Original Article (short paper)

Time-course of health-related adaptations in response to combined training in hypertensive elderly: immune and autonomic modulation interactions

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Abstract — Aims: This article is a methodological description of a randomized clinical trial (ClinicalTrials.gov U1111-1181-4455) aiming to evaluate the time-course (monthly) and associations between blood pressure changes and other health-related adaptations in response to exercise training in hypertensive elderly. **Methods:** The patients will be randomized to a control or combined training group interventions (aerobic and resistance exercise), with monthly assessments in four months. Although, the changes in baseline blood pressure is the primary clinical outcome, the secondary outcomes include: body composition, cardiorespiratory fitness, muscle strength, arterial stiffness, baroreceptor sensitivity, cardiovascular autonomic modulation, inflammatory markers, oxidative stress, growth factors, tissue remodeling markers, metabolic profile, renal function, cognitive function and quality of life. **Results:** To support the understanding of the blood pressure changes in hypertensive elderly, a time-course of exercise-induced adaptations including cardiovascular and immunological adaptations are fundamental for research in this field. **Conclusion:** To investigate the time-course of combined training-induced adaptations including all the diverse aspects of health in hypertensive elderly a well-controlled protocol design is necessary, mainly to clarify the relationship between cardiovascular and immunological exercise-induced adaptations.

Keywords: aging; hypertension; exercise; immune system; cardiovascular system.

Introduction

Cardiovascular diseases lead to nearly 17 million deaths per year worldwide, and 9.4 million of these deaths are attributed to hypertension[1,2]. The incidence of hypertension increases with age[3], reaching 63.2% of the elderly population in Brazil[4]. The pathogenesis of hypertension is still unclear, with heterogeneous and multifactorial etiology, but it is influenced by the kidney function, cardiovascular autonomic modulation, endothelial function and the immune system (IS)[5,6].

Recently, the IS and autonomic nervous systems have received attention regarding their influence in the genesis of hypertension. Both the IS and the autonomic nervous system control and interact with the other physiological systems and undergo remarkable changes during the aging process, including developing conditions such as low-grade chronic inflammation[7,8] and cardiac autonomic modulation imbalance[9,10]. Low-grade chronic inflammation contributes to many chronic diseases common to the elderly, such as hypertension, atherosclerosis, diabetes, rheumatoid arthritis and frailty syndrome[11,12]. Likewise, autonomic modulation imbalance, as a result of elevated sympathetic modulation[10] and reduced parasympathetic modulation[9], also increases the risk of chronic diseases and mortality[13,14]. It is noteworthy, the evidence for the interaction between these systems is the presence of β-adrenergic receptors in immune system cells, such as T cells, B cells, natural killer cells, macrophages, and neutrophils, providing the molecular basis to catecholaminergic signaling[15]. In addition, Tracey[16] showed that vagal stimulation is a potential inductor of anti-inflammatory markers increase and/or inflammatory markers reduction. Moreover, recent evidence has shown the influence of IS cells and inflammatory cytokines on cardiovascular autonomic modulation nucleus in the central nervous system contributing to the development of hypertension[17-19].

Figure 1 illustrates some factors related to the development and maintenance of hypertension adding the influence of physical training on the attenuation on these factors. Both aerobic training and resistance training promote immune adaptations and lower BP[20,21]. Regarding immune adaptations, some exercise-induced anti-inflammatory mechanisms have been proposed and the most known is the reduction of adipose tissue which in turns reduces adipose pro-inflammatory cytokines[20]. Another mechanism proposed in the literature is coordinated by the induction of an anti-inflammatory environment after each exercise session,

associated to the regulation of energy expenditure[20, 22]. Furthermore, both aerobic and resistance training, as well as the combination of these exercises types, produce significant cardiovascular benefits, especially in sedentary and populations at increased cardiovascular risk. These benefits comprise improvements in the parasympathetic and sympathetic modulation of heart and vessels[23-25], baroreflex sensitivity[26], central and peripheral arterial compliance[27-29], endothelial function[30], as well as the specific reduction in blood pressure[31-33]. Moreover, some studies have shown the effects of physical training on autonomic modulation in parallel with the reduction of inflammatory markers in healthy adults and elderly[34, 35].

