66 y)
160 volunteered to participate and completed two initial and three experimental testing
161 sessions. Baseline characteristics of participants in the three groups are shown in Table 1.
162 All participants were non-smoking and were instructed to replicate any vitamin or
163 supplement intake exactly prior to each experimental session (verified by food records
164 and interviews). T2D participants were on stable medications and were physician
165 diagnosed for at least six months (range 2-17 y) prior to the study, they were well
166 controlled (HbA1c <8.0%) and not on exogenous insulin. In addition, exclusion criteria
167 included diagnosed diabetic neuropathy, chronic kidney disease, heart and coronary
168 artery disease and any other contraindication to vigorous exercise. T2D participants on
169 oral hypoglycemic medications followed normal prescriptions, which were replicated

exactly for all experimental sessions. Diabetes medications included; Metformin only (n=9), DPP4 inhibitor only (n=1), SGLT2 inhibitor+GLP-1 agonist (n=1), Sulfonylurea+GLP-1 agonist (n=1). Hypertensive medications included; Ace-inhibitor (n=7), Angiotensin receptor blocker (n=2), calcium channel blocker (n=1). All non-T2D participants were free from any diagnosed chronic disease and not taking medications, except one participant in the UN-NG group who was taking 5 mg of felodipine (calcium channel blocker) daily for hereditary elevated blood pressure. All females were postmenopausal (no menstruation for >12 mo), except for two females in the TR-NG group.

Experimental protocol (*Figure 1*)

Pre testing

Height and weight were measured using a stadiometer and balance beam scale (Seca 700, Hamburg, Deutschland) and body composition assessed by DXA (Hologic Discovery DXA, MA, USA). A maximal incremental exercise test (increasing 1W every 4 s) to volitional exhaustion was performed on an electronically braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands) to determine maximal oxygen uptake ($\dot{V}O_{2\ peak}$), heart rate (HR_{peak}), and power output (W_{peak}). The test began at 30 W for T2D and UN-NG participants and 100 W for TR-NG participants.

Experimental trials

Participants completed three, 3-h experimental trials in a randomized order with at least 48 h recovery between (Figure 1). Exercise was controlled for 48 h prior to each trial, which began at either 1100 or 1600 (same time within participants) 4 h after consumption

of a standardized meal. No food or drink other than water was consumed throughout the trial. Physiological measures were taken at baseline, immediately (within 5 min), 1 and 2 h after exercise/sitting-control. Between measurements participants remained in the lab in a resting seated position. Baseline measurements for each experimental trial were taken after 15 min of supine rest. All measurements were performed in a temperature controlled, quiet and dimly lit room.

Cardio-based interval exercise (C-INT)

All participants completed 7 X 1-min intervals on the aforementioned cycle ergometer at 85% W_{peak}, alternated with 1-min recovery at 15% W_{peak} (Figure 1). Participants were instructed to increase their cadence to between 80-100 revolutions per minute (rpm) during the vigorous intervals. Heart rate (continuous 12-lead ECG), manual blood pressure (obtained in last 30-s of alternate work and rest intervals) and RPE (6) were recorded at the end of each interval.

Resistance-based interval exercise (R-INT)

All participants completed 7 X 1-min intervals of leg resistance exercise with 1-min recovery; with matched duration, pattern and muscle groups as C-INT (Figure 1). Familiarization for the three leg resistance exercises involved one set of 6-8 repetitions using a weight selected out of three levels consisting of 5 lb increments. The participants were asked if they could complete this exercise for 1-min based on an RPE of ~5 ('hard') such that they were able complete each 1-min interval. For each 1-min 'hard' interval participants completed as many reps as possible of each exercise, alternated with 1-min

recovery where participants walked to the next exercise station. Resistance level, repetitions, heart rate, blood pressure and RPE were recorded for each interval. This R-INT protocol was designed to target the same major muscle groups in a similar 1-min on:off pattern as C-INT, while eliciting a similar RPE (Table 2). Blood pressure (manual BP in last 30-s of each 1-min interval), heart rate (Polar H1, Kempele, Finland), and RPE were recorded in the last 10-s of each interval. Both exercise protocols began with a 3 min warm-up and ended with a 3 min cool-down performed on a cycle ergometer at a self-selected pace (rpm) at 30-50 W.

Control condition (CTL)

In the control condition participants sat upright for 20 minutes in place of the exercise time. Everything else including activity between the measurements and the timing thereof was the same as the exercise trials (Figure 1).

Physiological Measures

Flow-mediated dilation (FMD)

Brachial artery FMD was examined as an index of endothelial function using high-resolution ultrasound (Terason 3200) as per published guidelines (9, 39). Briefly, the right arm of each participant was extended 80° from the torso and a longitudinal image of the artery was obtained 2-3 cm from the antecubital fossa. A rapid inflation and deflation cuff was positioned on the forearm 1-2 cm distal from the olecranon process. Once the image was optimized in B-mode, simultaneous B-mode image and Doppler velocity

241 measurements (insonation angle maintained at 60°) were obtained. Ultrasound data was
242 recorded for a 1-min baseline, 30 s before cuff deflation and continued for 3 min
243 thereafter. The cuff was inflated to >60 mmHg above systolic blood pressure for 5-min to
244 induce forearm ischemia and the subsequent hyperemic stimulus. Probe placement and
245 ultrasound settings were maintained for each participant across each experimental trial.
246 Heart rate (single-lead ECG) and brachial blood pressure (manual sphygmomanometer)
247 were measured before each FMD measurement (Figure 1). Mean arterial blood pressure
248 (MAP) was calculated as 1/3*systolic blood pressure (SBP) + 2/3*diastolic blood
249 pressure (DBP).
250
251 *Brachial artery diameter and blood flow analysis*
252 Analyses of brachial artery diameter and blood velocity measures were performed using
253 edge detection software, which reduces user bias and increases accuracy (19, 48). Blood
254 flow ($mL.min^{-1}$) was calculated from the product of cross-sectional area and Doppler
255 velocity ((velocity*π*(diameter^2/4)*60) and shear rate (s^{-1}) was calculated as (four times
256 velocity/diameter) from synchronized diameter and velocity recordings (19). The shear
257 rate area under the curve (SRAUC) for the hyperemic stimulus was calculated from
258 simultaneous diameter and velocity data from cuff release to peak arterial dilation.
259 Baseline antegrade and retrograde shear rates (s^{-1}) were calculated from antegrade and
260 retrograde mean blood velocities (four times mean baseline antegrade or retrograde
261 velocity ÷ mean baseline diameter). Vascular conductance ($mL.min^{-1}.mmHg^{-1}$) was
262 calculated as the ratio of mean blood flow to mean arterial pressure. The coefficients of
263 variation of brachial artery diameter and %FMD were 2.1% and 7.3%, respectively,

based on baseline measurements pre-exercise between experimental trials.

