The effects of regular exercise on the vascular health of older adults with hypertension

Tese de Doutorado

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À minha família

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"One, remember to look up at the stars and not down at your feet. Two, never give up work. Work gives you meaning and purpose and life is empty without it. Three, if you are lucky enough to find love, remember it is there and don't throw it away."

Stephen Hawking

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LIST OF ABBREVIATIONS

AET – aerobic exercise training

AH – antihypertensive

BMI – body mass index

BP – blood pressure

BPV – blood pressure variability

BRS – baroreflex sensitivity

cIMT – carotid intima-media thickness

COMP – completers set

CVDs – cardiovascular diseases

DBP – diastolic blood pressure

EDUCATION – health education intervention

EXERCISE – exercise intervention

FAS – Full-analysis set

FMD – flow-mediated dilatation

HDL-c – high-density lipoprotein cholesterol

HF – high-frequency power

HRV – heart rate variability

LDL-c – low-density lipoprotein cholesterol

LF – low-frequency power

LF/HF – low-to-high frequency powers ratio

LMICs – low to middle income countries

NO – nitric oxide

NU – normalized units

PA – physical activity

PEH – post-exercise hypotension

PNN50 – percentage of RR interval with a difference of 50ms from the preceding RR interval

RMSSD – root mean square of successive differences

RR – mean RR interval

RT – resistance training

SBP – systolic blood pressure

SD – standard deviation

SDNN – standard deviation of normal RR intervals

SENS – sensitivity analysis set

RESUMO

O exercício físico é amplamente recomendado como estratégia de modificação de estilo de vida eficaz no tratamento da hipertensão. No entanto, diversas lacunas são observadas na literatura em relação à sua efetividade na modificação de certos parâmetros característicos da hipertensão na população idosa. No presente volume são apresentadas uma revisão da literatura relacionada ao efeitos do exercício na hipertensão, perfil lipídico e função endotelial, juntamente com dois artigos originais provenientes de um ensaio clínico randomizado e multicêntrico avaliando um programa de exercício combinado contra um programa para educação em saúde em idosos com hipertensão. Os desfechos apresentados são: sensibilidade barorreflexa e controle autonômico, no artigo 1 e função e estrutura vascular, no artigo 2. Os achados contrariam a hipótese de superioridade do exercício físico na modificação dos parâmetros avaliados, o que pode ser um indicativo de que a população idosa apresenta alguma irresponsividade ao exercício nas variáveis escolhidas.

Palavras-chave: Pressão arterial, atividade física, idosos, ensaio clínico.

ABSTRACT

Exercise is widely recommended as an efficacious lifestyle modification strategy in the treatment of hypertension. However, several gaps in the literature are observed in relation to its effectiveness in modifying certain characterizing parameters of hypertension in older adults. In the present volume will be presented a review of the literature related to the effects of exercise in hypertension, lipid profile and endothelial function, together with two original articles derived from a multicenter randomized clinical trial evaluating a combined exercise program against a health education program in older adults with hypertension. The outcomes presented are: baroreflex sensitivity and autonomic control, in article 1, and vascular function and structure, in article 2. The observed findings are contrary to the hypothesis that exercise would be superior in modifying the evaluated parameters, which might be an indicative that the older adult population presents a degree of irresponsiveness to exercise in the chosen variables.

Keywords: Blood pressure, physical activity, elderly, clinical trial

1. Introduction

The inexorable passage of time leads all living organisms to aging: from the unicellular bacteria, to the self-named higher-intelligence primates, that are ourselves. With the fast-paced advances of science and technology, our populations tend to live longer. Yet, there is a great difference between living and surviving to an old age. In contemporary times, the health-disease relationship has dramatically changed towards an increase in lifestyle-related health conditions such as obesity, dyslipidemia, hypertension, diabetes and cardiovascular diseases (1,2). This way, a healthy aging process is key for managing the physiological damages imposed by undesirable lifestyles and therefore for maintaining the dignity of those who contributed long years to our society, and now face the challenges of senescence.

In no longer than 15 years, the percentage of people older than 60 years will reach 20% of the total population in Brazil (3). Data from population-wide telephone inquiries show a self-reported prevalence of hypertension in adults older than 65 years of more than 60% in this country (4). Since hypertension is considered the most important preventable cardiovascular risk factor, and the highest contributing factor for lost of years-of-life adjusted for disability (5), the impact of this health condition on the quality of life in older adults is of uttermost importance.

Non-pharmacological approaches are undeniably relevant in the management of hypertension, such as the current guidelines underscore the importance of these measures as therapeutic strategies with the highest level of evidence (6–8). Indeed, the chronic effects of exercise interventions on blood pressure are well described (9–11). In older adults with hypertension, however, landmark studies, with robust designs and sample sizes, are still lacking. Through the identification of the knowledge gaps in this area of the literature, the HAEL Study (Hypertension Approaches for The Elderly: A Lifestyle Study) was carefully

created with the intend to add new and qualified evidence in respect to the implementation of these approaches specifically for older adults.

The HAEL Study is a multicenter single-blinded randomized controlled trial designed to pragmatically test the effectiveness of a combined exercise program in reducing the ambulatorial blood pressure of older adults with hypertension (12). The cornerstones behind this trial construction were: (i) a robust design with an active control and a significant sample size, (ii) high external validity due to the easily implementable interventions, (iii) transparency and reproducibility due to the data and methods sharing plan. Through these characteristics, the study was conceived as a potential tool to better understand what to expect regarding the health effects of the proposed interventions in these patients and therefore guide the practice of providing care in this population. All of which using a robust design focused on generalizability, with low-cost interventions.

The trial is still ongoing, and its ending is planned for the first semester of 2020. Two of the preconceived secondary analysis of the HAEL Study will be presented in this volume. These ancillary studies are justified to improve the understanding of possible changes related to physiological blood pressure determinants and regulators implied by the exposure to the proposed interventions in our population of interest. Herein the analysis of baroreflex sensitivity and autonomic control through blood pressure and heart rate variability measurements, as well as the vascular function and structure, analyzed through high-definition ultrasound imaging, of the participants from the HAEL study will be explored. The objective of the present document is to describe the results of these two analyses, as well as to present a comprehensive review of the literature in the context of cardiovascular health and exercise.

2. Review of literature

Exercise, cardiovascular health and risk factors for atherosclerosis: a narrative review on these complex relationships and caveats of literature

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ABSTRACT

The following narrative review addresses the relationship between physical activity and exercise with cardiovascular health, focusing primarily on the following risk factors for atherosclerosis: hypertension, dyslipidemia and vascular function. Cardiovascular diseases are intimately associated with mortality and morbidity and current societal organization contributes to the incidence of cardiovascular events. A worldwide epidemiological transition to cardiovascular deaths was observed in the last century, with important decrements in physical activity and diet quality. An atherogenic environment started to be the new normal, with risk factors such as dyslipidemia, hypertension and endothelial dysfunction observed in great portions of the population. Exercise is an important tool to improve overall health. For hypertension, a great amount of evidence now puts exercise as an effective therapeutic tool in the treatment of this condition. The effects of exercise in modifying blood lipid-lipoprotein are less clear. Despite the rationale remaining solid, methodological difficulties impair the interpretation of possible effects in these variables. Vascular function, as assessed by flow-mediated dilatation, is a good measure of overall vascular health and is consistently improved by exercise in many populations. However, in individuals with hypertension, the exercise literature still needs further description of possible effects on vascular function variables. Physical activity and exercise are associated with improved cardiovascular health, especially with reduced blood pressure, and should be encouraged on the individual and population level. Evidence regarding its effects on blood lipids and flow-mediated dilatation still need solid landmark studies to guide clinical practice.

Introduction

Cardiovascular diseases (CVDs) are not only the main cause of death worldwide, accounting for around 20% of deaths, but they additionally impose relevant morbidity and disability to those non-fatally affected by them (1). Additionally, CVDs also cause important financial burden, loss of quality of life for the families of those who survived an event, and are one of the most expensive conditions for public health spending due to its marked prevalence (1).

Contemporary societies face a pandemic of hard cardiovascular outcomes, and while the mortality of such events dropped (2,3), risk factors such as lack of physical activity (PA), hypertension and dyslipidemia still remain important. In the plethora of preventive strategies for health, exercise stands out as one intervention that can potentially address multiple classical cardiovascular risk factors (4,5), while possibly also affecting various surrogate measures of cardiovascular risk, such as cardiac structure (6), baroreflex sensitivity (7) and vascular health (8).

In the following review, we intend to explore the context of CVDs with emphasis in specific risk factors such as hypertension, dyslipidemia and endothelial dysfunction, their relationship with PA and exercise, how the current state-of-art can support these interventions, and what are the next steps to enhance the scientific knowledge in this field. We chose to explore these factors due to their importance for CVDs, together with the interesting presentation of the literature. Nonetheless we underscore that other mechanisms are of importance, such as diabetes and inflammation and comprehensive reviews on these topics can be found in the work of others (9,10).

Epidemiologic transition in low to middle income countries

Modern societies have been going through many changes driven by technological advances. Some of these changes were so deep that are now reflected not only in the way people live, but how they die. A transition from deaths related to communicable diseases to those caused by non-communicable diseases was first observed in developed countries, amidst the last century, and is often termed as an "epidemiologic transition" (11,12).

In low to middle income countries (LMICs), between 1960-1980, CVDs became the leading cause of mortality (3,13). Yet, three of the five leading causes of years-of-life-lost in 1990 were still related to poor sanitary and healthcare conditions (13,14). Data from Brazil in 2016 now show a shift towards non-communicable diseases. Moreover, conditions related to lifestyle such as ischemic heart disease, stroke, and diabetes have sharply gained importance and CVDs are now responsible for more than 30% of mortality in this country (3).

Urbanization and industrialization processes resulted in changes PA and dietary intake. In developed countries this was observed when work-related PA dropped (15) while consumption of high-fat and high-sugar foods had a substantial growth (16). Nowadays LMICs are no different, with rates of overweight and obesity, physical inactivity and all health conditions attributable to these factors comparable to those in more developed nations.

