

## Exercise training is effective for arterial stiffness and blood pressure rehabilitation in hypertensive adults

### Ejercicio Físico es efectivo para la rehabilitación de la presión y rigidez arterial en adultos con hipertensión

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**Abstract.** There is limited information regarding the arterial stiffness decrease in subjects with hypertension and risk factors to vascular-metabolic (i.e., of blood vessels) where the exercise induces a therapeutic and preventive role. This study aimed 1) to test the effects of 6 weeks of concurrent exercise including high-intensity interval plus resistance training (CT<sub>HIT+RT</sub>) on the arterial stiffness condition of individuals with different blood pressure controls, and 2) to compare the magnitude of exercise adaptations among different blood pressures and vascular characteristics. An experimental clinical randomized study was conducted in six categories (three controls and three experimental groups) of adults who were divided into six groups: control hypertensive (CG-HTN,  $n=10$ ), control elevated blood pressure (CG-ELE,  $n=10$ ), control normotensive (CG-NT,  $n=10$ ), experimental hypertensive (ExG-HTN,  $n=10$ ), elevated blood pressure (ExG-ELE,  $n=10$ ), or normotensive (ExG-NT,  $n=10$ ). The participants underwent 6 weeks of concurrent training with 5 min of high-intensity interval plus 5 min of resistance training (CT<sub>HIT+RT</sub>), where systolic pulse wave velocity of the brachial artery (PWV<sub>ba</sub>) (primary outcome) and additional secondary blood pressure, body composition, and vascular outcomes were measured before and after 6 weeks of intervention. After 6 weeks of CT<sub>HIT+RT</sub>, significant reductions in  $\Delta$ PWV<sub>ba</sub> were reported in ExG-HTN vs. ExG-NT (*diff.* 0.86 m/s<sup>-1</sup>) and between ExG-ELE and ExG-NT (*diff.* 0.76 m/s<sup>-1</sup>). In conclusion, 6 weeks of CT<sub>HIT+RT</sub> reduced arterial stiffness in adults with different blood pressure controls, but with a superior magnitude in HTN patients. Additional benefits include remission of high blood pressure in patients with hypertension.

**Keywords:** Arterial hypertension; Endothelial dysfunction; Pulse wave velocity; Augmentation index; Ankle brachial index

**Resumen.** Existe limitada información respecto a la reducción de la rigidez arterial entre sujetos con hipertensión y factores de riesgo para enfermedades vascular-metabólicas (i.e., de los vasos sanguíneos), donde el ejercicio induce un rol fisioterapéutico y preventivo. El objetivo del estudio fue 1) testear los efectos de 6 semanas de ejercicio concurrente de tipo alta intensidad interválico y de fuerza (CT<sub>HIT+RT</sub>) en la rigidez arterial de sujetos con diferente control de presión arterial y 2) comparar la magnitud de estas adaptaciones al ejercicio en diferentes variables secundarias de presión arterial y vasculares. Estudio clínico experimental aleatorizado desarrollado en seis categorías (3 controles y 3 experimentales) de adultos; controles hipertensos (CG-HTN,  $n=10$ ), control presión elevada (CG-ELE,  $n=10$ ), controles normotensos (CG-NT,  $n=10$ ), o experimental hipertensos (ExG-HTN,  $n=10$ ), presión elevada (ExG-ELE,  $n=10$ ), o normotensos (ExG-NT,  $n=10$ ). Los sujetos desarrollaron 6 semanas de CT<sub>HIT+RT</sub>, donde la velocidad de onda de pulso de la arteria braquial (PWV<sub>ba</sub>) (resultado primario) y variables de presión arterial, composición corporal y vasculares (resultados secundarios), fueron medidas antes y después de 6 semanas de intervención. Posterior a 6 semanas de CT<sub>HIT+RT</sub> se observaron diferencias significativas en la magnitud de reducción de  $\Delta$ PWV<sub>ba</sub> en el grupo ExG-HTN versus grupo ExG-NT (*diff.* 0.86 m/s<sup>-1</sup>) y entre el grupo ExG-ELE vs. ExG-NT (*diff.* 0.76 m/s<sup>-1</sup>). En conclusión, 6 semanas de CT<sub>HIT+RT</sub> reducen la rigidez arterial en adultos con diferente control de presión arterial, con una magnitud superior en pacientes hipertensos. Beneficios adicionales se encontraron en cese de la presión arterial elevada en los pacientes hipertensos.

**Palabras claves:** Hipertensión arterial; Disfunción endotelial; Velocidad de onda de pulso; Índice de aumentación; índice tobillo-braquial

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### Introduction

Endothelial dysfunction (EDys) is an inflammatory state of the endothelial cells in the arteries (i.e., into blood vessels) characterized by micro- and macro-vascular damage in vessels and their progression to platelet accumulation or atherosclerosis (Lobato et al., 2012). Hypertension (HTN) is a common risk factor associated with EDys and is highly associated with the future development of cardiovascular disease (Whelton et al., 2018). HTN is usually the result of a combination of lifestyle behaviors, including “physical inactivity” (i.e., not adhering to international physical activity guidelines

of adhering to 150 to 300 minutes/week of low to moderate physical activity, or 75 to 150 minutes/week of vigorous physical activity) (Bowden Davies et al., 2021), poor diet, tobacco habits, and alcohol consumption (Alvarez et al., 2023). Although the HTN prevalence in United States is around 45.6% (Chen & Chauhan, 2019), in South American countries as Chile the current prevalence of HTN in adults is of 26.9% following the last National Health Survey 2026-2017 (Petermann et al., 2017). On the other hand, EDys decreases arterial vasodilation, which can be measured by flow-mediated dilation and pulse wave velocity of the brachial artery (PWV<sub>ba</sub>), which is a marker of arterial stiffness (Heiss

et al., 2022; Thijssen et al., 2019).  $PWV_{ba}$  is a well-reported outcome that detects both “functional” and “structural” changes in the vascular wall (Kim et al., 2022; Yan et al., 2022). Interesting, while traditional brachial blood pressure electronic devices that measures systolic (SBP) and diastolic (DBP) blood pressure could only detect normal, or high blood pressure (i.e., elevated, or hypertensive state), nowadays other technologies could report  $PWV_{ba}$  which indicate the degree of the arterial stiffness that could predict early a future hypertensive condition while this population is asymptomatic under traditional blood pressure cuffs (Ring et al., 2014).