A significant study investigated the association of immune and autonomic systems in spontaneously hypertensive rats[18]. They found that aerobic training reduced inflammation in hypothalamic nuclei of cardiovascular control and increased baroreflex sensitivity after two weeks, increased parasympathetic modulation to the heart after 4 weeks, and reduced sympathetic modulation to the vessels and blood pressure after 8 weeks. However, hypertensive elderly develop hypertension with the association of multiple health conditions that might differ in some aspects from spontaneously hypertensive rats[36]. Furthermore, the time-course of these adaptations in humans is unknown.

This is the first randomized control trial able to describe the time-course of exercise-induced blood pressure changes in parallel to IS, autonomic modulation and a comprehensive assessment of health-related adaptations in elderly humans. Importantly, this study will investigate the effect of combined training, which shows promise for blood pressure reduction and it is recommended due to its essential and complementary benefits for elderly health[6, 37, 38].

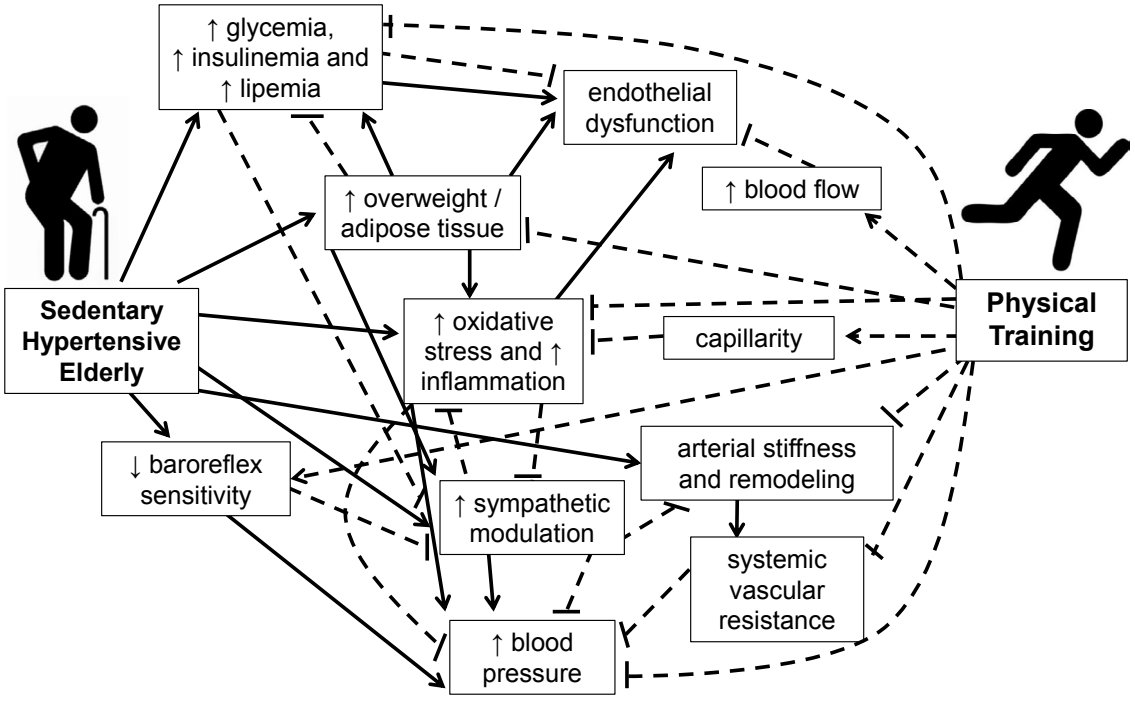

Figure 1. Interactions between alterations in sedentary hypertensive elderly individuals and the influence of physical training. The arrows represent the stimulus of the hypertensive condition (full line) and exercise (dashed line) on the changes indicated inside the rectangles, while the dashed lines ending with transverse lines represent inhibition for a given change.