Physical activity and exercise as the lost link between lifestyle and health

One key aspect of humans' successful evolution was the ability to run long distances. As a societal hunter-scavenger, sustaining a high-paced pursuit for food was a strong evolutionary advantage (17), and therefore, our bodies were built to be physically active. As modernization advanced, these characteristics became less needed and now individuals spend less and less energy during a regular day.

Morris et al. was the first to show an association between PA and CVD, when compared inactive and active workers, with a lower incidence of hard events shown in the latter. Since then, a great amount of evidence shows the benefits of PA. On the other hand, a decrease in occupational-related PA is noted, as demonstrated in a five-decade analysis (1960-2010), when a sharp increase in physically light (2.0-2.9 METs) and sedentary (<2.0 METs) work activities was coupled with plummeting levels of moderate activities (>3.0 METs) (15).

Although prospective randomized studies evaluating the effects of PA on all-cause or cardiovascular mortality are nonexistent, causative links between these factors are undeniable. One of the latest evidence to support such claim is a recent meta-analysis by Ekelund et al. who found that high amounts of moderate-to-vigorous PA were associated with the elimination of the risk of death associated with high sitting time (18). This new evidence added importance to PA, showing that it could mitigate the associations of sedentary behavior with hard outcomes that were once thought independent. Conversely, evidence from an observational analysis of 354,277 employees between 18-75 years in Sweden, showed a population decrease of 6.7% in cardiorespiratory capacity assessed by maximal oxygen consumption (19), showing that conditioning levels are dropping on a population level.

Taken together, these facts reveal a “pandemic of physical inactivity”. A recent report including 1.9 million participants showed a 27.5% prevalence of insufficient levels of PA worldwide (20). These numbers directly impact public health, with an attributable fraction to physical inactivity of 6% of coronary heart disease burden and 9% of premature deaths (21). This way, PA is now strongly recommended as a public health measure to diminish the impact of non-communicable diseases by many scientific societies and governmental institutions (4,22,23).

Atherosclerosis - the disease of the century

While hard cerebro/cardiovascular outcomes such as ischemic stroke or myocardial infarction can produce devastating consequences on their own, they have one silent and long-lasting underlying factor in common: a diseased artery. In these cases, susceptible sites on the vasculature have been going through a process of subendothelial lipoprotein retention, vascular wall inflammation and plaque formation. This process can take decades until it peaks either with vessel stenosis (and manifestations such as angina) or with plaque rupture and subsequent cellular death. The etiologic process of cerebro/cardiovascular diseases relies heavily on the complex pathophysiological process of atherogenesis (24,25).

In a post-mortem analysis of 2,876 subjects between 15 and 34 years old, Strong et al.(26) showed that atherosclerotic lesions were present in all aortas within the youngest age strata (15-29 years) and that the extent and prevalence of such findings increased in the oldest age group (30-34 years). These results are corroborated by other autopsy-based (27) and imaging (28) studies, demonstrating that the process of subendothelial fatty-streak accumulation begins early in life and tends to happen in every human. However, lipid trapping and accumulation is not sufficient to explain why this process tends to spin out of control leading to plaque growth and possible destabilization. Ultimately, the establishment of atherosclerotic disease is multifactorial, consisting of different components (physical, inflammatory, immunologic, metabolic and biochemical), all of which play a role in its development.

In the following sections, we will specifically address three of these factors: dyslipidemia, hypertension and endothelial dysfunction, later exploring their interface with physical activity and exercise. These factors were chosen due to their close relationship with atherogenesis and the potential to be affected by exercise.

Dyslipidemia and its role in atherosclerosis etiology

An imbalance in lipoprotein serum levels can disrupt homeostasis and lead to pathological conditions in the cardiovascular system. The term dyslipidemia was coined for any metabolic state that denotes this imbalance and is used to classify a number of conditions affecting lipoprotein metabolism and that imply in increased risk of disease. Subendothelial infiltration of apoB-containing lipoproteins, such as low-density lipoprotein cholesterol (LDL-c) is the basis of atherogenic processes (29). If plasma levels of these molecules are elevated, there is an increased chance of their infiltration and retention in the vascular wall, initiating plaque formation. A robust review of mendelian randomized studies has shown a logarithmic risk reduction for coronary heart disease for individuals exposed to lower LDL-c levels through life, independent by which mechanism these lower LDL-c levels are achieved (30).

High-density lipoprotein cholesterol (HDL-c) however, as opposed to LDL-c and other atherogenic molecules, plays a protective role in atherosclerosis pathophysiology. The main antiatherogenic property of HDL-c appears to be related to macrophage cholesterol efflux, in a process that leads to removal of cholesterol from macrophages for subsequent transport to the liver (31). Evidence shows that each increase in 1 mg/dL of HDL-c is related to 2-3% of CVD risk reduction (32).

Triglyceride levels, despite having a less clear association with CVDs, also compose the commonly assessed “lipid profile” and are believed to be important in the pathophysiology of atherosclerosis. In fact, hypertriglyceridemia affects LDL-c and HDL-c composition and metabolism, resulting in a dysfunctional and more atherogenic lipid profile (33). Therefore, disturbances in the balance between lipid levels, as supported by the information above, result in augmented CVD risk, especially in lipid profiles presenting what is called the *atherogenic dyslipidemic triad* (high triglycerides and LDL-c and low HDL-c).

Exercise and dyslipidemia

The physiological rationale for exercise interventions to positively alter the lipid-lipoprotein profile is clear. Several mechanisms could influence these changes, for example, improvements in the inflammatory profile, enhanced overall oxidative capability, and increased baseline and total daily energy expenditure. The logic behind this claim is such that exercise is indeed recommended as a tool for modifying serum lipids and to help address dyslipidemia (34). Nonetheless, when it comes to the evidence regarding the effects of exercise training in modifying lipid-lipoprotein profile, there is still much debate. A number of meta-analyses were published, with disagreeing results. We bring a non-exhaustive list of these studies to illustrate these disparate finding inside this literature.

Halbert et al. were pioneers in the synthesis of the effects of either aerobic or resistance exercise training on blood lipids profile. In their meta-analysis, 1,833 sedentary adults with no established disease were included in 31 trials (35). The authors reported that aerobic exercise training was effective in modifying all measures of serum lipids evaluated (total cholesterol: -3.9 mg/dL, LDL-c: -3.9 mg/dL, HDL-c: +1.9 mg/dL and triglycerides: -7.1 mg/dL). However, these results should be interpreted with caution due to the limited clinical significance of the effect sizes reported and the high heterogeneity presented among the selected studies. In the same study, only four trials examining the effects of resistance training were included, with no differences in serum lipid associated with the exposure to this modality of exercise.

Hespanhol-Junior et al. examined the effects of running-based training on health markers of previously sedentary subjects (36). Their meta-analysis included 2,024 subjects, distributed in 35 studies. In regard to lipid-lipoproteins, the authors found a significant intervention effect only on HDL-c (+2.2 mg/dL) and triglycerides (-13.7 mg/dL), with no effects observed on total cholesterol or LDL-c. Murtagh et al., on the other hand, examined the effects of walking

interventions on cardiovascular health outcomes, including lipids-lipoproteins, through a meta-analytical approach (37). Lipid-lipoprotein markers did not change with interventions. The results of a systematic review conducted by Tambalis et al. (38), agree with the notion implied by the opposite effects in HDL-c in running and walking interventions observed above. In their review, the authors state that only 6 out of 28 trials evaluating moderate-intensity aerobic training showed a significant improve in HDL-c, whereas 22 out of 37 trials of high-intensity aerobic training improved HDL-c. Therefore, a dose-response relationship on aerobic training intensity appears to exist in HDL-c responses to exercise, since higher intensities tend to elicit more favorable changes in this variable. However, this dose-response relationship is yet to be demonstrated experimentally.

The effects of resistance exercise training on lipid-lipoproteins were explored by Kelley & Kelley, on a re-evaluation of a previous (39) meta-analysis, using an improved statistical approach (40). The authors reported that, despite observed improvements for total cholesterol, LDL-c and triglycerides, the prediction intervals calculated for a true effect in a new study in all variables pointed to a neutral effect and therefore caution is advised when recommending resistance exercise training to modify blood lipid profile.

Kelley & Kelley, in another meta-analytic synthesis, explored the effects of aerobic exercise training alone, diet alone or the combination of these two approaches on serum lipid-lipoproteins. In the six included trials with direct comparisons between the interventions, exercise was not effective in modifying total cholesterol, LDL-c and HDL-c, but had a significant effect of -6.0 mg/dL in triglycerides. On the other hand, combining diet with exercise was not effective in modifying HDL-c values, whereas total cholesterol (-13.7 mg/dL), LDL-c (-8.8 mg/dL) and triglycerides (-13.3 mg/dL) were positively affected by this intervention.

Taken together, these results demonstrate that the effectiveness of exercise training in lipid-lipoprotein balance remains debatable. While the biological plausibility to this claim is still solid and evidence regarding impacts of aerobic exercise training intensity on HDL-c points to a possible dose-response effect, the literature on blood lipid-lipoproteins responses to exercise warrants further development. Therefore, as recommended by the current lipid management guidelines (41), comprehensive behavior change encompassing also dietary changes might be the most reasonable lifestyle approach to address dyslipidemia.

Hypertension - the silent companion of cardiovascular disease

Arterial blood pressure (BP) is the force exerted by the blood in any given unit area of the arteries walls. It is the result, in terms of fluid mechanics, of the interaction between the heart pumping blood during each cardiac cycle and the resistance exerted by the arteries to the produced blood flow. Hypertension is characterized by higher and sustained BP values and its prevalence exceeds 1.3 billion people worldwide - around 30% of the world's adult population (42). Its prevalence increases with age, with pooled estimates pointing to figures around 60% among individuals older than 60 years (42). Hypertension is an important public health issue since there is a strong association between BP levels and CVD, with data showing that each increase in 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk for acute myocardial infarction or ischemic stroke (43).

