# PHYSIOLOGICAL RESPONSE TO A TRAINING AND DETRAINING PERIOD IN VASCULAR PARAMETERS OF CARDIOMETABOLIC RISK FACTORS SUBJECTS: OPTIMIZING POST-EXERCISE STRATEGIES TO MAINTAIN HEALTH BENEFITS IN CHILEAN ADULTS

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**Study documents**

**Scientific background:** Atherosclerosis is a chronic disease characterized by the accumulation of lipid cells in the inner layer of artery walls, often as a result of oxidative damage to low-density lipoprotein (LDL-c) [1]. LDL-c accumulation can lead to inflammation in the major arteries (*e.g*., carotid and brachial arteries), which usually progress to fibroatheromas [2]. However, before the development of atherosclerosis, endothelial dysfunction (EDys) is a phenotypic (*i.e*., intermediate pathology condition) vascular alteration of the endothelium, characterized by a pro-thrombotic and pro-inflammatory state as result of imbalance between the actions of vasodilators and vasoconstrictors, modifying thus both 'function' and 'structure' of the vasculature [3]. Given that traditional methods for detecting EDys are highly invasive, expensive, and time-consuming (*e.g.*, coronary epicardial vasoreactivity, venous occlusion plethysmography), non-invasive methods based on ultrasound imaging have been rapidly implemented in clinical management [4,5].

EDys is often associated with several health conditions including arterial hypertension (HTN), obesity, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, and chronic renal failure [6]. In Chile, 26.9% of adults are HTN, and this prevalence is highly superior in elderlies [7], therefore, it is estimated that an important number of adults and older adults will develop EDys, that will progress to atherosclerosis, or to an atheromatous plaque that in turn will increase the risk of stroke. From 'functional' parameters, the percentage of flow-mediated dilation (FMD) has been a more suitable a non-invasive and strong marker of vascular health in adults, where low values of FMD (*i.e.,* <6.5%) denotes an impaired vascular function associated with cardiometabolic risk [4,8]. To both 'functional' and 'structural' modifications, the pulse wave velocity of the brachial artery (PWVba) is a recognized marker of arterial stiffness in adults , where >10 cm/s indicates high cardiovascular risk [9], and on the other hand, carotid-intima media thickness (cIMT) is a well established marker of structural vascular health [10].

It is well known in physical inactivity (*i.e.*, does not follow international physical activity guidelines of 300 min/week of low-moderate PA or at least 150 min/week of vigorous intensity [11,12]) is in higher prevalence in sedentary, obese, higher blood pressure, dyslipidaemias or suffering from metabolic syndrome, that there is a negative effect on both functional and structural vascular parameters such as FMD, PWVba, and cIMT [4]. Relevant American and Latin American expert panels have recommended performing moderate intensity continuous training (MICT) for 30-60 minutes per session most days of the week in subjects with elevated blood pressure or HTN patients [11]. In this sense, other experts have also confirmed that MICT is crucial for preventing and treating hypertension [12,13], and recent evidence highlight the time-efficient of high-intensity interval training [14,15], and resistance training for improving EDys similarly [16].

However, before starting any exercise training program in clinical populations such as those with elevated blood pressure or HTN, it will necessary to know the baseline of the cardiovascular response to the physical effort through of a progressive exercise volitional test, such as a cycling test [16,17]. A progressive volitional cycling test like the Astrand test provides useful information about the cycling power output (PO) in watts, which increases at different levels (*e.g.*, in women PO increases by 25 watts per level and in men it increases to 50 watts), while heart rate should also increase progressively at each level [17,18]. Interestingly, the theoretically predicted heart rate maximum ($HR_{predicted}$) using the well-known formula (*i.e.*, 220-age) is often overestimated or underestimated in physically inactive individuals [19]. Additionally, the use of heart rate maximum ($HR_{max}$) is poorly reported in physically inactive hypertensive populations that are generally unable to maintain a steady state at maximal intensity. From here, the heart rate peak

($HR_{peak}$) is a useful marker of cardio-vascular condition and it has been widely used for exercise prescription in the future. The aim of this study was to assess the relationship between EDys markers (FMD, PWVba, and cIMT) and heart rate during a progressive volitional cycling test in adults with hypertension. A secondary aim was to characterize cardiovascular, anthropometric, and body composition outcomes in normotensive, elevated blood pressure, and hypertension patients.