Methods

Subjects

The elderly hypertensives (over 60 years old) will be randomized to a control group (without intervention) or 4 months of combined exercise training, according to figure 2. The inclusion criteria are individuals from both sexes, non-physically active (frequency of regular physical activity less than two sessions per week), no participation in any regular training program over the last 6 months preceding the beginning of the interventions; stage 1 or 2 hypertension (Stage 1 = systolic blood pressure: 140 to 149 mmHg or diastolic blood pressure: 90 to 99 mmHg; Stage 2 = systolic blood pressure 160 to 169 mmHg or diastolic blood pressure: 100 to 109 mmHg)[39]; clinical evaluation by a physician (general physical examination, cardiological and clinical exercise testing) authorizing the practice of physical activity. The exclusion criteria are BMI > 35; Coronary artery disease, insulin dependent diabetes mellitus; Chronic obstructive pulmonary disease; Osteoarticular disease that limits the practice of the training proposed; Peripheral vascular disease; smokers; medications that may interfere with physiological responses to tests, such as beta-blockers. All of the selected individuals will be invited to sign the informed consent approved

by The Ethics Committee at University of Campinas (CAEE 54943216.7.0000.5404). The flow chart of the participant's selection is detailed in figure 3.

The sample size was calculated using G*Power 3.2.1 software, based on mean blood pressure (MBP) of a study with adults of middle age, before and after combined training [31]. Using a study design of an F test (ANOVA two way for repeated measurements), this analysis provided an *f* effect size of 0.29, with $p < 0.05$ and 95% power, yielding an n of 14 in each group. The effect size of combined training observed in a previous study of our group [40] of the secondary biomarker endpoints (glycemia, insulinemia, fat percentage, the interval between R waves, TNF-α, PCR, leptin, and adiponectin) were also calculated, resulting in less than the 28 individuals.

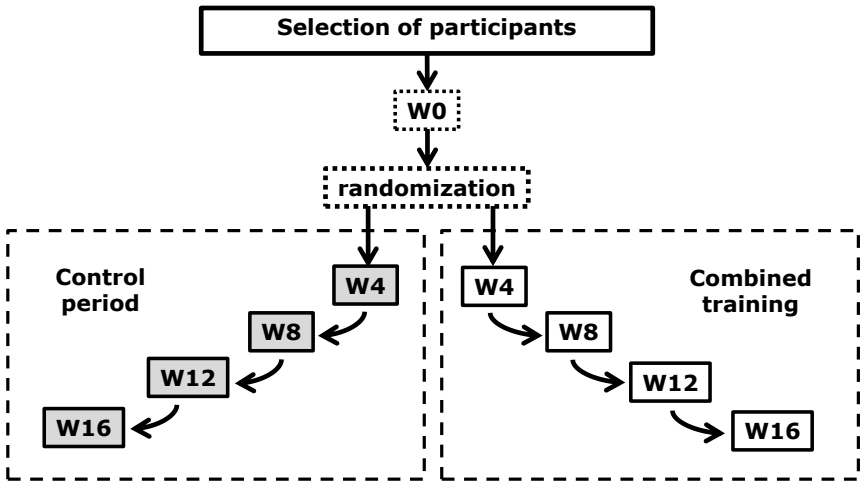

Figure 2. Experimental design. W: weeks of assessments; 0, 4, 8, 12 and 16 weeks along control and combined training period.

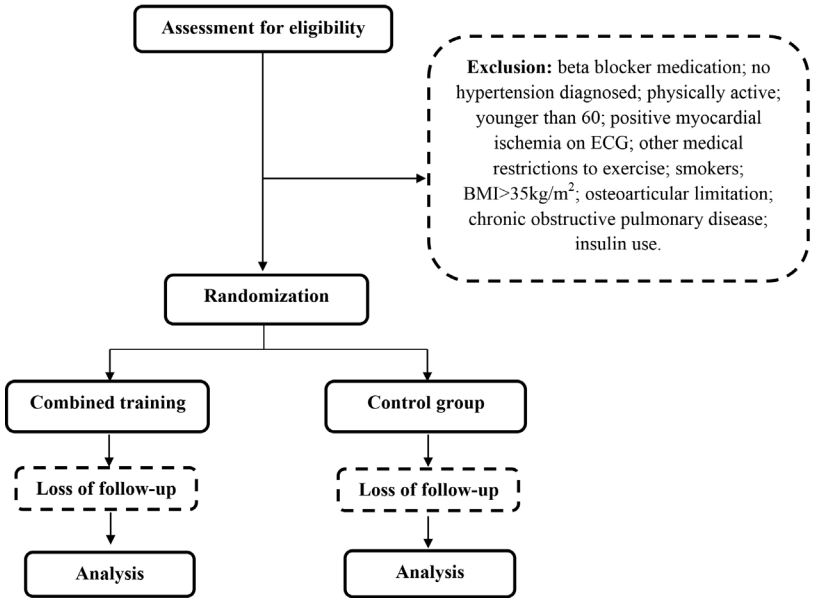

Figure 3. Flowchart of the participant`s selection.