The multifactorial etiology of hypertension adds to the complexity of this health condition. Since the bodily processes involved in BP regulation derive from varied physiological systems and their interactions (ie. nervous, humoral, cardiovascular, renal systems), maladaptation in any of these regulatory mechanisms can result in sustained elevated BP. Furthermore, chronic periods of high BP can also negatively impact these regulation processes, worsening BP levels even more. This vicious cycle sums up to the natural vascular aging process, resulting in a

scenario of sympathetic hyperactivation (44), impaired baroreflex sensitivity (45), shear-stress-related endothelial insults (46), endothelial dysfunction (47), structural changes in the vascular system (48) and in the heart (49). Its prevalence, imposed risk and tendency of worsening with age and/or lack of control, make hypertension the most relevant preventable cardiovascular risk factor in the contemporary ages (50). Yet, hypertension remains poorly treated in LMICs, with estimates of around only 10% of individuals with hypertension considered within controlled ranges of BP (51).

Recently, a robust randomized clinical trial designed to test intensive systolic BP treatment to a target below 120 mm Hg - against the usual target of 140 mm Hg - in hard cardiovascular outcomes was conducted. The trial had a premature ending because mortality rates were significantly different between groups, favoring intensive control (52). This new evidence prompted changes in the hypertension guidelines in the USA, which now considers the cutoff points of 130 mm Hg for systolic and 80 mm Hg for diastolic BP (53). These changes result in 46% of the adult American population with at least hypertension stage I. The new European guidelines, however, did not follow the changes, and the cutoff for hypertension in Europe remains 140/90 mm Hg (54). While the debate on cutoff points may persist in the following years, both guidelines agree when underscoring the importance of lifestyle changes such as healthy diet and exercise as part of hypertension treatment. Those are accessible and effective measures that can help lower population BP levels, increase quality of life and lower public health expenses, especially in countries with limited resources and poor healthcare coverage.

Exercise and hypertension

The acute and chronic responses to exercise – as defined by immediate/short-term and long-term adaptations, respectively – in BP levels are a widely studied physiological effects of this practice. These responses were described in many aspects of cardiovascular responses to effort,

ranging from how immediate changes take place in the cardiovascular system when exercising, to potential morphological adaptations induced by chronic reductions in BP related to exercise. To date, exercise is well regarded as a key lifestyle tool for hypertension, mentioned and endorsed with the maximal grade of evidence in most guidelines for hypertension management (53–55).

Acute effects of exercise in blood pressure

With descriptions dating more than 120 years (56), acute exercise-induced hypotension (named post-exercise hypotension [PEH]) is vastly explored, mainly because it is thought to be the driving force behind chronic BP changes with exercise (57). These acute effects are produced in varied exercise settings and in different populations. For example, Pescatello et al. demonstrated acute BP reductions that lasted for 12.7h in a control-matched sample of men with hypertension exposed to an aerobic exercise session (58). Later, the same group demonstrated an apparent intensity dose-response effect in a mixed sample of 45 men with prehypertension and hypertension, where the more pronounced effects of BP reductions were found in the day when the exercise intensity was higher, as compared with moderate and low intensities (59). Keese et al., showed the presence of PEH after different exercise modalities (aerobic, resistance and combined), with shorter durations observed in resistance exercise sessions when compared to aerobic or combined (60). Rondon et al. in an experiment with acute exercise and ambulatory BP monitoring (ABPM), demonstrated that that PEH is also observed in older adults with hypertension and can persist for 22h (61). Moreover, we have described that individuals with resistant hypertension, despite their pharmacological unresponsiveness, also exhibit PEH during 19h ABPM evaluations after an aerobic exercise session. In this population, however, lower intensities seemed to be more efficient in acutely reducing BP values when compared with moderate intensities (62).

These acute BP responses to exercise are derived from changes in hemodynamic regulation and its mechanisms are not fully elucidated to date. In fact, there is evidence showing acute effects of exercise in many different aspects of BP regulation (63), which can ultimately lead to BP reductions. Some of the known mechanisms behind these acute responses involve a compensatory sympathetic withdrawal (64), baroreflex resetting (65), peripheral vascular resistance reduction (66) – as a possible consequence of sustained histamine-induced vasodilation (67) – coupled with possible changes in cardiac output following an exercise session (61). More importantly, these acute reductions are closely related to chronic decreases in BP related to exercise training. A prospective interventional study evaluating 17 middle-aged individuals with prehypertension explored the relationship between exercise-induced acute and chronic BP changes, showing that the magnitude of acute reductions may predict the extent of chronic BP lowering after training (68). This close relationship raises the hypothesis that chronic exercise-induced BP reductions are an expression of a summation of recent acute exercise effects in BP values (57).

Chronic effects of exercise in blood pressure

Chronic exposure to exercise directly impacts BP values. The quantity and quality of evidence available to make this claim is such that many meta-analytic estimates show the positive chronic effects of various exercise modalities in BP (69–72).

Cornelissen et al., conducted one of the most robust meta-analytic investigation of chronic exercise effects on BP values (69). The authors explored the effects of exercise training in different modalities on BP parameters of individuals with varied categories of BP (normotension, prehypertension and hypertension). The authors included in their analysis 93 randomized clinical trials that lasted ≥4 weeks, totaling 5,223 patients in 153 intervention groups. Exercise type was divided in endurance, resistance, combined and isometric training.

Their most compelling finding was that for individuals with hypertension, aerobic exercise training could imply a reduction of 8.2 mm Hg for systolic and 5.2 mm Hg for diastolic BP. On the other hand, no significant BP reduction was observed in the other modalities, probably due to the inclusion of fewer studies in those arms in comparison with aerobic training.

Recently, however, the current paradigm that exercise prescription for hypertension needed to be focused on aerobic exercise and only complemented by other types of exercise started to be challenged. MacDonald et al. conducted a meta-analysis evaluating 64 controlled studies (n=2,344) to determine the efficacy of resistance training as a sole therapy to modify BP values (71). With the same approach, Corso et al., investigated 68 controlled studies (n=4,110) examining the effects of concurrent training (ie. combining resistance and aerobic training) on the same outcome (70). The authors of both meta-analyses found that, in individuals with higher baseline BP values, either resistance or combined resistance and aerobic training can be effective in chronically reducing BP values with an effect of ~5 mm Hg. With current evidence, it is safe to say that chronic exercise training in either aerobic or resistance modalities can be effective tools in modifying BP values and can be used as therapeutic tools for hypertension. These new evidences prompted a change in the current recommendations of exercise prescription for hypertension from the American College of Sports Medicine, that now considers both modalities to target BP (73,74).

Other modalities of exercise might also impact BP. Wu et al. recently conducted a meta-analysis on the effects of yoga training in BP (72). In their pooled analysis of 49 trials, yoga was more effective than control in reducing SBP and DBP values of individuals with prehypertension (-5.2 mm Hg for SBP and -2.8 mm Hg for DBP) and hypertension (-8.7 mm Hg for SBP and -4.8 mm Hg for DBP). These results were even more pronounced in those yoga interventions with breathing and meditation components. Yet, the authors warn that the

methodological quality of the included studies is low, and because of this fact, the confidence assigned to the meta-analysis results is sub-optimal.

Adding to the above evidence on the importance of exercise in the management of hypertension, Naci et al. in a robust network meta-analysis indirectly comparing more than 39.000 subjects demonstrated that exercise effects are comparable to those produced by common antihypertensive drugs in SBP (75). In their pioneer analysis, the authors have shown that, for individuals with SBP>140 mm Hg, both pharmacological and exercise interventions present a similar reduction effect of approximately 9 mm Hg. In this context, it is clear that exercise training is a notably efficient tool as a non-pharmacological therapy for hypertension. Despite the known limitations of network approaches in meta-analytic studies, the presented findings are novel and exciting, while might bear the potential to increase the importance given to exercise as an antihypertensive therapy (76).

Endothelial dysfunction and its association with hypertension and cardiovascular disease

A significant aspect of cardiovascular health is closely related to the endothelial function. The vascular endothelium, located in the intimal portion of the vascular wall, is responsible for secreting a myriad of vasoactive molecules, playing a key role in vasomotor balance. Likewise, these cells are also involved in a series of physiological processes such as the regulation of coagulation/anticoagulation cascades, inflammatory/anti-inflammatory activity, immunologic responses and morphological remodeling (77). Because of this important role in vascular homeostasis, impairments in endothelial cells function are a critical aspect in the pathophysiology of atherogenesis, (25) and therefore, the assessment of endothelial function was used to describe several populations of interest.

Endothelial vasodilatory function, mediated mostly by nitric oxide (NO) release, is considered one of the endothelium most relevant physiological modulations and can be assessed directly

or indirectly in various forms. With the advance biomedical sciences, developments of techniques, such as the catheter-based angiography, venous occlusion plethysmography and ultrasound imaging of flow-mediated dilatation (FMD), allowed the assessment of the endothelium-mediated vascular motricity. Together with these techniques, physiological studies allowed the role of endothelial cells to be more well elucidated with the understanding of the metabolism of NO and its correlates (L-arginine, nitrites and nitrates) (78), and the important role of NO modulation by nitric oxide synthase on vascular regeneration (79).

The use of high definition ultrasound is now preferred in vascular function evaluation due to its reduced costs and easiness to perform when compared with catheter-based assessments, and its accuracy when compared to venous occlusion plethysmography. Nowadays, other techniques such as finger plethysmography and peripheral artery tonometry have also been described (80,81).

The endothelial function assessment performed by ultrasonographic imaging of flow-mediated dilatation, commonly performed after an occlusion maneuver in the brachial artery, is considered a proxy of general vascular health. Evidence from a comprehensive meta-analysis of prospective observational studies showed that increased FMD is correlated with reduced risk for cardiovascular outcomes in both non-CVD and CVD populations. This pooled estimate of more than 17,000 patients, followed between 6 and 115 months, demonstrated that each increase of 1% in FMD is related to a 12% risk reduction for cardiovascular outcomes (82). Interventions that positively alter endothelial function, might bear the potential of protecting against future cardiovascular events, although controlled clinical studies prospectively evaluating changes in FMD and its associations with cardiovascular outcomes are lacking in the literature.