Exercise training is prescribed as a therapy for patients with EDys and HTN because it reduces SBP and DBP and improves several other vascular parameters (Oviedo et al., 2015; Pescatello et al., 2019; Román et al., 2019). Exercise training can also decrease the augmentation index (i.e., brachial [ $Aix_{ba}$ ] or aortic [ $Aix_{ao}$ ]), where higher values usually denotes greater load to the left ventricle (Munir et al., 2008), which is potentially proposed as dose-dependent by intensity (Forde et al., 2020; Ramírez-Vélez et al., 2020; Ramírez-Vélez et al., 2019) and inversely correlated with higher levels of skeletal muscle mass (Lee et al., 2021). Additionally, exercise training has also been related to other vascular improvements, including ankle brachial index (ABI) of 0.9 to 1.4 points as a normality range, where low rates suggest more risk of peripheral artery disease or atherosclerosis development (Farahati et al., 2020). In this sense, the American College of Sports Medicine (ACSM) (Garber et al., 2011) and the American Diabetes Association (ADA) recommend exercise in populations with cardiovascular or vascular and metabolic risk factors (ADA, 2023; Colberg et al., 2016; Kanaley et al., 2001). One of the main exercise training modalities frequently suggested to subjects with poor cardiometabolic control is resistance training (RT), which increases skeletal muscle mass, improves glucose control, and facilitates the skeletal muscle recovery by the increase of muscle strength together favoring a more oxidative than glycolytic metabolic control. On the other hand, the American Diabetes Association has recently promoted in the 2023 guidelines for diabetes control the recommendation to prescribe high-intensity interval training (HIIT) (Potosí-Moya et al., 2024), as a time-efficient exercise modality for improving glucose levels in populations with diabetes (ADA, 2023).

The combination of both HIIT and RT is known as concurrent training ( $CT_{HIIT+RT}$ ) (Gómez-Rossel & Merellano-Navarro, 2024), proposed as a method for inducing both physiological benefits of HIIT and RT in cardiometabolic subjects and those with HTN or diabetes. However, there is a scarcity of  $CT_{HIIT+RT}$  studies applied, including time-efficient protocols (i.e., exercise sessions  $\leq 30$  min per session) that can be more suitable for future exercise applications in clinical contexts. Thus, this study aimed to test the effects of 6 weeks of concurrent exercise including high-intensity interval plus resistance training ( $CT_{HIIT+RT}$ ) on the arterial stiffness condition of individuals with different

blood pressure controls, and 2) to compare the magnitude of exercise adaptations among different blood pressures and vascular characteristics. We hypothesized that 6 weeks of  $CT_{HIIT+RT}$  could decrease arterial stiffness by  $PWV_{ba}$  with greater magnitude in hypertensive than in normotensive blood pressure control adults.

## Material and methods

This experimental randomized controlled clinical study was conducted as part of the VASCU-HEALTH (i.e., from vascular and health terms) clinical trial in which hypertensive patients and normotensive adults are evaluated and monitored by exercise training by professionals of rehabilitation (Alvarez et al., 2023). In the first stage of the study, adult men and women participated in an initial evaluation of their cardiometabolic, vascular health and physical condition, but in the present study (second part of the clinical trial), had the possibility of an invitation for participating to an exercise training intervention of 6 weeks in the Exercise and Rehabilitation Sciences Institute of the Universidad Andres Bello (ICER-UNAB), where vascular outcomes were monitored by the present study.

### Participants

The present study was a randomized controlled experimental clinical trial developed in participants of different health conditions. Participants were adult members of the Universidad Andres Bello community (i.e., faculties, students, or professionals/technicians employees), and adults residents of neighborhoods around the university that were all invited by different media (e-mail and whatsapp) by social leaders to participate of the study. The study involved adults ( $>18$  years) with different blood pressure levels as normotensive, elevated BP, or hypertensive subjects not diagnosed or diagnosed under pharmacological treatment. The sample size was intentionally distributed immediately after blood pressure categorization into one of three blood pressure groups (normotensive, elevated blood pressure, or HTN condition) based on the American Heart Association blood pressure categorization (Whelton et al., 2018). The study was registered on the Clinical Trials.gov by the code NCT05710653.

The eligibility criteria were as follows: a) hypertension, elevated blood pressure (treated with updated pharmacotherapy) or normotensive blood pressure condition, b) normal, overweight, or obese condition determined by body mass index [ $BMI < 40 \text{ kg/m}^2$ ]), c) normoglycemic, hyperglycemic, or type 2 diabetes mellitus condition (treated with updated pharmacotherapy), d) physically inactive (last 3 months no exercise regularly), and e) address located in the local city of the study. Exclusion criteria were a) history of abnormal ECG (i.e., the question: Have you ever had an ECG that was considered altered by a physician?), or other cardiovascular abnormalities diagnosed by a physician; b) HTN stage 3 (systolic blood pressure [ $SBP$ ]  $\geq 169$  mmHg or

DBP >95 mmHg); c) type 1 diabetes mellitus; f) varicose ulcers, nephropathies, or muscle-skeletal disorders such as osteoarthritis); and g) the use of pharmacological treatment influencing body composition or weight loss, such as caffeine products or others. Participants provided a written consent to the study, the project was conducted by the Declaration of Helsinki and was approved by the Ethics Committee of Universidad Andres Bello, Chile (Approval N° 026/2022).

The sample size was calculated using G\*Power 3.1.9.7 sample size software. A minimum of ten subjects ( $n=10$ ) per group were determined to have a statistical power of  $\geq 80\%$  with a 95% confidence interval and an alpha error of 5%. Firstly, eighty-five ( $n=85$ ) participants were enrolled, including hypertensive, elevated blood pressure and normotensive adults and twenty-five ( $n=25$ ) were excluded for different reasons in this stage ( $n=13$  do not adhere to the inclusion criteria;  $n=3$  were under weight loss pharmacological treatment;  $n=2$  had address in rural areas;  $n=4$  report osteo-arthritis disease; and  $n=3$  report heart disease). Thus, from the ( $n=60$ ) subjects ( $n=20$  with HTN;  $n=20$  in elevated blood pressure; and  $n=20$  normotensive), these were allocated 1:6 according to their blood pressure classification, and by following six groups: control hypertensive (CG-HTN,  $n=10$ ), control elevated blood pressure (CG-ELE,  $n=10$ ), control normotensive (CG-NT,  $n=10$ ), or experimental hypertension (ExG-HTN,  $n=10$ ), elevated blood pressure (ExG-ELE,  $n=10$ ), or normotensive (ExG-NT,  $n=10$ ), and all values of SBP and DBP in mmHg).

### Experimental procedures. Measurements

#### Blood pressure categorization (Main outcomes)

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of participants were classified according to American Heart Association guidelines (Whelton et al., 2018). Normal blood pressure was defined as SBP/DBP less than 120/80 mmHg, elevated blood pressure (Ele) as SBP/DBP between 120-129/80 mmHg, stage 1 hypertension as SBP/DBP between 130-139/80-89 mmHg, and stage 2 hypertension as SBP/DBP  $\geq 140/90$  mmHg (Whelton et al., 2018). Additionally, pulse pressure (PP) and mean arterial pressure (MAP) were calculated. Readings were taken twice in the left arm using an automatic monitor (OMRON™, model HEM 7114, United States) with a pneumatic cuff positioned for at least 10 min prior to the seated position. To compare the magnitude of the pre-

and post-intervention effects, each outcome was shown in delta ( $\Delta$ ) changes as follows:  $\Delta$ SBP,  $\Delta$ DBP,  $\Delta$ PP, and  $\Delta$ MAP.