Experimental design

The participants of the present randomized clinical trial will be evaluated at baseline (W0), after 4 weeks (W4), after 8 weeks (W8), after 12 weeks (W12) and after 16 weeks (W16) of control or training intervention as described in Table 1. After baseline assessments all participants will be allocated to two groups balanced by age, BMI, blood pressure and the mean interval between R waves, using a computerized random function. Each participant will be tested at the same time (between 7 am and 12 pm) along 16 weeks control or exercise training intervention.

Table 1. Assessments details.

Outcomes	Time	Methods	Description
Physical fitness			
Aerobic fitness	W0/W8/ W16	Maximal oxygen consumption	According to our previous work [41], the subjects will perform a maximum-effort protocol on the treadmill (a Quinton TM55, Bothell, WA), with breath-by-breath gas analysis (CPX Medical Graphics, St.Paul, MN, USA). The ventilatory threshold, the respiratory compensation point and the maximum oxygen consumption (VO_2max) will be determined according to classical criteria [42, 43].
Muscle strength	W0/W8/ W16	Lower limb dynamic isokinetic and isometric strength; and handgrip strength	According to protocols previously described [44], an isokinetic dynamometer (Biodex System 4-Biomedical Systems, Newark, CA, USA), muscle strength will be assessed through the peak torque for isometric strength of leg extension [45] and isokinetic strength (60º/s) of concentric contractions of leg extension and flexion [46], an angle of 60º of flexion (0° = complete extension) [45]. Handgrip strength will be quantified through a Jamar dynamometer (Lafayette Instruments, Indiana, USA), positioned at the dominant hand of each individual for three trials. For all tests, participants will be stimulated to use maximal strength, as fast as possible and they will receive verbal encouragement [47].
Functional tests	W0/ W16	Sit and stand, TUG, sit and reach, gait speed, Berg's balance scale	Functional mobility tests of Rikli and Jones will be assessed, including 30 seconds chair-standing [48], Timed Up and Go[49], sit and reach test by Wells e Dillon [50], gait speed along 4.6 meters [51], Berg Scale for balance assessment [52, 53].
Physical activity level	W0/ W16	Habitual Physical Activity Questionnaire	Physical activity level within a period of time will be assessed by an Likert type scale which includes occupational activities, physical exercise and leisure activities based on responses to 16 items [54].
Clinical outcomes			
Body composition	W0/W4/ W8/ W12/ W16	Digital scale, stadiometer, tape	The weight will be measured by a calibrated scale (digital scale Filizola®, model ID1500) to the nearest 100g. Height will be measured to the nearest 0.5 cm using a stadiometer (Digital Filizola®). BMI will be calculated from these values (weight/height^2). The waist, hips and neck circumference will be measured by tape, as reliables markers of cardiometabolic risk [55-57].
		Body plethysmography	Body volume will be measured through a densitometric technique (changes in air volumes and internal pressure) at a plethysmograph chamber (BOD POD®) connected to a software [58]. With body volume value, it is possible to estimate the lean and fat mass, using the traditional Siri's equation [59].
		Ultrasound muscle mass	The thickness of biceps and vastus lateralis will be evaluated by ultrasound, according to previously described protocols [60, 61].
Blood pressure	W0/W4/ W8/ W12/ W16	Finger photoplethysmography	According to methods described in our previous study [62], systolic, diastolic and mean BP will be obtained using finger photoplethysmography, by Finometer Pro®(Finapres Medical System, Amsterdam, Holanda). The cuff is positioned at the distal phalanx of the middle finger of the right upper limb [63]. The measure will be performed at rest conditions according to American Heart Association's recommendations [1], calculating the average of 300 beats at a stationary period in supine rest.
Hemodynamics	W0/W4/ W8/ W12/ W16	Blood pressure derived parameters	Based on BP values and individual features the software of Finometer Pro®also estimates: stroke volume as the true integrated mean of the simulated flow waveform between the current upstroke and the dicrotic notch; pulse rate derived from the pulse interval; cardiac output (stroke volume * heart rate); total systemic peripheral resistance as the ratio of mean arterial pressure to cardiac output, assuming zero venous pressure (at the right atrium); and baroreflex sensitivity as a cross-correlation function of blood pressure and pulse interval [64].
Vascular autonomic modulation	W0/W4/ W8/ W12/ W16	Blood pressure variability	Time and frequency domains of BP variability will be given by the software Cardio series v 2.4, using the data collected by Finometer Pro®(Finapres Medical System, Amsterdam, Holanda) [65].
Cardiac autonomic modulation	W0/W4/ W8/ W12/ W16	Heart rate variability	Continuous R-R intervals will be acquired in the same rest conditions of BP registration, using a validated heart rate monitor (Polar RS800CX, Kempele, Finland)[66]. We will analyze heart rate variability (HRV) in both time and frequency domains [13], during five minutes stationary R-R intervals in Kubios HRV analysis software (MATLAB, version 2 beta, Kuopio, Finland)[67].
Peripheral artery disease	W0/W4/ W8/ W12/ W16	Brachial-ankle index	It will be identified by the difference of systolic blood pressure of upper and lower limbs (an indicator of atherosclerosis and peripheral arterial functionality) [68-70].