Endothelial dysfunction is widely associated with hypertension. Panza et. al (83) on an early observation of this relationship, compared the responses of forearm blood flow and vascular resistance to acetylcholine of patients with hypertension compared with normal controls, showing impaired endothelial responsiveness in hypertension. Similarly, Treasure et al. (84) showed impaired endothelium-dependent coronary vasodilation in subjects with hypertension when compared with normotensive controls. Additionally, vascular repair seems also impaired in hypertension, as shown by a cross sectional evaluation of 160 subjects, demonstrating that aging and hypertension are associated with a lower number or circulating endothelial progenitor cells (85). While the understanding if endothelial dysfunction is a consequence or a cause of hypertension is not clear, both conditions indicate poor cardiovascular health and strategies to address either one might bear the potential to affect the other.

Exercise and endothelial function

Even before the Nobel-winning discovery of the endothelial vasodilatory function (86), and the later understanding of the role of NO and shear-stress on this endothelial-derived vasodilation, the potential of exercise to modify vascular function sparked great interest. Early experiments using indirect measures of vascular function (i.e. venous occlusion plethysmography) were pioneer to demonstrate peripheral hemodynamic behavior during and after exercise (87).

Nowadays the notion that exercise can improve vascular function is well established. Mechanisms of these changes are related to short-term positive adaptations in NO bioavailability and regulation by endothelial nitric oxide synthase that can ultimately lead to vascular remodeling and sheer normalization (88). These mechanisms counteract the vascular maladaptation related to aging and should be considered as a first-line approach to vascular dysfunctions (89). In an example of these claims, a pooled analysis of 51 randomized controlled trials on the effects of exercise training in different modalities (aerobic, resistance or combined)

on FMD showed that all examined types of exercise can be effective in improving vascular function (8). In this analysis the mean effect sizes observed were among 2-3% increases in FMD for all modalities.

In patients with a history of CVD, such as coronary artery disease and heart failure, exercise interventions are demonstrated to restore endothelial function. Hambrecht et al., evaluated the coronary artery function of patients with coronary artery disease exposed to a 4-week high-frequency (daily) exercise training program compared to a control group receiving usual care (90). Arterial function was assessed through drug-infusion angiographies. The patients in the exercise group improved coronary vascular function as expressed by a 54% smaller acetylcholine-induced vasoconstriction, while no changes were observed in the control group. The same author, also demonstrated similar benefits in patients with heart failure exposed to an exercise intervention - when compared to non-exercising controls, these patients showed enhanced vascular function as expressed by a 203% increase in peripheral blood flow in response to acetylcholine (91).

In individuals with hypertension, however, it is not clear whether exercise can be effective to improve vascular function. A recent meta-analysis including 5 trials in individuals with hypertension exposed to aerobic exercise, found a +1.5% (95% confidence interval of -0.11% to +3.0%) improvement in FMD values (92). These results are indicative of a possible increase that still needs confirmation in future studies due to the neutral effects pointed by the confidence intervals.

Westhoff et al. evaluated a 12-week, 3 days/week program of walking-based interval training in variables of cardiovascular health, including FMD, in older adults with isolated systolic hypertension, compared to a sedentary control group (93). The authors reported a difference in the variation of pre-post FMD among the study arms, with the exercise group expressing an

increase in FMD values of 2.3%. Interestingly, the pre-post difference in FMD values did not achieve statistical significance (p=0.43). It is unknown, however, if these findings are generalizable to those with regular hypertension, that might have different impairments in their vascular control.

The current state-of-art challenges the notion that endothelial function impairments are easily reversible in samples with a dysfunctional vasculature. In individuals with hypertension, for example, the degree of vascular maladaptation can be such that exercise interventions in common research settings (ie. short-term, small sample sizes) might not be enough to elicit verifiable improvements in these parameters. Since endothelial dysfunction is associated with cardiovascular risk factors and chronic conditions, more studies with robust sample sizes and designs are needed to better understand the effects of exercise on vascular function of populations with different health conditions.

Final remarks

Physical activity and exercise are undeniably tied to improved cardiovascular health in varied scenarios. Interventions aiming to increase the time people spend in these activities can have positive impacts on individual and population health. Nonetheless, the exercise literature still needs further development to improve the understanding on whether exercise can be used to enhance specific markers of health, this fact is ultimately related to the methodological characteristics of the literature. A common caveat observed is that some areas (ie. effects of exercise on lipids and FMD) still lack a body of literature comprised of landmark robust studies, with enough quantity and quality to draw more definite conclusions on the potential of such interventions. On the other hand, however, exercise is better described as an effective treatment for hypertension and, while improvements in this area of knowledge are still needed, this fact

alone should be sufficient for stakeholders to stimulate the implementation of such practices in the public health context, especially in LMICs.

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3. Summary of the HAEL Study

Due to the observed gap in the literature regarding the chronic effects of exercise in blood pressure values of older adults with hypertension, our team conceived the HAEL Study. This gap was not only related to the number of studies in this context, but also in the methodological characteristics of such studies. HAEL stands for "Hypertension Approaches to the Elderly: A Lifestyle Study (NCT03264443) and the trial was constructed to evaluate the effectiveness of a 12-week combined training (aerobic and resistance exercise) in positively altering the ambulatory blood pressure of older adults with hypertension, when compared to a hypertension-focused health education. The robust sample size and gold-standard blood pressure measurements, done through ambulatory blood pressure monitoring, together with the trial design, warrant the scientific rigorousness to answer the research question it proposes. Is an exercise program more effective than educating people on hypertension to lower ambulatory blood pressure values of older adults with hypertension?

Additionally, the multicenter randomized clinical trial was thoroughly thought in a more pragmatic setting than most of the exercise literature. Although not fully pragmatic, many aspects of the HAEL Study conduction are focused on a real-world clinical setting. Above, on figure 1, a plot based on PRECIS-2 tool (www.precis-2.org), depicting the pragmatic characteristics of the trial. More information can be found on the PRECIS-2 registration page of the HAEL Study (https://www.precis-2.org/Trials/Details/500).

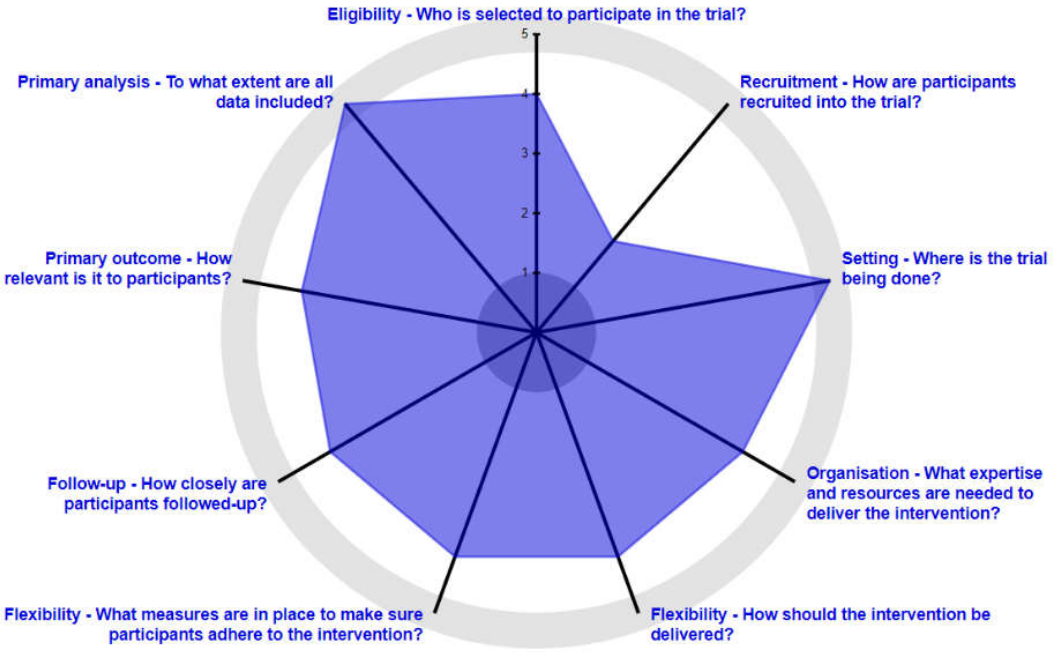

Figure 1 – PRECIS-2 plot of the HAEL Trial

Also, the HAEL Study is strongly based on transparency and data-sharing. We understand that a collaborative science can help to enhance the speed and the correctness of experiments and the answers or doubts that they produce.Herein, two of the prespecified secondary outcomes of the HAEL Study are presented: a baroreflex sensitivity and autonomic control evaluation based on blood pressure and heart rate variability, and a vascular health analysis based on flow-mediated dilatation and carotid intima-media thickness assessments.

The former article is based on an already finished data collection process. This study had to be interrupted during data collection, due to unanticipated equipment malfunction, which limited the randomization ability to dissolve differences between groups. However, we reason that the complete transparency in the reporting of our results might help the understanding of the behavior of these variables within this population.

The latter is an ongoing assessment that was brought to discussion in this thesis as a way to show and understand the progress of our research laboratory in the context of vascular assessments. Ultrasound vascular imaging is a somewhat new technique for the researchers in the Exercise Pathophysiology Laboratory of the Hospital de Clínicas de Porto Alegre. Corrections in our methods of assessment or in the interpretation of our findings might be very useful to the end of the trial conduction.

4. Article 1

Chosen Journal: PLOS One

Baroreflex sensitivity and autonomic modulation in older adults with hypertension undergoing lifestyle interventions: secondary outcomes of the HAEL Study

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ABSTRACT

PURPOSE: Hypertension affects more than 60% of older individuals and lifestyle interventions are recommended for managing this condition while to promoting healthy aging. Changes in baroreflex sensitivity (BRS) and autonomic modulation are plausible mechanisms of cardiovascular benefits of exercise. The aim of the present study was to evaluate BRS and autonomic control modulation of older adults exposed to lifestyle interventions. Our working hypothesis was that the exercise intervention would be superior to the health education program in positively altering these parameters. **METHODS:** In a secondary outcome analysis of the HAEL trial (NCT03264443), 34 older adults (mean age 67.7±7.0) with hypertension (mean blood pressure 142.3±22.5/78.8±12.6 mm Hg) were randomized to one of two 12-week interventions: EXERCISE (a 3 days/week, moderate-intensity, 1h-long, combined exercise program) and EDUCATION (a weekly health education program on hypertension management). BRS, frequency-domain indexes of blood pressure, and heart rate variability and time-domain indexes of heart rate variability were calculated pre and post interventions through a continuous blood pressure signal. **RESULTS:** Pre and post BRS values were 16.7±5.3 ms.mm Hg^{-1} BRS and 16.8±8.1 ms.mm Hg^{-1} for EDUCATION and 16.5±9.3 ms.mm Hg^{-1} and 18.0±10.1 ms.mm Hg^{-1} for EXERCISE (P=0.53). No differences were found in frequency-domain indexes of blood pressure variability and heart rate and time-domain indexes of heart rate variability. **CONCLUSION:** In older individuals with hypertension, no changes in BRS or autonomic control are induced by 12 weeks of exercise training. These subjects might present some degree of irresponsiveness to exercise in relation to autonomic control modulation.