This study will follow the CONSORT guidelines for randomised trials, will be developed in accordance with the Declaration of Helsinki (2013), and has been approved by the BIOETICAL COMMITTEE OF UNIVERSIDAD ANDRES BELLO (Approval 026/2022 of September 22$^{th}$). **Design:** An experimental clinical randomized study. **Methods:** This study is an experimental randomized controlled clinical trial in which (n=75) adults (men and women) were invited to participate in an exercise training intervention and were assigned to one of three groups based on their blood pressure levels: arterial hypertension (HTN), elevated blood pressure (Ele), or to a normotensive control group (CG). The study took place in Concepción, Chile between September 2022 and January of 2023. We used G*Power 3.1.9.7 statistical sample size software calculator, with an *alpha* error probability of $p<0.05$, and with 95% confidence interval (CI) for 3 groups (expecting medium to-large effect size) for obtain the sample size. Thus, a minimum of ten subjects per group would give a statistical power of ≥90%)].

The eligibility criteria for this study were: i) HTN, elevated blood pressure (controlled and on updated pharmacotherapy), or healthy normotensive; ii) normal weight, overweight, or obese (as determined by body mass index [BMI]); iii) normal or hyperglycaemic (T2DM, controlled and on updated pharmacotherapy); iv) living in urban areas of the city of Concepción; and v) demonstrated ability to adhere to all measurements and stages of the study. Exclusion criteria included: i) abnormal ECG; ii) uncontrolled

HTN (SBP ≥169 mmHg or DBP >95 mmHg); iii) morbid obesity (BMI ≥40 kg/m$^2$); iv) type 1 diabetes mellitus; v) cardiovascular disease (*e.g.*, coronary artery disease); vi) diabetes complications such as varicose ulcers on the feet or legs, or a history of wounds, nephropathies, or muscle-skeletal disorders (*e.g.*, osteoarthrosis); vii) recent participation in weight loss treatment or exercise training programs (within the past 3 months); and viii) use of pharmacotherapy that can influence body composition. All participants were informed about the study procedures and potential risks and benefits, and provided written consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Universidad Andres Bello, Chile (Approval N° 026/2022).

In the first stage of the enrollment (*n*=75) subjects were screened, and after exclusion criteria were applied (*n*=10) participants were excluded for various reasons ([*n*=3] due to bone diseases, [*n*=3] due to a history of heart disease, and [*n*=3] because they were already enrolled in other exercise activities and (*n*=1) due to declared weight loss treatment). Thus, a total of (*n*=65) subjects participated in this first stage of our clinical trial study. The final sample size was as follows per group; (HTN *n*=18, Ele *n*=22, and CG *n*=21).

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**Statistical Analysis Plan (SAP):** Data are presented as mean and (±) standard deviation (SD). The normality assumption for all variables was tested using the Shapiro–Wilk test. Wilcoxon's rank sum test was used for not normally distributed variables. A one-way ANOVA will be performed to test differences between groups and a *post hoc* [Sidack's] test after ANOVA for group comparisons (*i.e.*, HTN x Ele x CG). Additionally, we will report a trend analyses [*p*trend] to test potential (linear) tendence to increase or decrease a particular outcome through these categories of different blood pressure. Finally, using the first three steps of the progressive volitional cycling Astrand test (i.e., 25/50, 50/100, and 75/150 watt) we will apply a linear regression among EDys outcomes FMD, PWVba, cIMT to be associated with the heart rate (beats/min) in these three steps, and the $R^2$ will be tested as predictive capacity from this heart rate for EDys outcomes. These analyses will be performed using Graph Pad Prism 8.0 software (Graph Pad Software, San Diego, CA, USA). The alpha level was set at $p<0.05$ for statistical significance.