#### Arterial stiffness (Main outcomes)

For the PWV<sub>ba</sub> measurement, each subject was positioned on a stretcher in the supine position during 20 min of resting, where electronic equipment with a pneumatic cuff in the left arm was inflated x 2 times for 5 min (Arteriograph, TENSIOMED™, Hungary). The equipment was programmed automatically to inflate/deflate the cuff and show an electrocardiography figure. The systolic blood pressure of the ankle was inserted before the equipment, as well as the weight, height, date of birth, and arm circumference of the subject. This information was processed using the Arteriograph™ Software (v.1.9.9.2; TensioMed, Budapest, Hungary) on a desktop computer, and immediately by the software, a PDF sheet document was developed and stored. The Arteriograph™ equipment has been validated against gold-standard equipment (Ring et al., 2014). A cutoff point of  $>10$  ( $m/s^{-1}$ ) is considered a high cardiovascular risk in adults. To compare the magnitude of the pre-post intervention effects, PWV<sub>ba</sub> is shown as delta changes as follows:  $\Delta$ PWV<sub>ba</sub>.

#### Anthropometric and body composition (Secondary outcomes)

Weight (kg), waist circumference (WC, cm), body fat (in % and kg), and skeletal muscle mass (SMM, in %) were measured using digital bio-impedance equipment (OMRON™ model HBF-514C, United States). Height (m) was measured using a stadiometer (SECA model 214, United States). For this procedure, the subjects of each group arrived at the lab in the afternoon and using light clothing without shoes and any other metal accessories. Fat-free mass (FFM) was calculated. The basal metabolic rate (BMR, kcal/kg/min) was assessed from the same equipment. BMI was calculated by weight and height data, and the adiposity was categorized based on the 'underweight', 'normal weight', 'overweight' or 'obesity' condition by international categorization (WHO, 2000). To compare the magnitude of the pre- and post-intervention effects, each anthropometric/body composition outcome was shown in delta changes as follows:  $\Delta$ weight,  $\Delta$ WC,  $\Delta$ Body Fat,  $\Delta$ SMM,  $\Delta$ FFM, and  $\Delta$ BMR. (Table 1) shows the baseline characteristics of the participants.

Table 1.  
Baseline characteristics of subjects.

Outcomes (n =)	CG-HTN 10	CG-ELE 10	CG-NT 10	ExG-HTN 10	ExG-ELE 8	ExG-NT 10
Age (y)	44.8±12.8	34.2±11.2	37.5±11.6	44.5±9.9	50.3±14.8	42.5±15.5
Anthropometric/Body composition						
Weight (kg)	77.9±14.3	83.4±12.9	67.77.4	86.9±16.5	76.5±16.0	66.3±10.1
Height (m)	166±0.10	1.64±0.10	1.61±0.06	1.71±0.11	1.63±0.07	1.59±0.06
BMI (kg·m <sup>-2</sup> )	28.4±4.9	31.2±4.2	26.0±2.2	30.3±4.0	28.5±4.2	26.2±2.7
Body fat (kg)	26.8±12.1	32.4±10.8	24.4±6.7	31.6±7.2	29.7±9.6	26.3±6.3
Skeletal muscle mass (%)	32.0±6.5	28.4±7.7	29.8±7.7	28.2±3.7	26.1±3.0	25.2±3.7
Fat free mass (kg)	51.0±9.3	50.9±12.2	43.2±7.9	55.3±13.2	46.7±10.3	39.9±6.6
Waist circumference (cm)	96.1±5.8	102.0±11.6	90.9±8.4	104.0±9.4	98.3±10.9	90.1±11.2
Basal metabolic rate (Kcal/min/kg)	1595±222	1635±227	1430±180	1713±305	1510±235	1364±171

Blood pressure						
Systolic BP (mmHg)	145±7	125±3	109±7	142±12	123±2	111±8
Diastolic BP (mmHg)	87±10	84±8	74±9	89±12	82±10	75±5
PP (mmHg)	58±6	42±8	36±9	53±9	42±8	36±9
Mean arterial pressure (mmHg)	106±8	97±5	86±7	106±11	95±7	87±5
Heart rate						
Heart rate rest (beats/min)	74±8	72±7	74±10	75±7	78±13	79±12
Vascular						
SBP <sub>ank</sub>	161±12	137±9	127±11	156±23	129±18	122±13
DBP <sub>ank</sub>	86±9	80±4	75±8	89±15	91±24	73±8
SBP <sub>ao</sub>	131±17	113±14	104±11	130±19	121±8	108±8
PP <sub>ao</sub>	55±11	46±7	42±6	52±15	47±8	45±10
Ejection duration	298±12.1	317±21.9	303±33.0	305±12.8	316±11.6	320±13.4
AIx <sub>ao</sub> (%)	30.6±14.8	24.9±12.1	24.8±10.9	27.7±12.9	35.5±10.5	29.2±10.1
AIx <sub>ba</sub> (%)	-9.5±25.9	-24.0±22.4	-27.2±21.8	-19.6±25.5	-4.21±20.7	-10.8±24.0
PWV <sub>ba</sub> (m·s <sup>-1</sup> )	8.46±1.19	7.70±1.41	7.54±1.75	9.63±1.56	9.29±1.31	7.76±1.33
Ankle brachial index						
	1.18±0.09	1.22±0.10	1.15±0.07	1.18±0.09	1.15±0.06	1.11±0.12
Pharmacotherapy						
ACE inhibitors (n = / total)						
Beta blocker (n = / total)	1/10			1/10		
Metformin (n = / total)		1/10				

Data are shown as mean and SD to continuous outcomes. Groups are described as; (CG-HTN) Hypertension control, (ExG-HTN) Hypertension experimental, (CG-ELE) Elevated blood pressure control, (ExG-ELE) Elevated blood pressure experimental and (CG-NT) Normotensive control (ExG-NT) Normotensive experimental exercise group. (#) Denotes that heart rate peak was measured previously by a volitional progressive cycling test. (SBP<sub>ank</sub>) Systolic BP of the left ankle. (DBP<sub>ank</sub>) Diastolic BP of the left ankle. (SBP<sub>ank</sub>) Systolic BP aortic. (PP<sub>ao</sub>) Pulse pressure aortic. (AIx<sub>ao</sub>) Augmentation index aortic. (AIx<sub>ba</sub>) Augmentation index of the brachial artery. (PWV<sub>ba</sub>) Pulse wave velocity of the brachial artery. (ACE) Angiotensin-converting enzyme inhibitors.