FMD is expressed as the absolute change in artery diameter (absolute FMD = $postocclusion_{peak\ diameter}$ - $preocclusion_{mean\ diameter}$), the percent change in artery diameter from baseline (%FMD = 100*(absolute FMD/$preocclusion_{mean\ diameter}$), and to adjust for the potential confounder of baseline diameter (D_{base}) allometric scaling was used (D_{base} – adjusted FMD) (2, 39).

Statistics

Statistical analyses were performed using SPSS 22.0 (SPSS, Chicago, Illinois). One-way ANOVA was used to examine baseline differences between groups. A 3-factor (Group X Condition X Time) ANOVA with repeated measures on condition and time were used to assess significant differences between groups and conditions across time. Post-hoc analyses with Bonferonni corrections were used to evaluate significant interactions and main effects (using $p < 0.05$). Specifically, significant Group X Condition X Time interactions or Condition X Time interactions were probed for differences within groups between R-INT and C-INT, relative to CTL, at each time point. All data were first tested for normality and are reported as mean and standard deviation (SD). For the primary outcome of %FMD, and for MAP, magnitude-based inference analyses were performed according to contemporary views on statistical reporting, allowing for clinically meaningful inference (3). For this, the spreadsheet for confidence limits and inferences was downloaded from www.newstats.org. The smallest clinically beneficial threshold for %FMD was +1%, based on a recent meta-analyses which showed a 13% reduced risk of future cardiovascular events for every 1% improvement in %FMD (95% CI: 9% to 17%)

(23). In line with previous studies, a 2 mm Hg reduction in MAP was considered to be the smallest clinical threshold change for blood pressure (8).

Results

Characteristics of C-INT and R-INT exercise sessions

Participants successfully completed both the C-INT and R-INT protocols with no reports of discomfort or excessive changes in blood pressure. All participants completed 7 X 1-min intervals; however, for C-INT two T2D participants and one UN-NG participant reduced their workload by 10 W for the final two or three 1-min intervals because their RPE was >8 and HR was >95% of maximum. Analyses performed with and without the two non-postmenopausal women were not significantly different and did not change the interpretation of the results. Peak heart rate during the C-INT intervals was higher than R-INT ($p=0.01$), with no difference between groups (Table 2). Diastolic blood pressure was significantly higher during R-INT compared to C-INT ($p<0.01$) and in T2D participants compared to UN-NG and TR-NG ($p<0.01$, Table 2). Systolic blood pressure did not significantly differ between C-INT and R-INT exercise protocols or between groups (Table 2).

Brachial artery %FMD

There was a significant Group X Condition X Time interaction for %FMD (Figure 2, $p<0.01$). No change in %FMD was seen across time in CTL nor was it significantly different at baseline between trials within-individuals. TR-NG had a higher baseline %FMD (average of three pre-measures) than UN-NG (7.8 ± 2.2% vs. 6.6 ± 2.3%, $p=0.03$) and T2D (5.7 ± 1.6%, $p=0.01$), with no difference between T2D and UN-NG

311 (p=0.32). When adjusted for baseline diameter using allometric scaling (D_{base}-adjusted
312 FMD) there was a significant difference between groups at baseline (TR-NG: 7.7 ± 2.2%
313 vs. UN-NG: 6.6 ± 2.5% vs. T2D: 5.3 ± 1.4%, all $p<0.05$).
314 *T2D:* Post-hoc and inferential analyses indicated that in T2D %FMD was significantly
315 higher immediately (95% Confidence Interval: 3.0 to 5.9%), 1 h (CI: 0.8 to 4.2%), and 2
316 h (CI: 0.7 to 3.1%) after R-INT compared to CTL; the probability that these effects were
317 most likely beneficial/negligible/harmful were 100/0/0%, 96/4/0% and 94/6/0%,
318 respectively. After C-INT compared to CTL, %FMD in T2D was unchanged immediately
319 (CI: -0.5 to 3.1%), higher at 1 h (CI: 0.2 to 3.0%) and unchanged 2 h (CI: -4.5 to 4.3%)
320 following exercise; probability of beneficial/negligible/harmful were 64/35/1%,
321 81/19/0%, and 30/37/33%, respectively.
322 *UN-NG:* %FMD after R-INT in UN-NG was unchanged immediately (CI: -5.1 to
323 4.5%) and 1 h (CI: 0.3 to 2.8%), and higher 2 h following exercise (CI: 0.38 to 5.5%)
324 compared to CTL; probability of beneficial/negligible/harmful were 28/34/38%,
325 64/35/0.4% and 94/6.0/0.3%, respectively. After C-INT compared to CTL %FMD in UN-
326 NG was unchanged immediately (CI: -0.08 to 0.10%), 1 h (CI: -0.6 to 3.2%) and 2 h (CI:
327 -0.06 to 0.02%) following exercise; probability of beneficial/negligible/harmful were
328 0/100/0%, 63/36/1% and 0/100/0%, respectively.
329 *TR-NG:* %FMD after R-INT in TR-NG was unchanged immediately (CI: -0.48 to
330 0.12%), but higher 1 h (CI: 0.36 to 2.0%) and 2 h following (CI: 1.2 to 2.8%) compared
331 to CTL; probability of beneficial/negligible/harmful were 0/100/0%, 68/32/0% and
332 99/1/0%, respectively. After C-INT compared to CTL %FMD in TR-NG was unchanged
333 immediately (CI: -0.3 to 3.6%), and 1 h (CI: -0.4 to 3.6%) and higher 2 h (CI: 1.4 to