Keywords: blood pressure variability, heart rate variability, autonomic control, blood pressure, exercise, education.

INTRODUCTION

Hypertension is a remarkably relevant cardiovascular risk factor worldwide, present in more than a third of the world's adult population, with systolic blood pressure values >140mm Hg responsible for more than 8 million deaths in 2015 alone (1). Further concern exists in older populations since its prevalence increases with age, reaching more than 60% of individuals more than 60 years old in 2010 (2). While pharmacological approaches are of undeniable importance, non-pharmacological strategies are widely recommended for numerous clinical benefits. Chronic exercise is deemed as a desirable lifestyle choice for a healthy aging process, as well as a broadly known non-pharmacological approach in hypertension treatment(3).

There is robust evidence regarding exercise interventions effectiveness in chronically reducing blood pressure (BP) (4–6). Varied mechanisms may contribute to these beneficial effects – from improved vascular structure (7) and function (8), to changes in sympathetic activity (9). One significant aspect of these adaptations may lie specifically on the autonomic control since patients with hypertension are known to present with heightened sympathetic tone (10) and diminished baroreflex sensitivity (BRS) (11,12). This is notably important in older individuals, as the regular aging process poses negative influences on these physiological parameters (12,13).

The baroreflex is a negative-feedback neural mechanism, responsible for immediate adjustments in BP, serving as a buffer for hypertensive and hypotensive fluctuations in the cardiovascular system. BRS is a way to estimate the functioning of this reflex and is defined as changes in interbeat intervals in milliseconds per unit change in BP. Exposure to chronic exercise interventions is associated with improvements in BRS and autonomic control, especially in patients with heart failure (14,15), but also being demonstrated in older patients with hypertension (9). However, previous studies of exercise effects on these parameters were

limited to highly controlled interventions, or treatment-naive subjects, leaving a need to test whether low-cost/highly generalizable exercise interventions are effective in modifying these variables among this subset of the population in more realistic scenarios. Therefore, the aim of the present study was to assess the effectiveness of a pragmatic combined exercise intervention in BRS and autonomic control parameters in older adults with hypertension. Since there is a rationale for direct exercise-induced adaptations that could result in chronic modifications in in BRS and autonomic control, we hypothesize that the exercise intervention would promote superior adaptations to these parameters when compared to the health education intervention.

METHODS

This report describes the analysis of secondary outcomes in a multi-center single-blinded randomized clinical trial (NCT03264443). For the present study, we analyzed only patients recruited in the coordinator center, based in Porto Alegre, Brazil. A flow diagram describing the study design is presented in figure 1.

Eligibility Criteria

We included physically inactive (<2 weekly formal exercise sessions) older adults (≥60 years old) with hypertension. We excluded individuals with any of the following characteristics: recent history of cardio/cerebrovascular events (<12 months), severe cardiovascular, pulmonary or neurologic diseases, high weekly alcohol consumption, chronic renal disease needing dialysis, that underwent recent cancer treatment (<2 years), with cognitive impairments or exercise contraindications based on a graded test.

Randomization and blinding

Eligible subjects were randomly allocated to receive 12 weeks of either a combined exercise or a health education program. We conducted a 1:1 computer-generated center-stratified

randomization procedure. Subject group allocation was revealed only after initial assessments. Outcome assessors of operator-dependent evaluations were blinded to subjects' allocation.

Intervention and comparator

The exercise intervention (EXERCISE) was comprised of aerobic and resistance exercises, performed 3 days per week. Exercise sessions lasted ~60 minutes and consisted of a 5 minutes warm-up, 30 minutes of aerobic exercise, 20 minutes of resistance exercises and a 5 minutes cooldown. Intensity for both modalities was monitored through perceived-exertion scales, and participants were instructed to maintain an effort level of moderate or higher. Walking and/or running in a predefined track was the chosen modality for aerobic exercise training (AET). For resistance training (RT), 4 to 5 bodyweight/elastic-band exercises for the major muscle groups were used in 2-3 sets of 10-12 repetitions. Progression was encouraged as the subject became more fit. For this, we used increases in time – until reaching 30 minutes – and pace for AET and increases in resistance and/or difficulty for RT. All exercise sessions were supervised by experienced exercise professionals with kinesiology and/or physiotherapy backgrounds, together with undergraduate research assistants from the same areas.

The comparator group received a health education (EDUCATION) program, with weekly meetings. A multi-professional healthcare team, formed by kinesiology, physiotherapy, nursing, and pharmacy professionals, conducted interactive class-like meetings addressing information about hypertension treatment strategies (such as condition awareness, sodium reduction, medication adherence, physical activity, etc.). Participants in the EXERCISE arm received, during the cool-down period of every session, shortened verbal information on similar topics to those addressed in the EDUCATION arm.

Adherence to both interventions was encouraged with weekly electronic text messages. If a subject missed two subsequent sessions, a study staff member would contact him/her by phone to verify the reasons for absence and remember next session appointment.

In total, 36 sessions for EXERCISE and 12 for EDUCATION were scheduled. All interventions were conducted in group. A detailed description of the exercise and health education interventions, as well as a more comprehensive description of the study methods, can be verified elsewhere (16).

Outcome assessment

We recorded continuous beat-to-beat BP and heart rate signals (BIOPAC, Goleta, USA) at a sampling rate of 1000Hz to assess BRS and autonomic control through BP and heart rate variability indexes during two conditions: resting and a mental stress challenge.

In order to minimize any external influences in BP, before any procedure and/or signal recording, subjects laid quietly for 10 minutes in a semi-dark room with controlled temperature (20-23ºC). During this time, a staff member would then prepare the procedure, positioning a double-finger cuff in the proximal region of the second and third fingers of subjects' right hand. BP signal was obtained through the last 5 minutes of a 10-minute period and for 5 minutes during the mental stress challenge. This procedure was conducted prior (PRE) and after 12 weeks of intervention (POST).

Mental stress challenge

A simplified version of the Stroop word-color test (17) was conducted during continuous BP acquisition to induce sympathetic stimulation. The subjects were asked to identify in a cardboard the font colors of written color names in colored backgrounds, as fast as possible, for 5 minutes.

Baroreflex sensitivity, blood pressure and heart rate variability calculations

Systolic BP and RR interval time series were extracted synchronously from the raw data acquired by the continuous beat-to-beat blood pressure signal. Data extraction was performed using a customized computational script written in Visual Basic programming language. A set of time-domain indexes for the RR time series was evaluated inside a 300s window over the trace (mean RR interval [RR]; standard deviation of normal RR intervals [SDNN]; root mean square of successive differences [RMSSD]; percentage of RR interval with a difference of 50ms from the preceding RR interval [PNN50]). Mean systolic blood pressure and its standard deviation were also calculated. For BRS estimation we used a method proposed by Bernardi et al.(18), dividing the standard deviation of RR intervals by the standard deviation of systolic BP.

Both time series were cleaned for eventual artifacts (ie. ectopic beats) and then resampled for the spectral analysis. The power spectrum density was calculated using the Fast Fourier Transform with 2,048 samples, Hanning window, and frequency resolution of 0.0033Hz. The following frequency bands were computed: Very Low Frequency (0.0033Hz <VLF< 0.04 Hz), Low Frequency (0.04Hz< LF<0.15Hz), High Frequency (0.15Hz<HF<0.4Hz) and Wide Band (0.0033Hz<WB<1Hz). The statistical analysis was done using the respective normalized bands divided by (WB-VLF). A delta in LF/HF ratio for BP was calculated between resting and mental stress conditions in order to explore interventions effects on sympatho-vagal balance responses to stressful situations.

Office blood pressure

After a 5-min seated rest period, subjects BP was evaluated three repeated times (with an 1-min interval) in the arm with the highest BP. This assessment was conducted according current Brazilian Guidelines on Hypertension (19).

Statistical analyses

Sample size was calculated based on effect sizes derived from previous reports(20). For the reported *cohen d* effect sizes of 0.95, the required sample size was 10 subjects. We, therefore, estimated our sample size based on a more conservative *cohen d* effect size of 0.5, which required 26 subjects for 80% of power and p=0.05.

Statistical analyses of BRS and autonomic control variables were performed utilizing the Generalized Estimating Equations exploring the main effects of time and group as well as the interaction term group*time. Whenever applicable, a post-hoc test of Bonferroni was conducted. Data were analyzed using "gee" package for R running on R version 3.6.1 (R Foundation for Statistical Computing; Vienna, Austria). Results are expressed as means±SD or as otherwise stated. Our code is publicly available through the Open Science Framework website of the study (https://osf.io/56wrv/).

Two separate analyses were conducted: a full analysis set (FAS) for enrolled individuals allocated to one of the study's arms that had at least one valid datapoint (irrespective of intervention completion), and one analysis only comprised of individuals who completed all phases of pre-testing, intervention, and post-testing (COMP). For the FAS, if the subjects did not have a particular datapoint, data were imputed using the "Last Observation Carried Forward" method.

Ethical considerations

This project was submitted to ethical approval by our institutional review board (project number 17-0044) and is in accordance with all current ethical standards. All subjects were fully informed and provided written consent prior to the evaluations.

Results

Out of 152 potentially eligible subjects, 35 were included in the study and randomized for the interventions. One subject did not attend any of the collection sessions for the present analysis and was excluded from FAS. Five subjects did not complete the proposed interventions (4 in EXERCISE and 1 in EDUCATION). One subject from EDUCATION completed the intervention but did not attend the final evaluation visit. A subjects' flow diagram is presented in figure 1. Therefore, 34 subjects were included in the FAS analysis, and 26 in COMP analysis. A dropout rate of 5% was observed in EDUCATION, whereas 25% of the sample dropped out in EXERCISE.