#### Additional (Vascular Outcomes)

Systolic BP (SBP<sub>ank</sub>, in mmHg) and diastolic BP (DBP<sub>ank</sub>, in mmHg) of the left ankle were determined in the left leg (OMRON™, model HEM 7114, United States). Systolic aortic BP (SBP<sub>ao</sub>, in mmHg), aortic pulse pressure (PP<sub>ao</sub>, in mmHg), ejection duration (ED, in seconds), ankle-brachial index (ABI), augmentation indices of the brachial artery (AIx<sub>ba</sub>, in %), and aortic augmentation index (AIx<sub>ao</sub>, in %), all vascular parameters were measured by the electronic digital equipment (Arteriograph, TENSIO MED™, Hungary) (Ring et al., 2014). The equipment is connected by bluetooth technology to a laptop in which a software store and develop a PDF inform (Arteriograph Software v.1.9.9.2; TENSIO MED, Budapest, Hungary). To compare the magnitude of the pre-post intervention effects, each vascular outcome is shown in delta changes as follows:  $\Delta$ SBP<sub>ank</sub>,  $\Delta$ SBP<sub>ao</sub>,  $\Delta$ DBP<sub>ank</sub>,  $\Delta$ PP<sub>ao</sub>,  $\Delta$ AIx<sub>ba</sub>, and  $\Delta$ AIx<sub>ao</sub>.

#### Progressive volitional cycling test

Before and after the intervention, a volitional cardiorespiratory cycling test was performed to determine HR<sub>peak</sub> data by the Astrand cycling test. This test is a progressive and volitional cardiorespiratory test developed until subject exhaustion or interrupted by standardized criteria such as a) show revolutions per minute (rpm) of cadence <60 rpm, b) do not increase heart rate between stages, c) voluntarily to stop the test (Åstrand, 2003). The test progression increased the load step by step for men (50 watt) and women (25 watt). To the test, an electromagnetic cycle ergometer (model Ergoselect 200, ERGOLINE™, Lindenstrasse, Germany) was used. The heart rate was continuously monitored using a telemetric heart rate sensor (Model A370, Polar™, Finland), where we registered the maximum heart rate of each Astrand test stage.

HR<sub>peak</sub> was used in the session-by-session program, the new threshold for both 80-100 HR<sub>peak</sub> (intervals of work) and the exercise intensity for recovery time

( $\leq 70\%$  HR<sub>peak</sub>). Heart rate at rest (HRR) was measured using a watch cardiometer (A370; Polar™, Finland). Using a volitional progressive cycling Astrand test with an electromagnetic cycle ergometer (Ergoselect 200, ERGOLINE™, Germany), we determined the heart rate peak (HR<sub>peak</sub>). To compare the magnitude of the pre-post intervention effects, each heart rate outcome is shown as delta changes as follows:  $\Delta$ HRR and  $\Delta$ HR<sub>peak</sub>.

#### Rehabilitation exercise training program

The rehabilitation program was applied by using two exercise modalities such as high-intensity interval (HIIT) during five minutes using bikes (Impulse™, Model PS 300, SPARTA, Chile) plus resistance training (RT) during five minutes, modality of exercise frequently named as concurrent training (CT<sub>HIIT+RT</sub>). Thus, the program was of ten minutes of exercise plus around 20 minutes of recovery periods between each exercise interval, including around 30 minutes per session of time investment for participants. Firstly, to the 5 minutes of HIIT, participants were 60 s cycling (x 5 times) at vigorous intensity (80 to 100% heart rate peak (HR<sub>peak</sub>), previously tested by the Astrand test), interspersed by 120 seconds or less resting time to reach target heart rate recovery. We established previously that the parameter of  $\leq 70\%$  of HR<sub>peak</sub> was assume as an individual in recovery state and ready to start another exercise interval). To the next five minutes of RT, the subjects developed 3 strength exercises; biceps curl (2 sets), shoulder press (2 times), and back exercise (1 time) during 60 seconds at moderate intensity ( $\sim 20$  to 50% of 1RM) following the American College of Sports Medicine (Thompson et al., 2021). A resting period of 60 seconds was used to get a recovery state (previously stated by the rated of perceived exertion of 1-3 subjective (1-10) modified Borg scale to start the next RT exercise interval. Thus, the total exercise time

per session was 30 min (i.e., only 10 min of pure exercise), and more short-term duration (i.e., 6 weeks). The program was of 6 weeks.

### Statistical analysis

All data are shown in tables and figures as the mean  $\pm$ SD. Normality and homoscedasticity assumptions were checked using the Shapiro-Wilk test and Levene's test ( $F$ ), respectively. The Wilcoxon test was used for non-parametric data. One-way ANOVA was applied to test differences between the control (CG-HTN, CG-ELE, and CG-NT) and experimental exercise (ExG-HTN, ExG-ELE, and ExG-NT) groups. When the  $F$  value was significant, Tukey's *post-hoc* test was used to determine differences, particularly (HTN control vs. HTN experimental, ELE control vs. ELE experimental, and NT control vs. NT experimental exercise groups). Statistical analyses were performed using Graph Pad Prism 8.0 software (Graph Pad Software, San Diego, CA, United States). The alpha level was fixed at ( $p \leq 0.05$ ) for all statistical significance.

## Results

### Baseline characteristics

(Table 1) Describe baseline characteristics of the sample at level of anthropometric, body composition, blood pressure, heart rate and secondary vascular parameters (Table 1).

### Training-induced changes at anthropometric/body composition

In  $\Delta$ Weight, ExG-HTN was significantly different vs. CG-HTN ( $-0.46$  vs.  $-0.43$  kg), and ExG-NT vs. CG-NT ( $-0.77$  vs.) (Fig. 1, panel A). In  $\Delta$ Body Fat, ExG-HTN was significantly different vs. CG-HTN ( $-1.5$  vs.  $+0.6$  kg), ExG-ELE vs. CG-ELE ( $-1.0$  vs.  $+0.5$  kg), and ExG-NT vs. CG-NT ( $-1.3$  vs.  $+0.1$  kg), all  $p < 0.05$  (Fig. 1, panel B). No significant differences were observed in  $\Delta$ Body Fat among the exercise groups (Fig. 1, panel B). In  $\Delta$ SMM, there were significant differences between ExG-HTN vs. CG-HTN ( $+1.2$  vs.  $-0.02$  kg), ExG-ELE vs. CG-ELE ( $+0.6$  vs.  $-0.01$  kg), both  $p < 0.05$  (Fig. 1, panel C). No significant differences were observed in  $\Delta$ SMM among the exercise groups (Fig. 1, panel C). In  $\Delta$ FFM, ExG-HTN was significantly different vs. CG-HTN ( $+1.13$  vs.  $-0.25$  kg), and ExG-ELE vs. CG-ELE ( $+0.78$  vs.  $-0.59$  kg), both  $p < 0.05$  (Fig. 1, panel D). No significant differences were observed in  $\Delta$ FFM among the exercise groups (Fig. 1, panel C). In  $\Delta$ WC, Ex-HTN was significantly different vs. CG-HTN ( $-4.3$  vs.  $+0.7$  cm), ExG-ELE vs. CG-ELE ( $-2.0$  vs.  $+0.3$  cm), and ExG-NT vs. CG-NT group ( $-2.3$  vs.  $-0.7$  cm), all  $p < 0.05$  (Fig. 1, panel E). No significant differences were observed in  $\Delta$ WC between the exercise groups (Fig. 1, panel E). In  $\Delta$ BMR, ExG-HTN was different vs CG-HTN ( $+218.7$  vs.  $-15.5$  kcal/kg/min), ExG-ELE vs. CG-ELE ( $+93.0$  vs.  $-24.4$  kcal/kg/min), and ExG-NT vs. CG-NT group ( $+49.8$  vs.  $-20.4$  kcal/kg/min), all  $p < 0.05$  (Fig. 1, panel F). Significant differences were observed in the  $\Delta$ BMR between ExG-HTN