334 3.4%) following; probability of beneficial/negligible/harmful were 74/25/1%, 74/25/1%
335 and 99/1/0%, respectively.
336
337 **Absolute FMD (mm), D_{base} – adjusted FMD and Shear rate AUC**
338 There was a Condition X Group interaction (Figure 2, p=0.05) for absolute FMD (mm).
339 Post-hoc analyses indicated that in T2D absolute FMD was higher immediately after R-
340 INT compared to CTL (p=0.03). In TR-NG participants absolute FMD was higher1 h
341 (p=0.02) and 2 h (p=0.01) following R-INT compared to CTL, and higher 2 h (p=0.01).
342 after C-INT compared to CTL. There was no change in absolute FMD in UN-NG
343 participants (Figure 2). There was a significant Group X Condition interaction for D_{base} –
344 adjusted FMD (Table 3, p=0.03). In T2D D_{base} – adjusted FMD was higher immediately
345 (p=0.05) and 1 h (p=0.01) after R-INT compared to CTL, and higher 1 h (p=0.01) after
346 R-INT compared to C-INT. In UN-NG and TR-NG participants there were no significant
347 differences for R-INT compared to CTL, or C-INT compared to CTL, for D_{base} – adjusted
348 FMD at any time point (Table 3). In UN-NG D_{base} – adjusted FMD was higher after R-
349 INT than C-INT immediately post-exercise (p=0.05). Time to peak diameter was not
350 significantly different between conditions or groups (data not shown).
351 There were significant Condition X Time (p<0.01) and Condition X Group interactions
352 (p=0.04) for the hyperemia induced shear rate area under the curve (SRAUC). SRAUC
353 did not change in the CTL condition and was not different pre-exercise between groups
354 or visits. Post-hoc analyses indicate significantly higher SRAUC immediately and 1 h
355 after C-INT and immediately after R-INT compared to CTL in UN-NG and TR-NG
356 participants (Figure 2, all p<0.05) but no significant changes in SRAUC were seen

comparing CTL, C-INT or R-INT at any time point in T2D participants (Figure 2).

Blood flow and shear rate

There were Condition X Time interactions (Table 3, $p<0.05$) for baseline blood flow and baseline shear rate (Figure 3, $p<0.05$). Post-hoc analyses indicate in T2D and TR-NG participants baseline shear rate was significantly higher immediately after C-INT ($p<0.05$) and R-INT ($p<0.05$), compared to CTL. There was a significant Condition X Time interaction ($p=0.05$) for antegrade shear rate. Post-hoc analyses indicate antegrade shear rate was higher in UN-NG 1 h after C-INT compared to CTL ($p=0.047$). In TR-NG participants antegrade shear rate was higher immediately after R-INT ($p<0.05$) and C-INT ($p=0.02$), compared to CTL. There was a significant Condition X Time X Group ($p=0.048$) interaction for retrograde shear rate. Post-hoc analyses indicated a significantly lower retrograde flow after R-INT ($p=0.05$) compared to CTL in UN-NG participants.

Blood Pressure and Vascular Conductance

There was a significant Condition X Time interaction (Figure 4, $p<0.01$) for Mean Arterial Blood Pressure (MAP).

T2D: Post-hoc and inferential analyses indicated that, in T2D participants, MAP after R-INT was unchanged immediately (CI: -5.6 to 0.57 mmHg), lower at 1 h (CI: -6.2 to -0.51 mmHg), and 2 h (CI: -5.8 to -0.03 mmHg) following exercise compared to CTL; the probability that these effects were most likely beneficial/negligible/harmful were 64/36/0.4%, 84/16/0% and 75/25/0%, respectively. After C-INT, MAP in T2D was unchanged immediately (CI: -5.7 to 0.5 mmHg), 1 h (-5.0 to 0.7 mmHg) and 2 h (CI: -3.9 to 0.5 mmHg) following compared to CTL; probability of beneficial/negligible/harmful were 66/36/0%, 55/45/0% and 39/61/0% respectively.

UN-NG: MAP after R-INT in UN-NG was unchanged immediately (CI: -6.7 to 3.7 mmHg), lower at 1 h (CI: -10 to 0.2 mmHg) and unchanged 2 h (CI: -8.5 to 2.3 mmHg) following compared to CTL; probability of beneficial/negligible/harmful were 42/50/8%, 89/11/0% and 70/30/3%, respectively. After C-INT exercise compared to CTL MAP in UN-NG was lower immediately (CI: -12 to -1 mmHg), 1 h (CI: -9.9 to -1.9 mmHg) and 2 h (CI: -9.4 to -1.4 mmHg) following; probability of beneficial/negligible/harmful were 95/5/0%, 97/3/0% and 96/4/0%, respectively.

TR-NG: MAP after R-INT in TR-NG was unchanged immediately (CI: -11 to 6.5 mmHg), 1 h (CI: -11 to 5.5 mmHg) and 2 h (CI: -13 to 8.3 mmHg) following compared to CTL; probability of beneficial/negligible/harmful were 54/31/15%, 56/32/12% and 51/29/20%, respectively. After C-INT compared to CTL, MAP in TR-NG was unchanged immediately (CI: -3.7 to 0.3 mmHg), 1 h (CI: -4.1 to 0.7 mmHg) and 2 h (CI: -1.7 to 0.2 mmHg) following; probability of beneficial/negligible/harmful were 38/63/0%, 40/60/0% and 1/99/0%, respectively.

There were significant Condition X Time interactions for both SBP ($P<0.01$) and DBP ($p=0.01$; Table 3). There was a significant Condition X Time interaction (Figure 4, $p=0.05$) for Vascular Conductance (VC). Post-hoc analyses indicate in T2D and TR-NG participants VC was higher immediately after R-INT and C-INT (all $p<0.03$) compared to CTL. In UN-NG participants VC was higher 1 h ($p=0.03$) and 2 h ($p=0.04$) after C-INT compared to CTL.

Discussion

The main novel finding of this study is that resistance interval exercise (R-INT) acutely improves brachial artery endothelial function in age-matched T2D, UN-NG and TR-NG participants. In T2D participants, %FMD was 4, 2 and 2% higher respectively immediately, one and two hours after R-INT compared to CTL. In UN-NG and TR-NG participants, %FMD was not changed immediately after but was 2-4% higher at one and/or two hours after R-INT exercise. %FMD was higher two hours after C-INT in TR-NG participants and one hour after C-INT in T2D, compared to CTL. The exercise-induced increases in blood flow and shear stress were similar following R-INT and C-INT, suggesting that these parameters did not fully explain the differential improvements in endothelial function. In contrast to previous research on continuous high-intensity exercise (1, 11, 25), we found no evidence of a transient period of FMD impairment following INT. These findings are important given the increasing popularity of interval exercise in clinical and non-clinical populations. Our data indicate a potential therapeutic effect of leg resistance exercise performed as INT for improving endothelial function, particularly in people with T2D. These findings warrant the examination of the long-term impact of R-INT on vascular function.