Patient characteristics for both analyses are displayed on table 1. The groups were well balanced in respect to sex distribution, mean age and blood pressure values. A higher number of subjects were undertaking beta-blocker drugs in EDUCATION. Daily dosage of beta-blocker medications per intervention group is depicted in table 2.

In all analysis, no differences between the groups were observed in BRS and autonomic control. FAS and COMP BRS and BP variability spectral power results are displayed in table 3. Time and frequency domain indexes for HRV are presented in table 4.

Pre and post rest-to-stress deltas in BP LF/HF ratio (in arbitrary units) in FAS analysis were of 0.11±0.26 and 0.19±0.17 for EDUCATION and 0.15±0.26 and 0.14±0.24 in EXERCISE, respectively. Pre and post rest-to-stress deltas in BP LF/HF power in COMP analysis were of

0.09±0.27 and 0.18±0.17 for EDUCATION and 0.11±0.26 and 0.09±0.21 in EXERCISE, respectively. No differences between the groups were found in any of these comparisons (P>0.05).

Changes from baseline in systolic BP in FAS analysis were -3.1 mm Hg, 95%CI [-13.9 to +7.7] after EDUCATION and -3.7 mm Hg, 95%CI [-18.8 to +11.4] after EXERCISE. Changes from baseline in diastolic BP in FAS analysis were +2.4 mm Hg, 95%CI [-1.8 to +6.6] after EDUCATION and +0.7 mm Hg, 95%CI [-4.1 to +5.6] after EXERCISE. Changes from baseline in systolic BP in COMP analysis were -3.1 mm Hg, 95%CI [-13.9 to +7.7] after EDUCATION and -3.7 mm Hg, 95%CI [-18.8 to +11.4] after EXERCISE. Changes from baseline in diastolic BP in COMP analysis were +2.7 mm Hg, 95%CI [-1.9 to +7.4] after EDUCATION and +0.7 mm Hg 95%CI [-7.1 to +8.4] after EXERCISE. No differences between groups were found in any of these comparisons (P>0.05).

DISCUSSION

The present study demonstrates that in older individuals with hypertension the exposure to a 12-week exercise program based on combined training compared to a health education intervention implied in no detectable modification in BRS and in autonomic control indexes expressed by frequency-domain analysis of BPV and HRV and time-domain analysis of HRV assessed by our methods. Our results also did not show any difference between groups regarding office blood pressure and autonomic balance change in an experimental stressful challenge. These results are contrary to our working hypothesis and might suggest a degree of irresponsiveness of these individuals to short-term exercise interventions. However, exercise training benefits are well described, and our results do not challenge the current state-of-art that exercise is effective in the management of hypertension.

Our BRS and autonomic control results add to the diversity in methodology and responses found in the literature, showing that influences of exercise training in these variables in hypertension might still be debatable and vary depending on the selected population, study characteristics and method of assessment. Hypertension is a health condition markedly characterized by its sympathetic hyperactivity and diminished BRS (11) and age can also negatively affect this control (13). While the rationale for chronic exercise-mediated changes in these parameters exists, in a meta-analytic investigation of the effects of exercise training in HRV, Sandercock et al. (21), found that exercise-induced changes in autonomic control are influenced by age. In their pooled analysis, the authors found that older individuals seemed to be unresponsive to these autonomic control modulations. Monahan et al., showed that BRS declines with age and is positively correlated with arterial compliance, and although the authors demonstrated that an exercise intervention can restore these markers of cardiovascular health, their sample was limited to middle-aged subjects (22) and it is unclear how older ages could negatively affect or even blunt the responsiveness of this variable to exercise interventions.

Laterza et al. (9), on the other hand, showed a BRS restoring effect of a 4-month exercise intervention in never treated patients. However, these authors evaluated BRS through infusion of vasoactive drugs and monitoring muscle sympathetic nerve activity and heart rate, a technique that differs significantly from ours. Additionally, the use of treatment-naive subjects in the referred study, although important for mechanistic explorations, limits our ability to directly compare our samples. Our study was conducted in a more pragmatic scenario, where standard-of-care is already implemented and might influence the physiological reserve available for such responses. These key differences might explain the contradiction between our findings and the referred study.

Brito et al. (23) recently found improvements in BRS in treated patients with hypertension (30-65 years old) submitted to 10 weeks of exercise training. Yet, the present study, differently from Brito et al., did not limit the participation of patients taking medications that affect autonomic balance (ie. beta-blockers) - which currently represent nearly 20% of patients under pharmacological treatment with hypertension in Brazil (24). Beta-blockers positively affect BRS indexes (25), and limiting its influence by withdrawing such drugs for experimental procedures likely affect observed responses during experiments. Nonetheless, due to the characteristics of our study, we decided not to interfere in the pharmacological scheme that patients would usually present. Also, the data generated in our study offers restricted comparability to those generated by Brito et al. because the latter reported log-transformed analyses, which limits the interpretation of the reported findings in a clinical context.

Evidence from animal models have shown that in spontaneously hypertensive rats, reduced BRS may blunt cardiovascular and autonomic adaptations to exercise training (26). In this regard, since age and the duration of hypertension are closely related do BRS impairments and are the key characteristics of our sample, these factors might be overlapping mechanisms where poor BRS and autonomic control responsiveness to lifestyle interventions can happen in older adults with this condition.

Our results did not provide statistically detected differences in office blood pressure values. Although both intervention groups have presented numerically lower post values (from 3-5 mm Hg) in systolic blood pressure, when compared with pre-testing, any statistical treatment might have been affected due to a limitation in the current sample size. This analysis was included as an ancillary outcome in the present study, but no sample size calculation was performed for it. If confirmed in future analyses, results of this magnitude might be an indicative that both interventions can potentially lower blood pressure, a characteristic deemed

in an active control group. On the other hand, the current results do not support any detectable changes in either autonomic control of blood pressure or office blood pressure values in older adults with hypertension exposed to lifestyle interventions.

Our study presents a number of limitations. First, we underscore that despite the sample size calculation showing adequate power for our BRS analysis, effect sizes derived from previous studies might be overestimated, which could have underestimated the number of patients needed to show a significant difference between groups, since our results go to the same direction of the study used as a reference (20). However, to the best of our knowledge we used the best evidence available, with sample characteristics similar to ours. If the BRS and autonomic control assessment technique shown here is to be applied, we strongly suggest sample sizes bigger than the presented, in robust repeated measures models as the ones herein shown, that deal with absolute values (not as percentages or transformations as reported in many studies) to better estimate the effects of exercise in the chosen variables. Additionally, we underscore that it was not possible to analyze groups of the same size because unanticipated equipment malfunction happened during the trial conduction. Because of this fact, we decided to stop data acquisition processes to ensure data quality.

Also, because of this early stopping, we ended up with more patients taking beta-blockers in EDUCATION and our results should be interpreted in light of this information. In our sample a significant baseline difference favoring EDUCATION was found between groups in HRV high-frequency power, which could be attributable to a higher number of individuals taking beta-blockers in EDUCATION (especially within the completers). However, when checking beta-blockers use by drug and dosage, as shown in table 2, group differences appear less relevant. Anyhow, to ensure consistency, our team visually inspected the results separated by beta-blockers users and non-users and the magnitude and direction of results remains similar

to what we have found. No subgroup analysis was conducted in this context due to the limited group sizes that would be generated by this division.

CONCLUSIONS

Older individuals with hypertension exposed to 12 weeks of combined training compared to EDUCATION did not present any changes in BRS or autonomic control evaluated by frequency domain spectral analysis of BPV or HRV, neither time-domain indices of HRV. Interestingly, these results were accompanied by a lack of difference between groups in office blood pressure. Taken together, the presented results could indicate some degree of blunted responsiveness to exercise-induced changes in blood pressure regulatory mechanisms, that could ultimately impair blood pressure reductions related to chronic exercise in the selected population. However, evidence about exercise-induced cardiovascular benefits is robust and lifestyle programs aiming its practice should be encouraged. Future studies utilizing similar techniques and different training protocols are still warranted to fully elucidate autonomic control responses to exercise in older individuals under treatment for hypertension.

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AUTHORS CONTRIBUTIONS

L. P. S. - was involved in the elaboration the study conception and design, data acquisition, analysis and interpretation and drafting the manuscript.

C. E. B - was involved in the elaboration the study conception and design, data acquisition, and in the revision of the manuscript for important intellectual content.

E. F. - was involved in data analysis and in the revision of the manuscript for important intellectual content.

L. O. P., N. L. O. and R. S. M. - were involved in the elaboration the study conception and design, data acquisition, and in the revision of the manuscript for important intellectual content.

D. U. - was involved in the elaboration the study conception and design, data interpretation and in the revision of the manuscript for important intellectual content.

REPRODUCIBILITY STATEMENT

The HAEL Study Group endorses the practice of sharing of scientific data and we intend that that the data from the study contributes to the further understanding of the topics herein explored. The study has consent from participants as well as IRB approval to share de-identified data. Data sets, variables' dictionary and statistical analysis script will be made available online upon registration and acceptance of the data sharing terms and policy. Data usage will be under the PI's auspice.