and ExG-ELE (*diff.* 125.7 kcal/kg/min,  $p < 0.05$ ) and between ExG-HTN and ExG-NT (*diff.* 168.9 kcal/kg/min,  $p < 0.0001$ ) (Fig. 1, panel F).

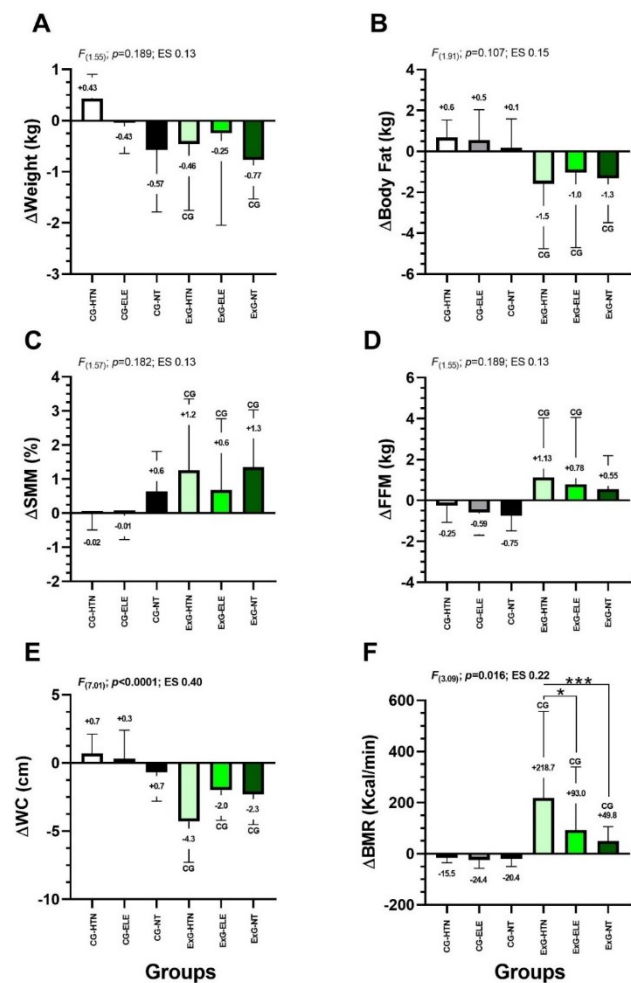


Figure 1. Anthropometric and body composition delta changes ( $\Delta$ ) after six weeks of CTHIT + RT intervention. The groups are described as control hypertensive (CG-HTN), control elevated blood pressure (CG-ELE), control normotensive (CG-NT), experimental hypertensive (ExG-HTN), experimental elevated blood pressure (ExG-ELE), and experimental normotensive (ExG-NT). The outcomes are described as ( $\Delta$ SMM) Delta Skeletal muscle mass. ( $\Delta$ FFM) Delta fat-free mass. ( $\Delta$ WC) Delta Waist circumference. ( $\Delta$ BMR) Delta Basal metabolic rate. (Bold values) Denote significant group interactions by One-way ANOVA. (CG) Denotes significant differences vs. similar HTN, ELE, or NT categories in the control group by Tukey's *post hoc* test at  $p < 0.05$ . (\*) Denotes Significant difference at  $p < 0.05$ . (\*\*\*) Significant differences at  $p < 0.0001$ .

### Blood pressure and heart rate at rest and during exercise (secondary outcomes)

In  $\Delta$ SBP, ExG-HTN was different vs. CG-HTN ( $-13.5$  vs.  $+0.01$  mmHg), ExG-ELE vs. CG-ELE ( $-6.7$  vs.  $+0.4$  mmHg), and ExG-NT vs. CG-NT group ( $-5.4$  vs.  $+0.7$  mmHg), all  $p < 0.05$  (Fig. 2, panel A). Significant differences were observed in  $\Delta$ SBP between the ExG-HTN and ExG-ELE groups (*diff.* 6.8 mmHg,  $p < 0.05$ ), and between ExG-HTN and ExG-NT (*diff.* 8.1 mmHg,  $p < 0.05$ ) (Fig. 2, panel A). In  $\Delta$ DBP, ExG-HTN vs. CG-HTN group ( $-5.2$  vs.  $-0.1$  mmHg), and ExG-NT vs. CG-NT ( $-3.2$  vs.  $-1.0$  mmHg), both  $p < 0.05$  (Fig. 1, panel B). No significant differences were observed in  $\Delta$ DBP between the exercise groups (Fig. 2, panel B). In  $\Delta$ PP, ExG-HTN was different vs CG-HTN ( $-8.3$  vs.  $+0.1$  mmHg), and ExG-ELE vs.

CG-ELE (-5.1 vs. +0.5 mmHg), both  $p < 0.05$  (Fig. 2, panel C). In  $\Delta PP$ , there were significant differences between ExG-HTN vs. ExG-NT (*diff* 6.1 mmHg,  $p < 0.05$ ) (Fig. 2, panel C). In  $\Delta MAP$ , ExG-HTN was different vs. CG-HTN (-7.9 vs. -0.07 mmHg), ExG-ELE vs. CG-ELE (-3.3 vs. +0.07 mmHg), and ExG-NT vs. CG-NT group (-3.9 vs. -0.04 mmHg), all  $p < 0.05$  (Fig. 2, panel D). Significant differences were observed in  $\Delta MAP$  between ExG-ELE and ExG-ELE (*diff* 4.6 mmHg,  $p < 0.05$ ) (Fig. 2, panel D). In  $\Delta HRR$ , ExG-HTN was different vs. CG-HTN (-3.1 vs. +0.4 beats/min)  $p < 0.05$  (Fig. 2, panel E). No significant differences were detected in  $\Delta HRR$  among the exercise groups (Fig. 2, panel E). In  $\Delta HR_{peak}$ , there were significant differences between ExG-HTN vs. CG-HTN (+7.4 vs. -2.9 beats/min) (Fig. 2, panel F). In  $\Delta HR_{peak}$ , ExG-HTN was different vs. CG-HTN (+7.4 vs. -2.9 beats/min), ExG-ELE vs. CG-ELE (+4.3 vs. -0.3 beats/min), ExG-ELE vs. CG-ELE (+9.5 vs. -1.6), all  $p < 0.05$  (Fig. 2, panel F). No significant differences were detected in  $HR_{peak}$  among the exercise groups (Fig. 2, panel F).