Effect of Acute Resistance INT on FMD

When compared to a time-matched seated control condition, R-INT led to higher %FMD at all time points after exercise in T2D and one and two hours following R-INT in UN-NG and TR-NG participants. To the best of our knowledge this is the first study to show

improved endothelial function after an acute bout of resistance type exercise. The favorable effect of R-INT for T2D and UN-NG participants may be attributed to the pattern of shear stress during resistance-based leg exercise. Indeed, it is known shear rate patterns *during* exercise modulate changes in endothelial function after exercise (40). Unfortunately due to technical limitations of obtaining quality images using vascular ultrasound we were not able to measure blood flow and shear rate during exercise. However, diastolic and mean arterial blood pressures were higher during R-INT compared to C-INT, suggesting the potential for greater hemodynamic-mediated shear stress during R-INT. Previous work has demonstrated that changes in endothelium-dependent dilation depend on combined increases in blood pressure and heart rate, not heart rate alone (18). However, whether there is an upper threshold for beneficial increases in pulse pressure and rate during exercise is unknown. Previous studies have shown higher exercise blood pressure with greater intensities of handgrip exercise impairs local vascular function (17, 30, 33). In the current study endothelial-dependent dilation was consistently improved after R-INT, despite significantly elevated MAP, however the increase in MAP was ~50% lower than Okomoto et al. (33) after handgrip exercise (peak change in MAP +17 mmHg in T2D). Discrepancies in the endothelial response to resistance exercise in our study compared to others (17, 30, 33) may also be attributed to the dynamic interval nature of the resistance exercise used in the current study, which involved a light load lifted for many repetitions (37 ± 12 reps/min) to induce fatigue and a perceived effort of 'hard' (RPE of ~5) in the last 10-s of each 1-min interval, which was followed by 1-min of recovery each time. Additionally endothelial

function was measured away from the active muscle bed and it has previously been shown that upper, but not lower, limb resistance exercise increases arterial stiffness (34).

Other potential mechanisms mediating FMD responses to INT

The underlying factors modulating the changes in endothelium-dependent vasodilation after INT remain unclear. Due to the systemic nature of exercise, including interval exercise, various neurogenic, local and hormonal stimuli may determine endothelial function. In the current study, blood flow, SRAUC (shear stimulus), baseline mean and antegrade shear rates were elevated after both C-INT and R-INT exercise. The largest increases in blood flow and shear rate were immediately after exercise (excluding during exercise), with a time dependent return to baseline when measured again 1 and 2 h after exercise. Shear stress is a potent stimulator of nitric oxide production and improves endothelial-dependent dilation *in vivo* and *in vitro* (40). The elevated SRAUC after C-INT and R-INT relative to CTL was lower in T2D than TR-NG and UN-NG participants (Figure 2), but the changes in baseline blood flow, mean, antegrade and retrograde shear rates were similar between groups and after C-INT and R-INT (Figure 3). Similar to previous research (28) we saw no relationship between SRAUC and FMD after exercise ($r=0.00$, $p=0.95$). In the current study the largest improvements in FMD were seen when the hyperemic and baseline shear rate had returned near pre-exercise levels (Figure 2). Elevated blood flow, shear rate, and SRAUC provide a strong stimulus for increasing endothelial nitric oxide production, mediating vasodilation (40). It is plausible that the subsequent post-occlusion hyperemia immediately after exercise may not be able to cause further vasodilation as it may already be near maximally stimulated. This may explain

why in the current study most improvements in endothelial function were seen one and/or two hours into recovery.

Time-course and mediators of the FMD response to INT

It is generally reported that vigorous activities (>80% $\dot{V}O_{2\ peak}$) result in a transient depression in FMD immediately after exercise (1, 11, 25). The current study saw no significant reduction in FMD after INT when performed as cardio or resistance exercise. It is thought that the transient reduction in FMD after high-intensity exercise is due to elevated sympathetic activity, changes in arterial diameter and/or oxidative stress [reviewed in: (11)]. The consistent improvements seen one/two hours compared to immediately after INT in the current study may be due to reduced sympathetic activity one/two hours post-exercise and hence an improved vasodilator response. Meaningful reductions in blood pressure were seen in UN-NG participants across the two hours after C-INT and R-INT. In addition vascular conductance was improved immediately after exercise in all groups. The sustained hyperemia after INT in the current study is an important finding and may reflect a longer lasting stimulus for favorable artery remodeling and function (41). Importantly, this response was similar in T2D, UN-NG and TR-NG participants.

Potential influence of training status

In TR-NG participants endothelial function was improved two hours after C-INT, and one and two hours after R-INT. In contrast %FMD was only significantly improved two hours after R-INT in UN-NG participants. This finding is in agreement with others (22,

45), who show cardio-based exercise consistently improves FMD in more active participants compared to less active participants. Improvements in %FMD after both R-INT and C-INT in highly trained participants may be due to a higher antioxidant capacity to scavenge oxidants produced during high-intensity exercise, thereby increasing nitric oxide bioavailability (24). It is also important to note that the highly-trained TR-NG participants in the current study performed a greater volume of exercise (higher absolute intensity but same relative intensity), for example 85% of W_{peak} for TR-NG participants was +119 W greater than T2D and +94 W greater than UN-NG participants. Although we cannot rule out any influence of higher total work, previous studies have shown the acute endothelial response does not appear to be mediated by total energy use (10, 22). Indeed Currie et al. (10) showed that %FMD was improved similarly after continuous and INT exercise, despite ~50% lower total work for INT exercise. It is inherently difficult to match the work between groups and between resistance and cardio-based exercise. Matching the muscles used and the time and pattern of exercise was deemed more important and appropriate for this study.

Study Limitations

A consideration in the current study is that we did not measure endothelial-independent dilation (vascular smooth muscle function). However, previous studies, including two after INT exercise, show there is no change in endothelial-independent dilation following an acute bout of exercise (10, 25, 30, 40, 43). The current study design precluded endothelial-independent dilation measures to avoid potential confounding factors of

repeated maximal stimulations with nitroglycerin and interactions with exercise over time.

The groups in this study are matched by age only, therefore we cannot rule out any influence of body mass, medications or long-term diet on blood flow and endothelial responses to exercise. Age was considered by the authors to be the most important and pragmatic variable to match whilst examining whether the presence of T2D and/or fitness (training status) influenced the changes in endothelial function after two modes of acute interval exercise. It would be quite difficult to find obese adults with no metabolic or cardiovascular risk factors that engaged in 2.5-5 hours and >7 hours of exercise training per week so groups were matched on age only.

Increases in blood flow and shear rate during exercise can cause vasodilation through local regulatory mechanisms that may influence baseline diameter, which may confound the %FMD calculation (36). To adjust for changes in baseline diameter allometric scaling was used according to current recommendations (2). The same significant relationship as %FMD was seen for FMD corrected for diameter in T2D after R-INT. However, for TR-NG participants the changes in FMD after R-INT and C-INT when corrected for diameter were no longer significant, despite similar trends as %FMD.