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TABLES

Table 1 – Sample characteristics

	Full analysis set			Completers		
	Total Sample	**Education**	**Exercise**	**Total Sample**	**Education**	**Exercise**
N	34	18	16	26	16	10
Male, N(%)	23(68%)	12(67%)	11(68%)	16(62%)	10(63%)	6(60%)
Age, years±SD	67.7±7.0	68.7±7.4	66.5±6.5	68.5±7.6	69.4±6.8	66.5±7.7
SBP, mmHg±SD	142.3±22.5	141.2±20.6	143.5±25.0	138.9 ±20.7	140.0±20.5	137.1.0±21.9
DBP, mmHg±SD	78.8±12.6	78.4±12.1	78.6±13.6	76.5±11.2	76.2±10.4	76.9±13.1
AH medications, median(range)	2(1-5)	2(1-4)	2(1-5)	2(1-4)	2(1-4)	2(1-4)
Beta-blocker use, N (%)	12(35%)	7(39%)	5(31%)	9(34%)	7(43%)	2(20%)
Diabetes, N(%)	3(9%)	2(11%)	1(7%)	2(8%)	2(12%)	0
VO_{2peak} $ml.kg^{-1}.min^{-1}$±SD	26.6±5.8	26.8±6.2	26.4±5.5	26.5±6.3	26.7±6.5	26.1±6.4
BMI, kg/m^2 ±SD	30.1±4.8	29.1±4.6	31.1±4.9	29.6±4.8	28.6±4.5	31.2±5.1
Waist circumference, cm±SD	104.1±13.4	103.3±13.3	105.2±14.0	103.2±13.6	101.9±13.0	105.3±14.9

SBP= systolic blood pressure; DBP= diastolic blood pressure; AH= antihypertensive; BMI= body mass index;

Table 2 – Daily dosage ofbeta-blockers per intervention group

	Metoprolol 100mg	Metoprolol 50mg	Atenolol 100mg	Atenolol 50mg	Atenolol 25mg	Propranolol 80mg	Propranolol 40mg	Propranolol NR
	Full analysis set							
Education (n)	1	1	1	3	0	0	0	1
Exercise (n)	1	0	1	0	1	1	1	0
	Completers							
Education (n)	1	1	1	3	0	0	0	1
Exercise (n)	0	0	1	0	1	0	0	0

Table 3 – Baroreflex sensitivity and spectral analysis of blood pressure variability

		Education		Exercise		
	n	Baseline	Change from baseline	Baseline	Change from baseline	P-value*
BRS (ms.mm Hg^{-1})						
FAS	34	16.7±5.3	+0.1 (-4.7 to +4.9)	16.5±9.3	+1.4 (-1.5 to +4.4)	0.53
COMP	26	17.3±5.1	+0.1 (-5.3 to +5.5)	14.7±5.5	+2.3 (-2.2 to +6.8)	0.41
BPV – HF (NU)						
FAS	34	0.47±0.06	+0.01 (-0.02 to +0.04)	0.46±0.07	+0.01 (-0.03 to +0.04)	0.80
COMP	26	0.47±0.06	+0.01 (-0.02 to +0.05)	0.45±0.06	+0.01 (-0.04 to +0.06)	0.93
BPV – LF (NU)						
FAS	34	0.33±0.08	-0.02 (-0.05 to +0.01)	0.29±0.07	+0.01 (-0.02 to +0.05)	0.11
COMP	26	0.33±0.08	-0.02 (-0.05 to +0.02)	0.29±0.05	+0.02 (-0.03 to +0.07)	0.13
BPV – LF/HF						
FAS	34	0.72±0.23	-0.06 (-0.16 to +0.04)	0.64±0.16	+0.01 (-0.08 to +0.11)	0.21
COMP	26	0.72±0.22	-0.07 (-0.12 to +0.05)	0.67±0.17	+0.02 (-0.14 to +0.17)	0.27

Values presented as mean±SD; *= value for group*time interaction; BRS= Baroreflex sensitivity; FAS= Full analysis set; COMP= completers analysis; BPV= Blood pressure variability; HF= High frequency power; LF= Low frequency power; NU= Normalized units

Table 4 – Heart rate variability (time-domain and spectral analysis)

		Education		Exercise		
	n	Baseline	Change from baseline	Baseline	Change from baseline	P-value
RR (ms)						
FAS	34	1023.6±140.4	+2.8 (-42.0 to +47.7)	980.2.3±140.5	+25.2 (-27.3 to +77.7)	0.40
COMP	26	1038.7±135.5	+3.2(-47.3 to +53.7)	910.5±152.6	+40.3 (-41.3 to +121.9)	0.32
SDNN (ms)						
FAS	34	49.1±21.5	+6.1 (-4.7 to +16.8)	55.5±15.2	+6.1 (-3.8 to +15.9)	0.99
COMP	26	50.1±20.9	+6.8 (-5.1 to +18.8)	53.6±12.8	+9.8 (-5.2 to +24.7)	0.70
RMSSD (ms)						
FAS	34	64.3±26.3	+8.1 (-8.8 to +25.0)	67.4±25.5	+3.4 (-7.2 to +14.0)	0.54
COMP	26	66.6±26.7	+9.1 (-9.8 to +28.0)	63.1±18.2	+5.4 (-11.3 to +6.5)	0.70
PNN50 (%)						
FAS	34	34.8±15.2	+1.8 (-7.4 to +10.9)	37.8±16.07	+2.6 (-4.7 to +10.0)	0.84
COMP	26	35.9±15.7	+1.9 (-8.3 to +12.3)	36.4±11.8	+4.2 (-7.3 to +15.7)	0.71
HRV - HF (NU)						
FAS	34	0.49±0.06	-0.01 (-0.04 to +0.16)	0.44±0.09	+0.01 (-0.04 to +0.05)	0.40
COMP	26	0.49±0.06	-0.01 (-0.04 to +0.18)	0.43±0.07	+0.01 (-0.06 to +0.08)	0.45
HRV – LF (NU)						
FAS	34	0.24±0.07	-0.02 (-0.04 to +0.15)	0.29±0.12	+0.01 (-0.02 to +0.05)	0.57
COMP	26	0.24±0.06	-0.02 (-0.05 to +0.16)	0.26±0.10	+0.02 (-0.03 to +0.07)	0.40
HRV– LF/HF						
FAS	34	0.47±0.12	+0.03 (-0.07 to +0.14)	0.59±0.28	+0.06 (-0.08 to +0.21)	0.67
COMP	26	0.47±0.11	+0.04 (-0.08 to +0.16)	0.54±0.20	+0.10 (-0.13 to +0.33)	0.53

Values presented as mean±SD; *= value for group*time interaction; HRV= Heart rate variability; FAS= Full analysis set; COMP= completers analysis; HF= High frequency power; LF= Low frequency power; NU= Normalized units

FIGURES

FIGURE 1

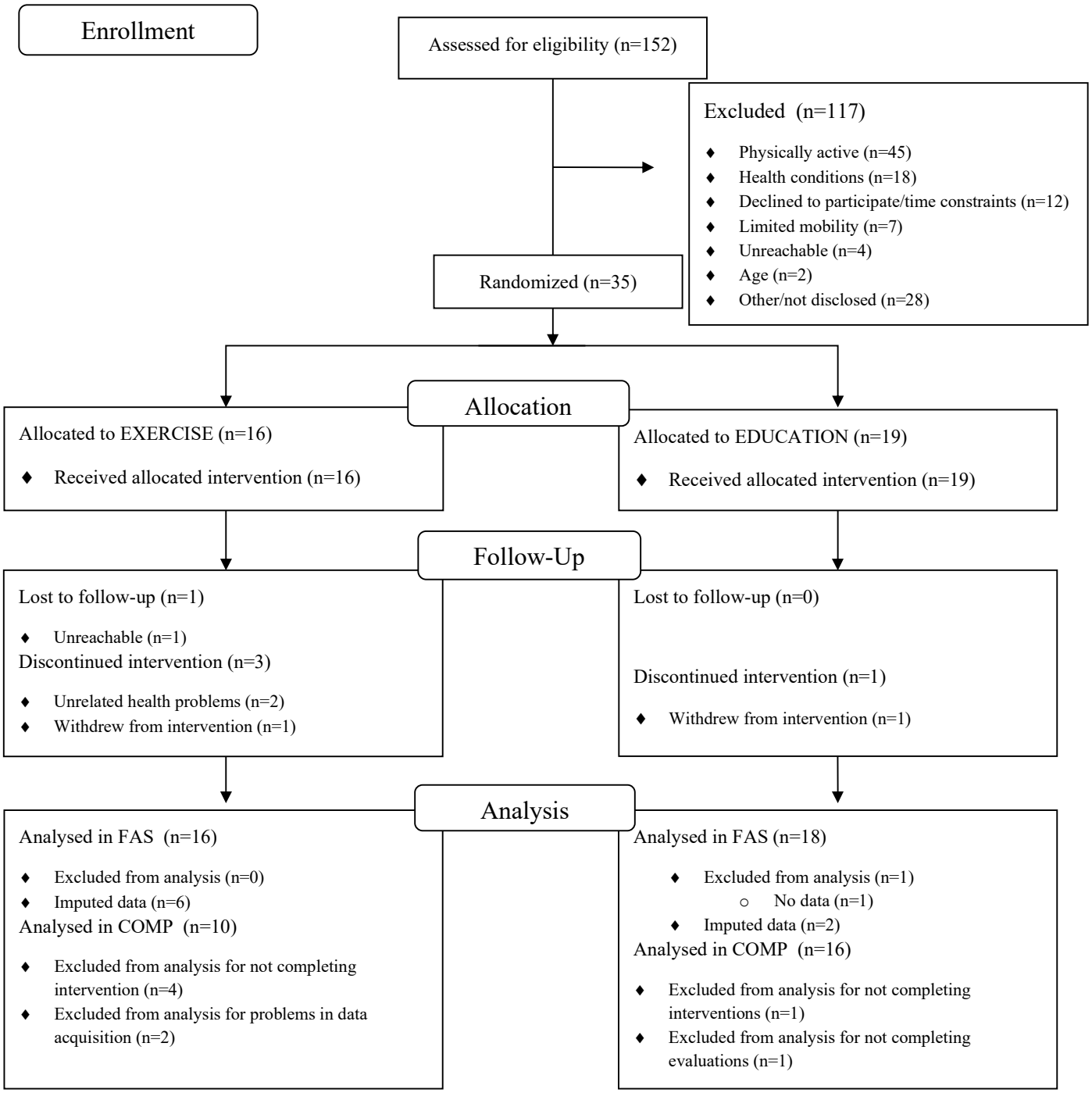

Figure 1 – Participants' flow-chart. FAS= full analysis set; COMP= completers analysis.