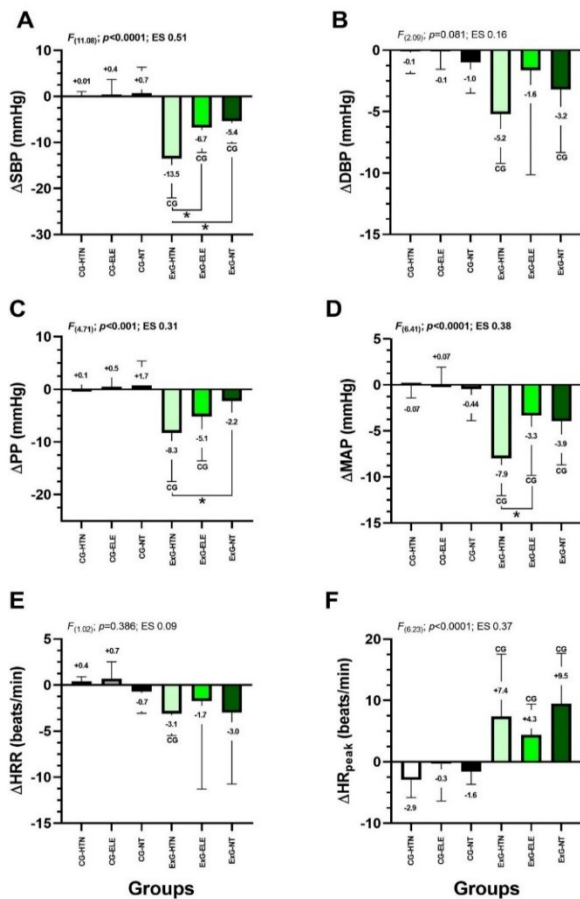


Figure 2. Blood pressure and heart rate outcomes changed after 6 weeks of  $CT_{HHT+RT}$  intervention. The groups are described as control hypertensive (CG-HTN), control elevated blood pressure (CG-ELE), control normotensive (CG-NT), experimental hypertensive (ExG-HTN), experimental elevated blood pressure (ExG-ELE), and experimental normotensive (ExG-NT). Outcomes were described as: (SBP) systolic blood pressure. (DBP) diastolic blood pressure. (PP) Pulse pressure. (MAP) mean arterial pressure. (HRR) Heart rate at rest. ( $HR_{peak}$ ) Heart rate peak obtained from a cycling exercise test. (Bold values) Denote significant group interactions by One-way ANOVA. (CG) Denotes significant differences vs. similar HTN, ELE, or NT categories in the control group by Tukey's post hoc test at  $p < 0.05$ . (\*) Denotes Significant difference at  $p < 0.05$ .

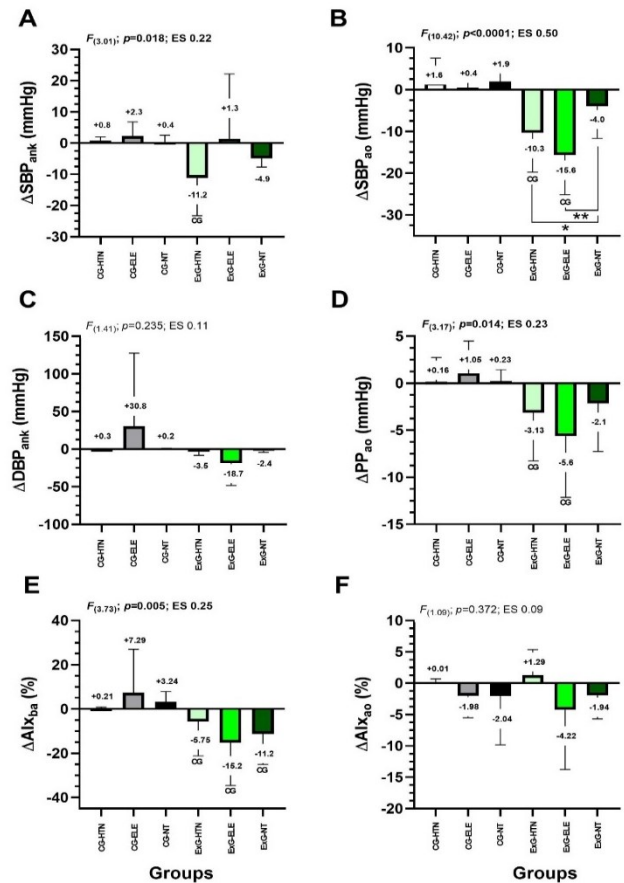


Figure 3. Blood pressure and secondary vascular outcomes changed after 6 weeks of  $CT_{HHT+RT}$  intervention. The groups are described as control hypertensive (CG-HTN), control elevated blood pressure (CG-ELE), control normotensive (CG-NT), experimental hypertensive (ExG-HTN), experimental elevated blood pressure (ExG-ELE), and experimental normotensive (ExG-NT). Outcomes were described as follows: ( $SBP_{ank}$ ) ankle systolic blood pressure. ( $DBP_{ank}$ ) Ankle diastolic blood pressure. ( $PP_{ao}$ ) Aortic pulse pressure. ( $SBP_{ao}$ ) aortic systolic blood pressure. ( $\Delta AIX_{ba}$ ) Augmentation index of the brachial artery. ( $\Delta AIX_{ao}$ ) Aortic augmentation index. (Bold values) Denote significant group interactions by One-way ANOVA. (CG) Denotes significant differences vs. similar HTN, ELE, or NT categories in the control group by Tukey's post hoc test at  $p < 0.05$ . (\*) Denotes Significant difference at  $p < 0.05$ . (\*\*) Significant difference at  $P < 0.01$ .