It is important to note that the T2D participants had completed a brief familiarization period prior to these acute investigations, as they were participating in a longer-term study (NCT02251301). This involved six sessions of INT; 4 X 1-min intervals eliciting an RPE of ~5 were performed in the first three sessions, thereafter the number increased by one interval each session until they reached 6 intervals. This was deemed necessary to ensure the T2D participants could complete 7 X 1-min interval sessions, were

accustomed to this type of vigorous exercise, and did not experience any abnormal HR or blood pressure responses to INT. Endothelial function measured before and after the two-week habituation period was unchanged (+0.5 ± 2.4%, p=0.50, data not shown), however the endothelial responses seen in the current study may not generalize to inactive T2D participants or those completely naïve to INT.

Conclusions

In conclusion, this study shows that resistance-based interval exercise is a time-efficient and effective exercise method to acutely improve endothelial function in T2D, age-matched UN-NG and TR-NG participants. This is the first study to investigate the acute effect of this novel form of INT and demonstrates its potential utility in older adults with and without T2D. Although the mechanisms underlying the changes in endothelial function with cardio- and resistance-based INT are unclear, the pattern of high-and low-intensity exercise stimulates an increase in blood flow and shear rate post-exercise and did not cause a transient decrease in endothelial function as found previously for continuous vigorous exercise. The chronic effects of repeated resistance-based versus cardio-based INT warrants investigation to elucidate whether these acute responses transpire to long-term vascular adaptations in these groups.

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Figures

Figure 1. Schematic illustrating the timeline of the experimental trials; including a figure illustrating the cardio-based (C-INT) and resistance-based (R-INT) interval exercise protocols which were performed in a random order with a sitting-control condition (CTL). Flow-mediated dilation and blood pressure were measured before (Pre), immediately (0), 1 and 2 hours after each experimental trial.

Figure 2. %FMD, Absolute FMD (mm), and shear rate AUC before, immediately, 1 h and 2 h (mean ± SD) after control (CTL), resistance interval exercise (R-INT) and cardio interval exercise C-INT in type 2 diabetes (T2D: A, D, G), age-matched untrained normoglycemic (UN-NG: B, E, H) and highly-trained normoglycemic (TR-NG: C, F, I) participants. * $p < 0.05$ compared to CTL.

Figure 3. Baseline mean (lines), antegrade and retrograde shear rate ($s^{-1;}$ bars) before, immediately, 1 h and 2 h after control (CTL), C-INT and R-INT for T2D (A), UN-NG (B) and TR-NG (C) participants. * $p < 0.05$ compared to CTL.

Figure 4. Mean arterial blood pressure (MAP) and vascular conductance before, immediately, 1 h and 2 h after control, C-INT and R-INT in T2D (A, D), age-matched UN-NG (B, E) and TR-NG (C, F) participants. * $p < 0.05$ compared to CTL.

Tables

Table 1. Baseline characteristics of type 2 diabetes (T2D), untrained normoglycemic (UN-NG) and trained normoglycemic (TR-NG) adults.

	T2D	**UN-NG**	**TR-NG**
n=	12 (6 males)	12 (6 males)	11 (7 males)
Age (y)	57.5 ± 5.0	55.3 ± 9.1	55.1 ± 7.0
BMI (kg/m^2)	35 ± 7	26 ± 5	23 ± 3*
Body fat (%)	32.4 ± 7.5	23.9 ± 4.2*	15.8 ± 5.9*†
$\dot{V}O_{2\ peak}$ (mL/kg/min)	19 ± 4†	29 ± 6*	45 ± 7*†

HR_{peak} (bpm)	161 ± 12	160 ± 20	170 ± 9

595 Values are mean ± SD. * $p < 0.05$ vs. T2D. † $p < 0.05$ vs. UN-NG. BMI = body mass
596 index, HR_{peak} = maximal heart rate, $\dot{V}O_{2\ peak}$ = cardiorespiratory fitness.
597

598

599 *Table 2.* Blood pressure, heart rate and RPE during the high-intensity intervals for cardio
600 and Resistance INT (R-INT) for type 2 diabetes (T2D), UN-NG and TR-NG participants.

	C-INT			**R-INT**		
Variables	**T2D**	**UN-NG**	**TR -NG**	**T2D**	**UN-NG**	**TR-NG**
Rating of perceived exertion	5 ± 1	5 ± 2	5 ± 1	5 ± 2	5 ± 2	5 ± 1
% of HR_{peak}	88 ± 6 †	90 ± 6 †	87 ± 6 †	67 ± 7	70 ± 10	64 ± 8
Systolic Blood Pressure (mmHg)	192 ± 15	177 ± 18	174 ± 16	196 ± 18	178 ± 25	191 ± 24
Diastolic Blood Pressure (mmHg)	87 ± 6	79 ± 3*	77 ± 8*	95 ± 6†	87 ± 6†	90 ± 6†

601 Values are mean ± SD. T2D = Type 2 diabetes, CTL = Control, C-INT = cardio-based interval
602 exercise, R-INT = Resistance-based interval exercise RPE= rate of perceived exertion, * $p < 0.05$
603 vs. T2D. † $p < 0.05$ vs. C-INT, HR_{peak} = maximal heart rate.

Table 3. Flow-mediated dilation and hemodynamic responses across time during the sitting-control (CTL), acute cardio-based and resistance-based INT conditions in T2D, age-matched untrained (UN-NG) and trained normoglycemic (TR-NG) participants.