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Table 1. Continued

Outcomes	Time	Methods	Description
Arterial stiffness	W0/W4/ W8/ W12/ W16	Central and peripheral pulse wave velocity by applanation tonometry	Pulse wave velocity is obtained by SphygmoCor® (AtCor Medical) according to guidelines for clinical application of central and peripheral stiffness [71].
Carotid arterial compliance	W0/W4/ W8/ W12/ W16	Carotid diameter by ultrasound with simultaneously blood pressure	Images of the left carotid common artery diameter 2cm under the carotid bifurcation will be collected by ultrasound (Nanomaxxtm, SonoSite, EUA), acquired with the linear transducer of 10-5MHz, at M mode, where a sequence of pictures for 5 seconds is registered [62]. CC is calculated considering the difference between maximal and minimum diameters along the 5 seconds pulse, associated with systolic and diastolic BP at the same moment, gauged by a digital sphygmomanometer (Omron HEM-7113, Omron Corp, Kyoto, Japan) [62], according to the equation CC = ([Sd - Dd]/Dd)/(SBP - DBP)[62, 72].
Arterial wall thickness	W0/W4/ W8/ W12/ W16	Carotid intima-media thickness by ultrasound	It will be registered by ultrasound image (Nanomaxxtm, SonoSite, EUA) acquired with the linear transducer of 10-5MHz, from left carotid common artery 2 cm under the carotid bifurcation and analyzed through the software image J (U.S. National Institutes of Health, Bethesda, Maryland, USA) as described elsewhere [73].
Endothelial function		Flow-mediated dilation	The diameter of brachial artery will be measured through ultrasound (Nanomaxxtm, SonoSite, EUA), acquired with the linear transducer of 10-5MHz, before and after 5 minutes of occlusion in the forearm (250mmHg) [74]. The diameter will be recorded for 30 seconds in the baseline condition (supine rest) and after 30, 60 and 90 minutes of vascular occlusion.
Metabolic profile	W0/W4/ W8/ W12/ W16	Blood analysis	The blood samples will be obtained from the antecubital vein and collected into serum, heparin- and EDTA-plasma Vacuette® tubes, after a minimum of 12h fasting. Blood sample will be centrifugated at 3000rpm for 10min, separated in aliquots and stored at -80°C. Glucose, total cholesterol, HDL, LDL, VLDL and triglycerides will be analyzed.
Systemic Inflammatory markers, Growth factors, Oxidative stress and tissue remodeling markers	W0/ W4/W8/ W12/ W16	Blood analysis in ELISA	The same samples mentioned above will be used to analysis of IL-6, IL-10, TNF-α, CRP, VEGF, BDNF, Antioxidant assay kit,TBARS, MMP-9, and TIMP-1 will be analysed in duplicate by immunoenzymatic method ELISA (enzyme-linked immunosorbent assay, ELISA, ELX 800 Biotek, USA model) by means of ultrasensitive kits (R & D Systems) using a specific kit for each of the markers.
Cognitive functions	W0 / W16	Stroop test, MMSE, ISLT, and GMLT.	We will apply the computerized version of the Stroop test: TESTINPACS®[75]. The participants use the forefingers of both hands to press one of the two options of the keyboard key ([←] or [→]). In step 1, the participants have to choose the right name for the color displayed on the screen. In step 2, participants have to choose the right name for the color writing displayed on the screen, with the letters colored always in white. In step 3, participants have to choose the right name for the color of the word letters instead the name of the color written. After receiving the instructions for the test, they will perform one familiarization trial. The software registers the number of hits and the time to answer in milliseconds. We will also apply the MMSE for sample characterization [76] which evaluates the temporal orientation, spatial orientation, immediate memory, memory recall, attention, calculation, and language [77]. It consists of a questionnaire, in which the evaluator questions and proposes the tasks evaluated, adding points to successes. Learning, executive function and memory will be evaluated by ISLT and GMLT and later recall using the software Costate (Melbourn, VIC, Australia)[78]. ISLT consists in a list of 12 words (e.g. Eggs, Orange, Toothpaste, etc.) verbally presented. The evaluator counts the cumulative number of items recorded by the participant, along three trials. GMLT evaluates the ability of the participant to learning the pathway along the 10x10 grid through the total time needed to discover the way, the movements per second, number of legal and illegal trials, according to the rules previous provided to the participant. After the GMLT, the ISLT will be solicited again (later recall) to evaluate memory.
Depression	W0/ W16	GDS-15	The GDS-15 is a short version of the original scale which is one of the most frequently used tools for tracking depression in the elderly [79]. It is composed by 15 questions easy to understand that avoid somatic complaints, detecting mood disorders and can be administered by a trained interviewer.