### Secondary blood pressure and vascular parameters (Secondary outcomes)

In  $\Delta SBP_{ank}$ , there were significant differences between ExG-HTN vs. CG-HTN (-11.2 vs. +0.8 mmHg) (Fig. 3, panel A). No significant differences were detected in  $\Delta SBP_{ank}$  among the exercise groups (Fig. 3, panel A). In  $\Delta SBP_{ao}$ , there were significant differences between ExG-HTN vs. CG-HTN (-10.3 vs. +1.6 mmHg), and between ExG-ELE vs. CG-ELE (-15.6 vs. +0.4 mmHg) both  $p < 0.05$  (Fig. 3, panel B). Significant differences were detected in  $\Delta SBP_{ao}$  between the ExG-HTN and ExG-NT groups (*diff* 6.3 mmHg,  $p < 0.05$ ) and between ExG-ELE and ExG-NT (*diff* 11.6 mmHg,  $p < 0.01$ ) (Fig. 3, panel B).  $\Delta DBP_{ank}$  did not differ among the groups (Fig. 3, panel C). In  $\Delta PP_{ao}$ , there were significant differences between ExG-HTN vs. CG-HTN (-3.13 vs. +1.05 mmHg), and ExG-ELE vs. CG-ELE (-5.6 vs. +1.05 mmHg), both  $p < 0.05$  (Fig. 3, panel D). No significant differences were detected in  $\Delta PP_{ao}$  among the exercise groups (Fig. 3, panel D). In  $\Delta AIX_{ba}$ , there were significant differences between ExG-HTN vs. CG-HTN (-5.75 vs.



+0.21 %), ExG-ELE vs. CG-ELE (−15.2 vs. +7.29 %), and between ExG-NT vs. CG-NT (−11.2 vs. +3.24 %) (Fig. 3, panel E). No significant differences were detected in  $\Delta\text{Alx}_{\text{ba}}$  among the exercise groups (Fig. 3, panel E). No significant interactions were detected in  $\Delta\text{Alx}_{\text{ao}}$  among any of the groups (Fig. 3, panel F).

### Arterial stiffness and secondary vascular parameters

In  $\Delta\text{PWV}_{\text{ba}}$ , there were significant differences between ExG-HTN vs. CG-HTN (−1.22 vs. +0.15  $\text{m/s}^{-1}$ ), ExG-ELE vs. CG-ELE (−1.12 vs. +0.14  $\text{m/s}^{-1}$ ), both  $p < 0.05$  (Fig. 4, panel A). No significant differences were detected in  $\Delta\text{PWV}_{\text{ba}}$  among control groups (Fig. 3, panel D). Significant differences were detected in  $\Delta\text{PWV}_{\text{ba}}$  between the ExG-HTN and ExG-NT groups (*diff.* 0.86  $\text{m/s}^{-1}$ ,  $p < 0.0001$ ) and between ExG-ELE and ExG-NT (*diff.* 0.76  $\text{m/s}^{-1}$ ,  $p < 0.05$ ) (Fig. 4, panel A). Finally, no significant interactions were observed in  $\Delta\text{ABI}$  and  $\Delta\text{ED}$  among all groups (Fig. 4, panels B-C).

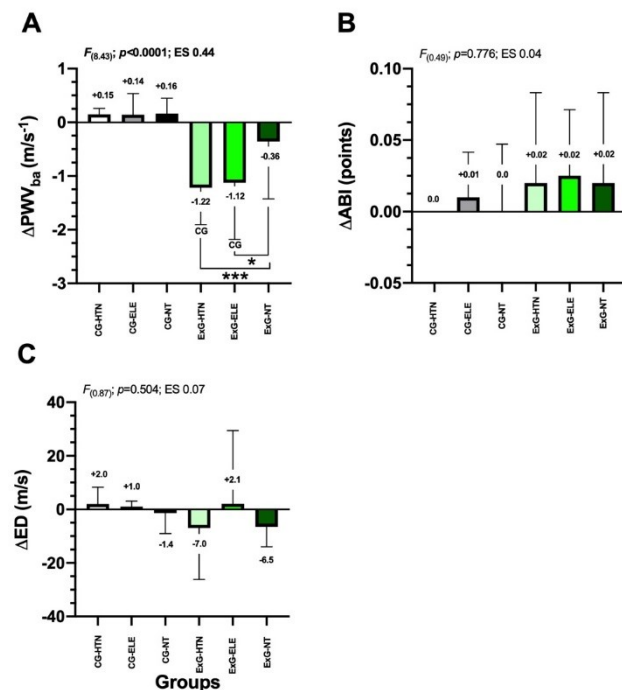


Figure 4. Arterial stiffness was measured by pulse wave velocity of the brachial artery ( $\text{PWV}_{\text{ba}}$ ), and secondary vascular outcomes, ankle brachial index (ABI), and ejection duration (ED), all expressed as delta changes after 6 weeks of  $\text{CT}_{\text{HIIT+RT}}$  intervention. The groups are described as control hypertensive (CG-HTN), control elevated blood pressure (CG-ELE), control normotensive (CG-NT), experimental hypertensive (ExG-HTN), experimental elevated blood pressure (ExG-ELE), and experimental normotensive (ExG-NT). The outcomes are described as ( $\Delta\text{PWV}_{\text{ba}}$ ) delta pulse wave velocity of the brachial artery. ( $\Delta\text{ABI}$ ) Delta ankle-brachial index. ( $\Delta\text{ED}$ ) Delta of ejection duration. (Bold values) Denote significant group interactions by One-way ANOVA. (CG) Denotes significant differences vs. similar HTN, ELE, or NT categories in the control group by Tukey's post hoc test at  $p < 0.05$ . (\*) Denotes Significant difference at  $p < 0.05$ . (\*\*\*) Significant differences at  $p < 0.0001$ .

## Discussion

This study aimed 1) to test the effects of 6 weeks of con-

current exercise including high-intensity interval plus resistance training ( $\text{CT}_{\text{HIIT+RT}}$ ) on the arterial stiffness condition of individuals with different blood pressure controls, and 2) to compare the magnitude of exercise adaptations among different blood pressures and vascular characteristics. The main findings of this study showed that *i*) 6 weeks of  $\text{CT}_{\text{HIIT+RT}}$  significantly reduced  $\Delta\text{PWV}_{\text{ba}}$  by a major magnitude in ExG-HTN compared with ExG-NT (*diff.* 0.86  $\text{m/s}^{-1}$ ), and similarly *ii*) in those with elevated blood pressure ExG-ELE when compared with ExG-NT (*diff.* 0.76  $\text{m/s}^{-1}$ ). These findings were displayed with additional and known major beneficial adaptations in other blood pressure outcomes (SBP, PP, MAP), in favor of those with higher blood pressure (i.e., HTN and elevated blood pressure experimental groups) than those with normal blood pressure.

(Hasegawa et al., 2018) conducted a study of 8 weeks of MICT in sedentary adults (2 session/week, 45 min at 60–70%  $\text{VO}_{2\text{peak}}$ ), and they reported a decrease of body fat from 28.5 to 27.7% ( $\Delta -0.8\%$ ), and increased serum adiponectin from 7.8 to 9.3  $\text{ng/mL}$  ( $\Delta +1.5\ \mu\text{g/mL}$ ), and the Nobel recently identified adipokines C1q/tumor necrosis factor-related proteins (CTRP3) from 199.3 to 253.7  $\text{ng/mL}$  ( $\Delta +54.4\ \mu\text{g/mL}$ ), and CTRP5 from 9.2 to 16.8  $\text{ng/mL}$  ( $\Delta +7.6\ \mu\text{g/mL}$ ).