	CTL				C-INT				R-INT			
	Baseline	**Immed-ex**	**1 hour**	**2 hour**	**Baseline**	**Immed-ex**	**1 hour**	**2 hour**	**Baseline**	**Immed-ex**	**1 hour**	**2 hour**
T2D												
Baseline diameter (mm)	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 1.0	4.3 ± 0.9	4.4 ± 0.9	4.4 ± 1.0	4.4 ± 1.0	4.3 ± 1.0	4.3 ± 0.8	4.2 ± 0.9	4.3 ± 0.9	4.2 ± 1.0
Peak Diameter (mm)	4.5 ± 0.9	4.6 ± 1.0	4.6 ± 1.0	4.5 ± 0.9	4.6 ± 0.9	4.7 ± 1.0	4.7 ± 1.0	4.5 ± 1.0	4.5 ± 0.8	4.6 ± 1.0	4.6 ± 1.0	4.5 ± 1.0
D_{base} –adjusted FMD	5.7 ± 1.6	5.1 ± 1.6	5.2 ± 1.3	5.6 ± 1.4	6.0 ± 2.2	7.1 ± 5.6	4.7 ± 6.2	6.8 ± 3.1	5.0 ± 1.6	8.6 ± 5.8*	9.9 ± 9.1*†	5.8 ± 5.1
Blood flow ($mL.min^{-1}$)	117 ± 55	109 ± 47	124 ± 65	117 ± 58	93 ± 26	148 ± 61*	130 ± 23	74 ± 28	93 ± 38	130 ± 62*	96 ± 36	91 ± 42
Systolic BP (mmHg)	124 ± 11	126 ± 12	128 ± 12	127 ± 11	128 ± 13	124 ± 21*	124 ± 20*	124 ± 11*	125 ± 12	125 ± 12	123 ± 9*	122 ± 7*
Diastolic BP (mmHg)	79 ± 8	81 ± 6	80 ± 7	80 ± 5	77 ± 8	76 ± 8	79 ± 6	79 ± 6	79 ± 9	78 ± 5	77 ± 5	78 ± 4
UN-NG												
Baseline diameter (mm)	4.2 ± 0.8	4.1 ± 0.8	4.1 ± 0.7	4.1 ± 0.9	4.3 ± 1.0	4.1 ± 0.9	4.2 ± 1.0	4.1 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 0.9	4.4 ± 0.9
Peak Diameter (mm)	4.5 ± 0.9	4.4 ± 0.9	4.4 ± 0.8	4.3 ± 0.9	4.6 ± 0.9	4.4 ± 0.9	4.5 ± 0.9	4.4 ± 0.9	4.5 ± 1.2	4.5 ± 1.0	4.6 ± 1.1	4.7 ± 0.9
D_{base} –adjusted FMD	6.5 ± 2.0	6.8 ± 3.1	6.2 ± 3.0	7.1 ± 2.2	6.0 ± 4.1	6.3 ± 3.6	6.0 ± 4.9	6.5 ± 3.1	7.5 ± 5.1	9.6 ± 6.2†	8.9 ± 5.1	8.8 ± 6.5
Blood flow ($mL.min^{-1}$)	102 ± 53	104 ± 65.57	94 ± 41	93 ± 56	134 ± 95	141 ± 76	160 ± 73*	138 ± 102*	100 ± 58	122 ± 44	134 ± 72	142 ± 83
Systolic BP (mmHg)	122 ± 12	124 ± 12.00	125 ± 13	125 ± 12	123 ± 10	118 ± 15	120 ± 11*	122 ± 13	123 ± 14	123 ± 15	119 ± 12*	122 ± 16
Diastolic BP (mmHg)	81 ± 7	81 ± 6	83 ± 7	82 ± 6	79 ± 5	74 ± 9*	76 ± 7*	76 ± 7*	79 ± 8	79 ± 6	78 ± 5	79 ± 8
TR-NG												
Baseline	4.4 ± 0.8	4.3 ± 0.8	4.4 ± 0.9	4.3 ± 0.8	4.2 ± 0.4	4.3 ± 0.9	4.4 ± 0.8	4.3 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 0.9	4.4 ± 0.9

diameter (mm)												
Peak Diameter (mm)	4.7 ± 0.8	4.6 ± 1.0	4.7 ± 0.9	4.7 ± 0.9	4.7 ± 0.8	4.8 ± 0.9	4.8 ± 0.9	4.8 ± 1.0	4.5 ± 0.8	4.6 ± 0.9	4.7 ± 0.9	4.7 ± 0.9
D_{base} –adjusted FMD	8.4 ± 2.0	7.7 ± 1.9	7.5 ± 2.1	7.3 ± 2.7	8.3 ± 2.0	9.2 ± 4.1	9.5 ± 2.6	10.4 ± 2.7	7.5 ± 1.9	7.1 ± 1.7	8.8 ± 2.1	9.3 ± 1.8
Blood flow ($mL.min^{-1}$)	144 ± 109	133 ± 104	139 ± 113	128 ± 98	127 ± 86	186 ± 122*	128 ± 84	100 ± 53	116 ± 64	153 ± 95*	129 ± 55	94 ± 74
Systolic BP (mmHg)	116 ± 9	114 ± 11	104 ± 34	105 ± 34	117 ± 10	109 ± 9*	101 ± 33*	101 ± 33*	113 ± 8	111 ± 6	99 ± 32*	100 ± 32*
Diastolic BP (mmHg)	74 ± 9	74 ± 8	68 ± 22	68 ± 22	77 ± 6	74 ± 6	68 ± 22	68 ± 22	74 ± 6	71 ± 7	66 ± 22	67 ± 22

Values are mean ± SD. T2D = Type 2 diabetes, CTL = sitting-control, C-INT = cardio-based interval exercise, R-INT = Resistance-based interval exercise, Immed-ex = immediately after exercise/control, FMD = Flow-mediated dilation, D_{base} –adjusted = Allometric scaled FMD to diameter, BP = Blood Pressure. * $p < 0.05$ vs. CTL. † $p < 0.05$ vs. C-INT.