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Table 1. Continued

Outcomes	Time	Methods	Description
Renal function	W0/W8/ W16	aMDRD	The serum creatinine will be used as a marker of renal function, by applying two equations set for estimation of glomerular filtration rate [80]. The equations are aMDRD based on the serum creatinine variables, age, race and gender [81], which applies best to the elderly [82]and the formula of Cockroft-Gault (CKD-EPI) [80, 83].
Quality of life	W0/ W16	WHOQOL-brief and SF-36 questionnaire	It is important to measure the quality of life (QOL), because the other assessments would not identify the subjective portion of wellbeing and satisfaction of the elderly, essential to be considered in a comprehensive health assessment. QOL will be assessed by WHOQOL-brief [84], in which QOL is divided into four domains: physical, psychological, social relationships and environment. Furthermore, the assessment of QOL will be complemented by the SF-36 questionnaire that is able to register the benefits of health-related QOL [85].
Monitoring			
Medication	W0/W4/ W8/ W12/ W16	A detailed questionnaire and DDD	Overall medication prescriptions by the clinicians of the patients will be required since the first visit. The name, dosages, frequency and time of the day to take the medications will be periodically checked. The assessment of medication changes, regarding the intensity of therapy, will be quantified as the daily defined dose (DDD) through the method developed by the World Health Organization [86].
Infection	W0/W4/ W8/ W12/ W16	WURSS-21 and DALDA	Possible upper respiratory tract infections will be monitored through Wisconsin Upper Respiratory Symptom Survey (WURSS-21) and Daily Analysis of Life Demands in Athletes (DALDA)[87], to differentiate this confounding factor of exercise training effects.
Dietary intake	W0/ W16	Food frequency questionnaire	The Portuguese version of Food frequency questionnaire [88] will be applied to check whether participants are changing the dietary intake along intervention. They will be instructed to retain the same habits, mainly concerning about total caloric intake, sodium, fat, oxidant and antioxidant aliments which directly affects the blood pressure.