These results were displayed with blood pressure decreases in SBP ( $\Delta -9\ \text{mmHg}$ ), DBP ( $\Delta -4\ \text{mmHg}$ ), HRR ( $\Delta -3\ \text{beat/min}$ ) and PWV ( $\Delta -0.13\ \text{m/s}^{-1}$ ) equivalent to a  $\Delta -11.4\%$  of PWV reduction and measured from the carotid to femoral anatomic points. A study of exercise training in HTN patients from (Molmen-Hansen et al., 2012), reported that 12 weeks of HIIT (4×4 min at 85–90%  $\text{VO}_{2\text{max}}$ , walking/running, 38 min total session) or MICT (60%  $\text{VO}_{2\text{max}}$ , walking/running, 47 minutes total session) both exercise modalities reduced 24-hour SBP by  $\Delta -12\ \text{mmHg}$  (HIIT) and  $\Delta -4.5\ \text{mmHg}$  (MICT). Our results in the present study are in accordance with these authors; however, our  $\text{CT}_{\text{HIIT+RT}}$  is applied in a more feasible time-investment clinical context.

The arterial stiffness reduction in patients with HTN is in concordance with the same effects that exercise training promotes in reducing blood pressure in as SBP or DBP more in hypertensive subjects than in normotensive subjects (Pescatello et al., 2015; Pescatello et al., 1999). Interestingly, the training-induced effects on PWV reductions were negatively associated with both CTRP3 and CTRP5 adipokines, linking MICT exercise with increases in adipokines and subsequent reduction of arterial stiffness. In the present study, we decreased PWV  $\Delta -1.22\ \text{m/s}^{-1}$  in ExG-HTN, and in ExG-ELE  $\Delta -1.12\ \text{m/s}^{-1}$  and body fat decreases ( $\Delta -1.5\ \text{kg}$ ) in Ex-HTN and ( $\Delta -1.0\ \text{kg}$ ) in Ex-ELE groups. Our study protocol is interesting for future application in association with more complex plasma and molecular proteins, and above from the clinical perspective.

Conversely, not all research has established a correlation between elevated PWV and higher blood pressure, particularly in terms of SBP and DBP. For instance, Kim et

al. (Kim et al., 2007) did not find a relationship between PWV and SBP/DBP; however, they found that pulse pressure significantly predicted arterial stiffness behavior measuring PWV by invasive methods. However, more recent epidemiological studies in ( $n=1449$ ) Finnish adults (30-45 y), reported that the PWV measured from 2007 to 2011 was directly and independently associated with SBP/DBP measured in 2011, concluding that PWV predict the progression of blood pressure being a valuable tool for HTN prediction (Koivisto et al., 2018). (Ashor et al., 2014) reported that aerobic exercise improved arterial stiffness by reducing PWV, and this effect was enhanced with higher aerobic exercise intensity and in participants with greater arterial stiffness at baseline, being in coherence with the present results.

Other studies have reported that a greater cross-sectional muscle area of the thigh in Male adults are associated with lower PWV<sub>ba</sub> (Ochi et al., 2010). The effects of exercise training on hypertension normalization are well known (Cade et al., 1984; Guimaraes et al., 2010; Olea et al., 2017; Pescatello et al., 2015). Some of the mechanisms by how? Exercise reduces blood pressure due to acute transitory mechanisms, including i) reduction in vascular peripheral resistance (Wilkins et al., 2004), ii) increase in nitric oxide (Augeri et al., 2009), iii) decrease in vasoconstrictor factors (Low et al., 2007), iv) increase in shear stress (Birk et al., 2012), v) decrease in sympathetic nervous activity (Halliwill, 2001), and other structural chronic adaptations at the vascular wall (Pedralli et al., 2020). From a molecular perspective, the angiogenesis promoted by exercise in small blood vessels is dependent on several physiological processes, including biochemical (i.e., nitric oxide and vascular endothelial growth factor), cellular mediators (i.e., circulating angiogenic blood cells), and paracrine signaling mechanisms, such as exosomes (i.e., extracellular vesicles that are exported from skeletal muscle to other organs). Angiogenesis is dependent on several physiological processes, including biochemical (i.e., nitric oxide and vascular endothelial growth factor), cellular mediators (i.e., circulating angiogenic blood cells), and paracrine signaling mechanisms such as exosomes (i.e., extracellular vesicles exported from skeletal muscle to other organs) (Ross et al., 2023).

### **Strengths and limitations**

Some strengths were that *i*) we used a simple and validated equipment (Arteriograph™) for PWV<sub>ba</sub> measurement using a brachial cuff that could be replicated easily in other clinical context without more specific procedures, and *ii*) the CT<sub>HIT+RT</sub> exercise therapy was proposed using a time-efficient clinical context which is a time per session of  $\leq 30$  min per session. As limitations, we did not include other more robust physical fitness outcomes, such as cardiorespiratory variables, to correlate with vascular outcomes, or did not include other muscle strength variables to test muscle strength after the 6 week intervention.

## **Conclusion**

In conclusion, 6 weeks of CT<sub>HIT+RT</sub> reduced arterial stiffness in adults with different blood pressure controls, but with superior magnitude in hypertensive patients. Additional benefits include high blood pressure remission in the mean group of hypertensive patients. Future studies should explore the underlying mechanisms by which CT<sub>HIT+RT</sub> promotes these benefits in vascular health.

## **Acknowledgments**

We like to recognize all those participants who accepted to participate in our research at the Universidad Andres Bello, and that additionally participated of all stages of this study.

## **Statement of ethics**

The study was conducted by the Declaration of Helsinki and approved by the Institutional Review Board of the BIOETHICAL COMMITTEE OF UNIVERSIDAD ANDRES BELLO (Approval 026/2022 of September 22<sup>nd</sup>).

## **Conflicts of interest statement**

C.A., L.P., P.I., M.T., D.J.-M., J.D., D.C.A., O.A., J.C.-M., and P.D.-F declare no conflict of interest.

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## **Author contributions**

C.A. designed the study. C.A. performed the experiments. C.A., L.P., P.I., M.T., D.J.-M., J.D., D.C.A., O.A.-M., J.C.-M., and P.D.-F. analyzed the data. All authors interpreted the data and wrote the manuscript. All authors reviewed, revised, and approved the final manuscript.

## **Informed consent statement**

“Informed consent was obtained from all subjects involved in the study.”

## **Data availability statement**

The current study’s datasets are available from the corresponding author on reasonable request.



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