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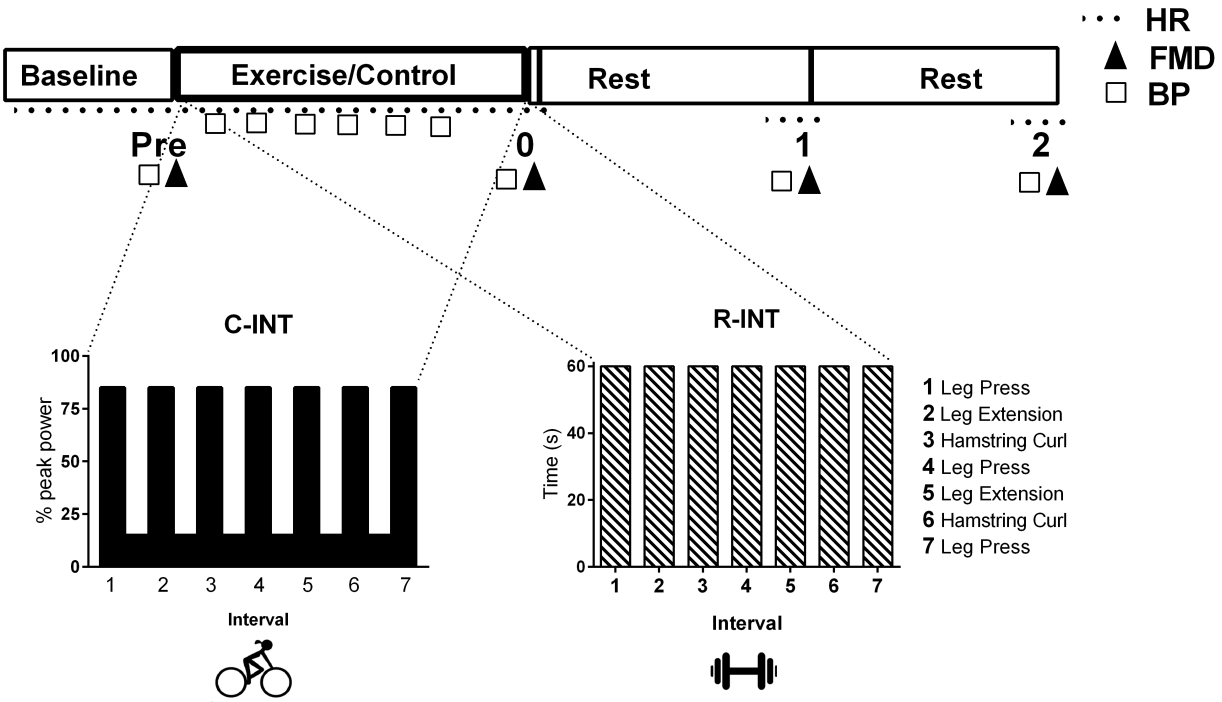
HR
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C-INT
% peak power
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1 2 3 4 5 6 7
Interval
R-INT
Time (s)
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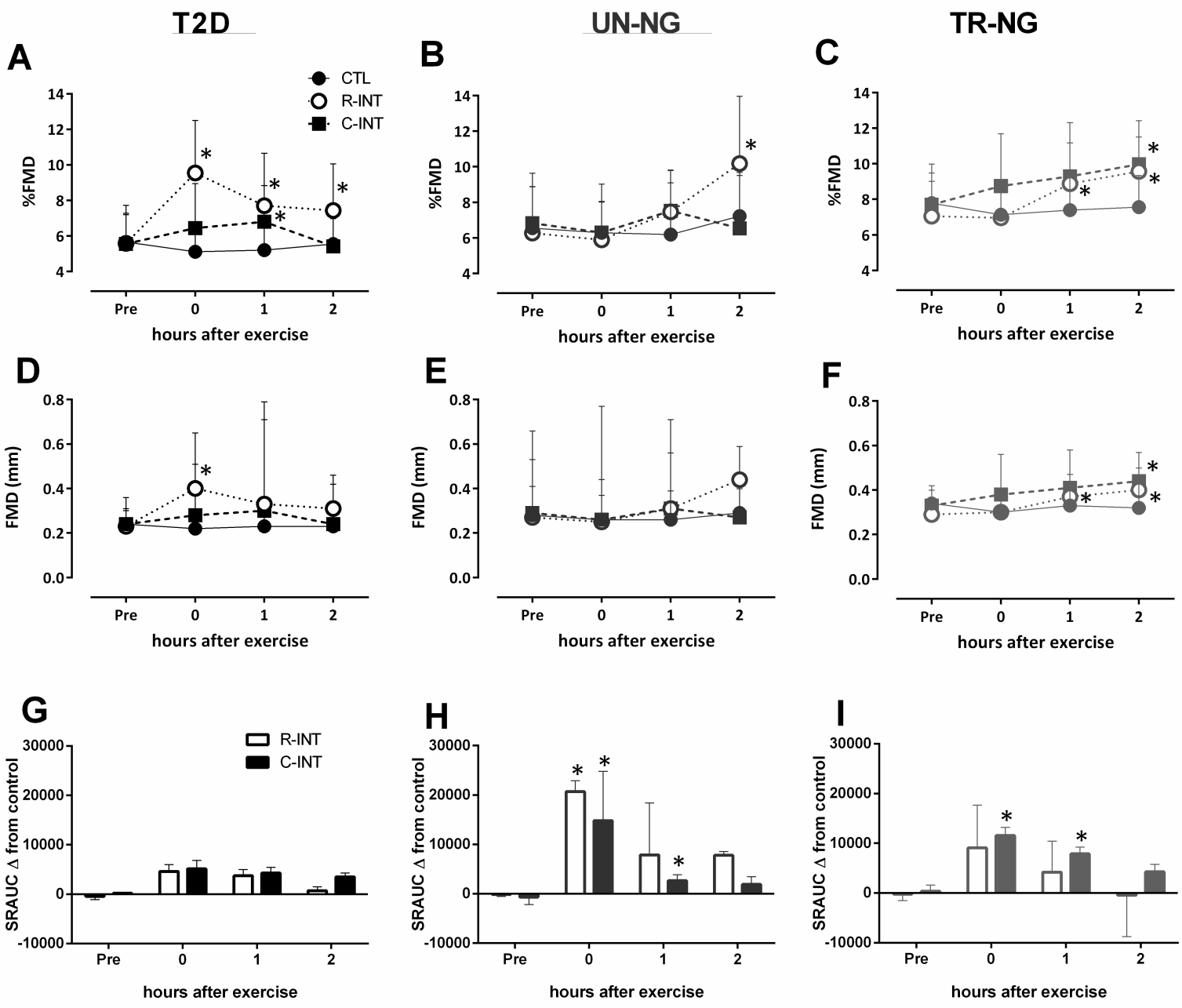
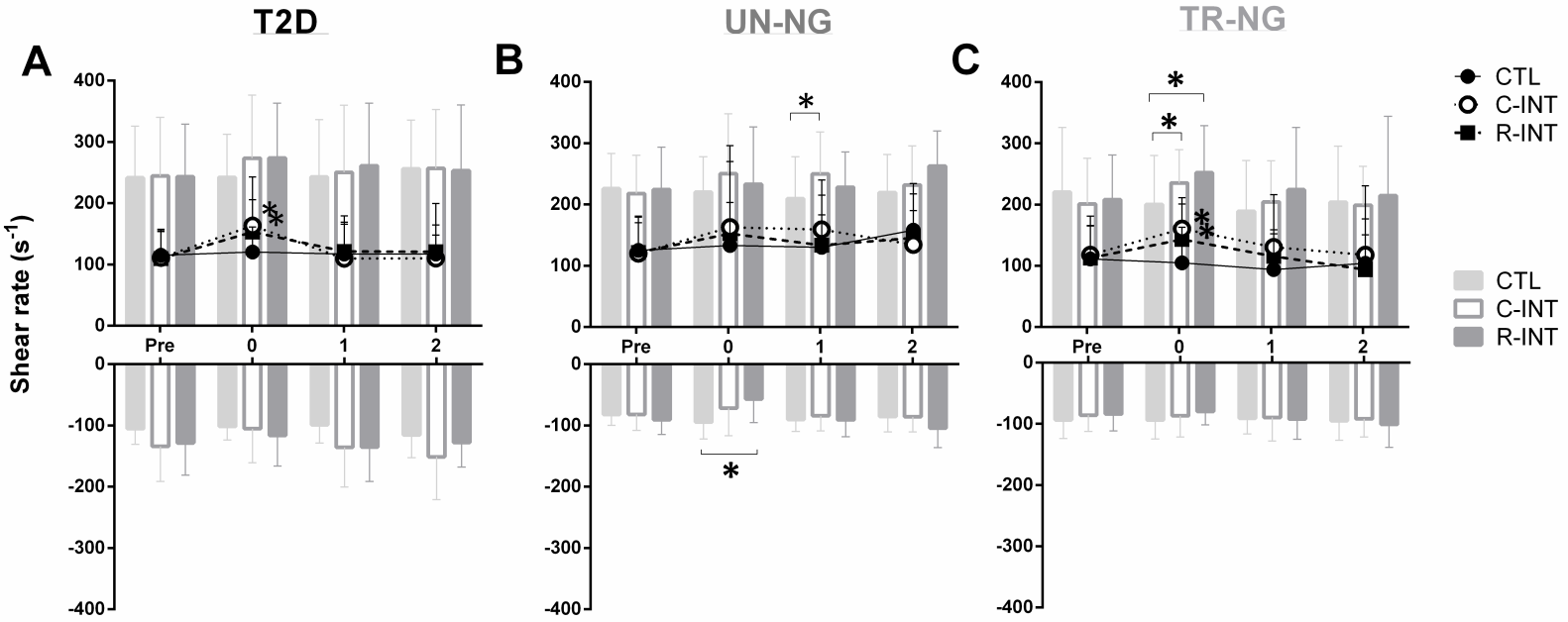
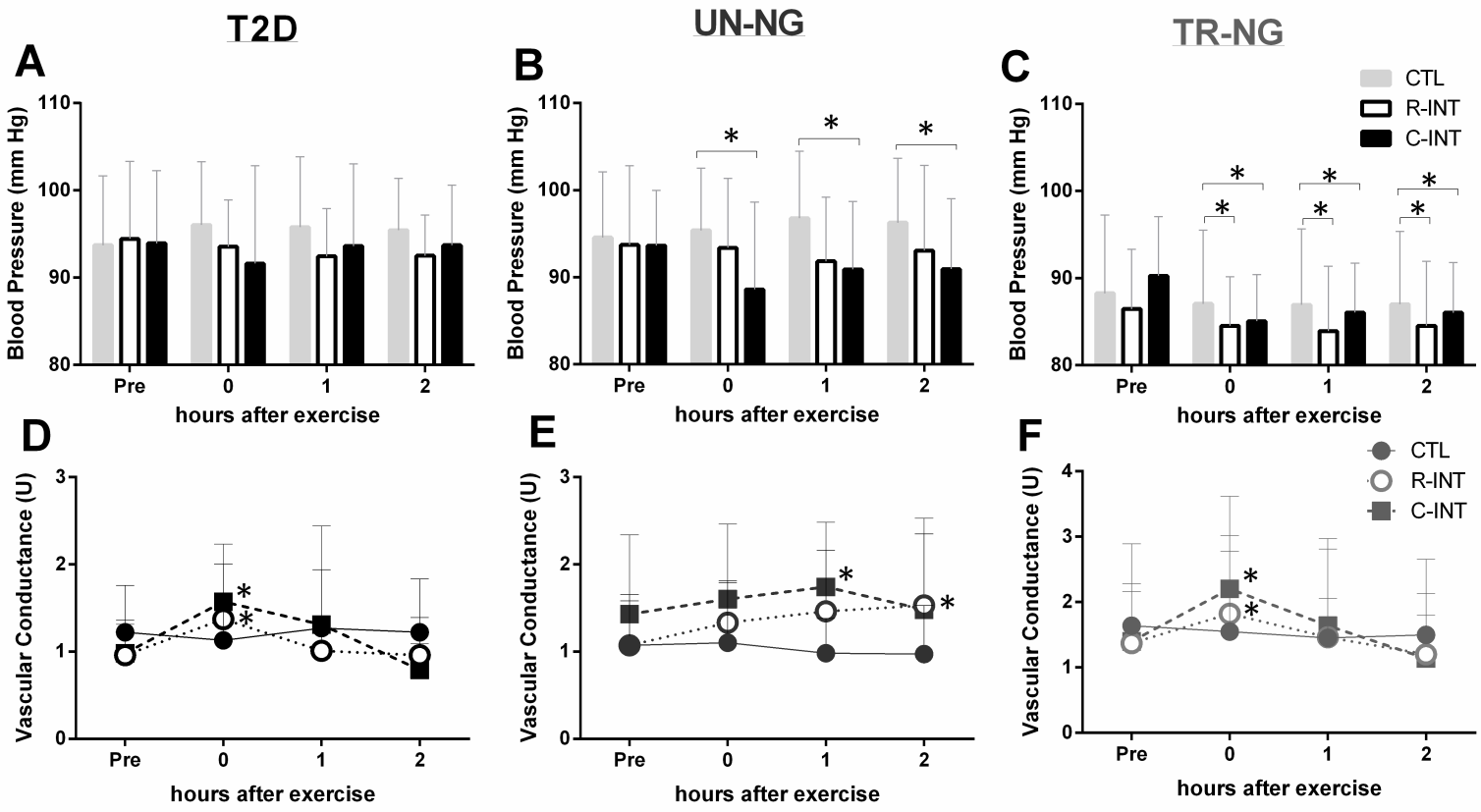
Interval
1 Leg Press
2 Leg Extension
3 Hamstring Curl
4 Leg Press
5 Leg Extension
6 Hamstring Curl
7 Leg Press


T2D
UN-NG
TR-NG
A
B
C
CTL
R-INT
C-INT
%FMD
hours after exercise
Pre
0
1
2
D
E
F
FMD (mm)
G
H
I
R-INT
C-INT
SRAUC Δ from control


T2D
UN-NG
TR-NG
A
B
C
Shear rate (s-1)
400
300
200
100
0
-100
-200
-300
-400
Pre
0
1
2
*
CTL
C-INT
R-INT
CTL
C-INT
R-INT


T2D
UN-NG
TR-NG
A
B
C
D
E
F
Blood Pressure (mm Hg)
110
100
90
80
Pre
0
1
2
hours after exercise
CTL
R-INT
C-INT
Vascular Conductance (U)
3
2
1
0
4