Note: TUG: Time up and go; MLTPAQ: Minnesota Leisure Time Physical Activity Questionnaire; BMI: Body mass index; BP: Blood pressure; CC: Carotid compliance; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Systolic diameter of the carotid artery; DD: Diastolic diameter of the carotid artery; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: very low density lipoprotein; IL-6: Interleukin 6; IL-10: Interleukin 10, TNF-α: Tumor necrosis factor alpha; CRP: C-reactive protein; VEGF: Vascular endothelial growth factor; BDNF: Brain-derived neurotrophic factor; TBARS: Thiobarbituric acid reactive substances; MMP-9: Matrix metalloproteinases 9; TIMP-1: Tissue inhibitor of metalloproteinase 1; ELISA: Enzyme-linked immunosorbent assay; MMSE: Mini mental exam test; ISLT: International Shopping List task; GMLT: Groton Maze Learning Test; GDS-15: Geriatric depression scale; aMDRD: abbreviated modification in diet in renal disease; WHOQOL brief: World health organization quality of life brief questionnaire; SF-36: Short Form Health Survey ; QOL: Quality of life; DDD: daily defined dose; WURSS-21:Wisconsin Upper Respiratory Symptom Survey; DALDA: Daily Analysis of Life Demands in Athletes.

Training Protocol

Participants will be advised to maintain their normal diet and all their prescribed medications during the 16 weeks of intervention. The protocol of 16 weeks of combined training was based on exercise guidelines for hypertensive and elderly[38, 89]. It is noteworthy the purpose of the minimum amount of resistance exercise recommended in these guidelines and a larger amount of aerobic exercise, due to the higher effectiveness from aerobic exercise on cardiovascular adaptations described in the literature[21, 27]. The exercise sessions will be individually supervised. It will consist of seven resistance exercises for the major muscle groups followed by continuous walking and/or running twice per week and one additional session of only aerobic training, according to the prescription described in table 2. All training sessions will be held in the Integrated Laboratory of the Faculty of Physical Education, UNICAMP (LabFEF). Participants in the control group will not receive any treatment; however, they will monthly visit the research laboratory to make the same assessments which will be carried out for the training group.

Statistical analysis

Previously to the main analysis, data transformation should be held for non-normally distributed data. Mixed models for repeated measures should be applied for each variable considering the five-time points and two groups, followed by Bonferroni post hoc in case of significant interactions ($p<0.05$). Complementary, the effect size of the adaptations at each time point will describe the magnitude of the difference between the combined training and control group, informing how long it does take to modify the organism of hypertensive elderly. Correlations and regressions between deltas will enable us to understand the cause-effect between adaptations along the time-course. Individual's responses may vary, justifying evaluation of responders and non-responders for key variables (such as blood pressure, autonomic cardiac modulation, body composition, cytokine concentrations and systemic oxidative stress markers).

Results

The results of this study will provide a detailed description of the chronological sequence, every 4 weeks, of organic adaptations obtained during 16 weeks of combined training in the hypertensive elderly subjects, serving as a basis for future studies that aim to understand this complex relationship of the dynamics of the adaptations investigated.

Table 2. Combined training program.

	Type of exercise	Intensity	Volume	Frequency
Resistance exercise	leg extension and flexion, leg press, heel lift, bench press, pulley, and abdominal	RPE between 5-6 (in a 10 point scale)	1 set of 10-15 repetitions	twice per week
Endurance exercise	walking/running on treadmill and field	46-63% VO_2max. (speed)	50 minutes continuous	three times per week

Note: RPE: ratio of perceived exertion; VO_2max: maximum oxygen consumption.

Discussion

Combined training by itself is able to reduce systolic and diastolic blood pressure of hypertensive subjects[90], but due to the higher effectiveness of aerobic vs. resistance training[91] we proposed a larger amount of aerobic exercise in the present program. The blood pressure reductions might arise, as a consequence of improvement in a variety of factors including sympathovagal balance, arterial function and structure, baroreflex sensitivity, systemic inflammation and weight control. Thus, in the next paragraphs, we are going to discuss how each of these adaptations is expected to develop along exercise training time-course.

The reduction in circulating blood glucose, advanced glycation end products (AGEs) and increase in insulin sensitivity could occur as a result of increased energy substrate utilization during exercise[92-94] and the up-regulation of auxiliary glucose uptake intracellular mechanisms, independent of insulin, by active muscles in every training session[95]. These changes might attenuate oxidative stress, vascular tissue damage, and an increase in nitric oxide biodisponibility[96, 97] which added to increase in endothelial vascular shear stress (increased blood flow during exercise) would improve endothelial function and vasodilation, leading in turns to arterial compliance and baroreflex sensitivity improvements[18, 29, 98]. These changes may precede the increase in parasympathetic modulation and the reduction of sympathetic modulation to the heart and vessels, respectively[18, 34, 57, 99, 100]. Improvements in cardiovascular autonomic modulation could also be induced by neuronal protection against potential glucose neurotoxicity[101].

Body fat reduction is progressive during the training program due to the increase in energy expenditure during and after each training session. That is associated with an increased mitochondrial biogenesis which occurs in skeletal muscle and other tissues[55, 98], increased metabolic rate[94, 102] and fat oxidation[103, 104]. The fat reduction, together with the improvement in glucose uptake, reduced the concentration of the final advanced glycation end products and proinflammatory markers, in turns improving insulin sensitivity. Nevertheless, the training protocol proposed herein may not induce substantial fat reduction, enough to influence beneficial adaptations through this pathway.

The overload on muscle fibers induces muscle damage following each exercise session and may increase the concentration of inflammation and reactive oxygen species at the beginning of the training period[105, 106]. After several weeks of exercise training there is an expected reduction of reactive oxygen species (initially high) and increase in the antioxidant capacity[106, 107], which might also culminate in blood pressure reduction by the mediation of reduced T cell activation response to angiotensin II, and vascular endothelial function improvement[108, 109].

The cardiovascular autonomic modulation adaptations contribute directly to the reduction of heart rate and blood pressure at rest[18]. Cardiovascular autonomic modulation adaptations may reduce systemic inflammation in different ways: by increasing parasympathetic modulation and thereby inhibit TNF-α production by splenic macrophages primarily[16, 110]; reducing the secretion of free fatty acids (lipolysis reduction) by decreasing sympathetic hyperactivity for the adipocytes, and by stimulating the hypothalamic-pituitary-adrenal axis to increase the production of glucocorticoids, thereby inhibiting the production of proinflammatory cytokines[106]. A reduction in body fat would further reduce the amount of macrophages M1 and increase macrophages M2 to adipose tissue, which enhances the regulatory T cell activity and reduces the expression of toll-like receptors, stimulating reduction of TNF-α production, IL -6 and increasing IL-10 and adiponectin production[20, 40,111]. Other mechanisms that stimulate the pro-inflammatory reduction, are the signaling cascades triggered by muscular IL-6 every exercise session, which in turn stimulates monocytes and macrophages to reduce TNF-α production and increase IL-10 production, respectively[20]. The reduction of body fat with exercise training and reduced pro-inflammatory markers may also reduce C-reactive protein production by the liver. Possibly, these inflammatory changes accentuate or contribute to the maintenance of the expected blood pressure reduction and reduce cardiovascular risk by several other means after the training period[20, 35, 109].

There are also two other important adaptations induced by aerobic and resistance training for the elderly. First, the increase in maximum oxygen consumption which is an independent predictor of mortality [112], may be obtained after at least 8 weeks training by the increase in arteriovenous oxygen difference and especially by the increase in cardiac output (by myocardial

contraction force increase, end-diastolic volume increase and improvements in autonomic control efficiency)[113]. Second, an increase in muscle mass is important for good health, functional independence and falls avoidance in age[38, 114, 115]. These changes may occur even at the beginning of the intervention[61, 103, 116].

Furthermore, we expect improvements in cognitive function, functional performance, and quality of life [117-119]. These complementary benefits might be related to the cardiovascular functions improvements, metabolism, strength, aerobic fitness and also psychological and social effects that emerge from exercise training intervention[104, 120-123].

In summary, this study will open the way towards the chased understanding of the relationship between autonomic and immune system exercise-induced adaptations, especially regarding their effects on blood pressure. Furthermore, the follow up of diverse organic adaptations along exercise training stimulus will contribute to the understanding of the complex relationship among organic structures and functions, describing a comprehensive time-course analysis of elderly healthy and quality of life.

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