5. Article 2

Responses of vascular health to lifestyle interventions in older adults with hypertension: an interim analysis of the HAEL Study

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ABSTRACT

PURPOSE: Lifestyle changes are recommended approaches for hypertension and may bear unexplored clinical benefits in vascular health of older adults. The aim of the present study was to evaluate the effects of exercise and health education programs on markers of vascular health assessed by measurements of flow-mediated dilatation (FMD) and carotid intima-media thickness in older adults with hypertension. METHODS: This is an interim analysis of the HAEL Study (NCT03264443). Seventy-four subjects (35 males, 67.3±5.9 years old, mean blood pressure 138.0±22.0/80.3±13.0 mm Hg) with hypertension were randomized to two lifestyle-based interventions lasting 12 weeks. EXERCISE group took part in a combined exercise program 3 days/week, at moderate intensity, for 1h, whereas EDUCATION group was exposed to a hypertension-based health education program once a week. Ultrasound assessments of brachial artery FMD and carotid intima-media thickness were performed prior to (PRE), during (MID) and at the end of interventions (POST). RESULTS: Baseline (means±sd) and change from baseline (means and 95%CI) after six and twelve weeks in FMD values in EDUCATION were 6.1±3.9%, -1.2% (-3.2 to +0.7), and -0.9% (-2.8 to +1.0), respectively, whereas in EXERCISE were 5.3±3.5%, -0.5 (-2.6 to +1.7), and +0.3 (-2.0 to +2.6), respectively (P=0.24). Baseline carotid intima-media thickness values and after six and twelve weeks were 0.69±0.11 mm, -0.01 mm (-0.07 to +0.04), and -0.02 mm (-0.09 to +0.06) for EDUCATION, respectively, whereas for EXERCISE were 0.71±0.15 mm, -0.03 mm (-0.08 to +0.02), and -0.04 (-0.07 to +0.01), respectively (P=0.38). CONCLUSION: Long lasting endothelial dysfunction and morphological adaptations associated with age and hypertension did not present changes to three-month lifestyle interventions. These results suggest that short-term exercise or health education interventions might not be sufficient to reverse vascular maladaptation related to aging and hypertension. **Keywords:** flow-mediated dilatation, carotid intima-media thickness, blood pressure, exercise, education.

INTRODUCTION

Lifestyle management of hypertension is an indispensable part of its treatment approaches. Recent guidelines underscore the relevance of these strategies, presenting non-pharmacological treatments such as exercise and healthy eating in the higher class of recommendation and level of evidence (1). In older adults, where the prevalence of this condition surpasses 60% (2), adoption and maintenance of exercise can not only help to lower blood pressure (BP), but also to promote a healthy aging process, positively impacting different physiological systems and mitigating functional declines associated with age (3).

Vascular aging and its close relationship with arterial stiffness, due to inflammatory, metabolic and neurohumoral mechanisms, are one of the key links between hypertension and its increased prevalence with age (4). On the other hand, the notion that chronic exposure to physical activity and exercise is associated with improved vascular function assessed by flow-mediated dilatation (FMD) is well established (5–9), while structural changes assessed by carotid intima-media thickness (cIMT) might still be debatable (10,11).

Combining aerobic and resistance exercises in a training program, a strategy called combined or concurrent training, is an efficient way to obtain the majority of cardiovascular and skeletal muscle adaptations to exercise. A recent meta-analysis showed that this modality of training is also effective for BP reduction among individuals with hypertension (12). Additionally, resistance training is an essential feature of an exercise program to older adults as it promotes the maintenance of skeletal muscle strength and function in this population and is widely recommended across different health conditions (13).

Evidence regarding the efficacy of combined training in vascular function and structure of older adults with hypertension, however, is scarce. Therefore, the present study intended to evaluate parameters related to vascular health (FMD and cIMT) in this age group exposed to a combined

exercise program compared with a health education program. Because the well documented circulatory stimuli elicited by exercise as well as vascular adaptation in varied sets of patients, we hypothesized that the exercise program would promote superior adaptation in FMD and cIMT, considering the first as the main outcome variable in the present study.

METHODS

The present study is a partial analysis of a multi-center single blinded randomized clinical trial (NCT03264443). For this report, only patients recruited in the coordinator center, in Porto Alegre, Brazil, were analyzed.

Eligibility Criteria

Physically inactive (<2 exercise sessions per week) older adults (60 years or older) with hypertension were recruited through media and in-person advertisements, social media posts and patient lists. Individuals with a recent history of cardio/cerebrovascular events (<1 year), severe cardiovascular, pulmonary or neurologic conditions, increased alcohol consumption, chronic renal disease with the need of dialysis, that underwent recent cancer therapy (<2 years), with cognitive impairments or exercise contraindications based on a graded test, were excluded.

Randomization and blinding

Randomization was conducted with a 1:1 ratio through a computer-based center-stratified procedure. Group allocation was kept unknown until the completion of baseline assessments and operator-dependent evaluations were conducted by blinded assessors that were unaware of subjects' allocation.

Intervention and comparator

The proposed exercise program (EXERCISE) encompassed aerobic and resistance exercises, with a 3 days/week frequency. Each session lasted approximately 1h and encompassed a 5-minute warm-up, 30 minutes of aerobic exercise, ~20 minutes of resistance exercises and a 5-minute cooldown. Intensity was monitored through perceived-exertion scales in all exercises, and participants were instructed to maintain an effort level of at least moderate. For the aerobic exercise training (AET), subjects walked/ran in a predefined track and for resistance training (RT), 2-3 sets of 10-12 repetitions on 4 to 5 bodyweight/elastic-band exercises for the major muscle groups were used. Progression was constantly encouraged throughout the program. In order to do so, increases in time – until reaching a maximal time of 30 minutes – and pace for AET and increases in resistance and/or difficulty for RT were possible. Experienced exercise professionals with backgrounds in exercise sciences supervised all exercise sessions.

The health education group (EDUCATION) received a health-focused educational program, with weekly encounters. The program was conducted by a multi-professional team encompassing kinesiology, physiotherapy, nursery and pharmacy professionals. The sessions were conducted as interactive class-like meetings and addressed varied information about hypertension treatment strategies (non-pharmacological approaches, stress reduction, sodium management, etc.). Individuals allocated to the exercise program received shortened educational information, with a similar content to the EDUCATION group inside the cool-down period.

Adherence to the interventions was encouraged weekly with electronic text messages, sent to the subjects at the end of each week. If an individual missed two subsequent sessions with no prior warning, a staff member would make contact by phone to remember the next session.

A total of 36 sessions for EXERCISE and 12 for EDUCATION were scheduled. All intervention sessions were conducted in groups. A detailed description of the exercise and

health education interventions, as well as a more comprehensive description of the study methods, can be found elsewhere (14).

Outcome assessment

We used a high-resolution ultrasound system (HD7X, Phillips, Netherlands), equipped with a 7-12 MHz linear array probe to determine FMD and cIMT from images of the brachial and right common carotid artery, respectively. Two sonographers with proper training for the chosen techniques conducted the experiments and pre-post assessments were always conducted by the same person.

For FMD assessments, subjects were instructed to present themselves in a fasted state of at least 8h, avoid recent physical exertion, and take morning medications as usual. After arriving to the laboratory, subjects laid quietly in a semi-dark temperature-controlled (20-23º) room for 15 minutes before assessments. After that, the sonographer would record a 1-minute baseline loop of brachial artery diameter. The subject's forearm blood flow was subsequently interrupted by a 5-minute occlusion maneuver with a cuff inflated to 220-240 mm Hg, placed 2-3 cm proximally and medially to the antecubital fossa. As soon as the cuff was released, the sonographer would record a 3-minute loop of the vascular response. Images were analyzed using an edge-detection software (Brachial Analyzer, Medical Imaging Applications, Coralville, IA) and FMD was calculated as the percent difference between averaged post-occlusion maximal diameter and baseline diameter of the brachial artery. All tests followed FMD assessment current recommendations by the time of the study planning (15).

For cIMT assessments, that were usually done after FMD, subjects remained laid down and exposed their necks by tilting their heads back and approximately 45º to the left. Images were obtained through 60-90" in the right common carotid artery, proximally to the carotid bulb. cIMT was calculated through an automated software (Carotid Analyzer, Medical Imaging

Applications, Coralville, IA), as the average of all acquired loops. All ultrasound assessments were conducted between 8 and 11am and happened in three occasions: prior to interventions (Baseline), during the 6th week of intervention (MID) and after intervention (POST).

BP was measured in both arms after a 5-minute sitting rest. An average of three consecutive measurements at least one minute apart, performed in the arm with the highest BP value was recorded as the BP value in baseline, MID, and POST intervention. Procedures for BP assessment followed current Brazilian guidelines (16).

Statistical analyses

The sample size was calculated based on effect sizes derived from previous reports (7). For the reported *cohen d* effect size of 0.5, the required sample size was of 34 subjects for 80% power and p=0.05.

Statistical analyses of FMD and cIMT were performed utilizing the Generalized Estimating Equations exploring the main effects of time and group as well as the interaction term group*time. Whenever applicable, a post-hoc test of Bonferroni was conducted. Data were analyzed using “gee” package for R running on R version 3.6.1 (R Foundation for Statistical Computing; Vienna, Austria) and are expressed as means±SD or as otherwise stated.

Two main analysis strategies were proposed: full-analysis set (FAS) - in which all allocated subjects with at least one datapoint, irrespective of trial completion were analyzed - and per-protocol (COMP) in which we analyzed only trial completers. The computational code used for our statistical analyses is publicly available through the Open Science Framework website of the study (osf.io/56wrv/).

Sensitivity analysis

Due to the pragmatic characteristics of the study, changes in the patients' pharmacological scheme were permitted. Because of this fact, and the physiological aspect of the FMD assessments, we proposed a sensitivity analysis (SENS) for FMD values, based only on subjects with unaltered pharmacological scheme that completed the trial. Changes in antihypertensive drugs or other medications that could affect FMD assessments were considered as: (i) permanent changes in pharmacological scheme that implied in addition, dose-adjusting or removal of drugs that might potentially affect FMD assessment, (ii) changes in patient presentation regarding pre-post condition (ie. forgetting to take one or all medications, eventual use of drugs such as adrenergic receptor agonists, antihistamine drugs, etc.).

RESULTS

By the time of the elaboration of this report, 92 subjects were included in the study and randomized, with 46 allocated to each one of the study arms in the coordinator center. Since the trial is still ongoing, some subjects (n=7) are still under intervention and are not included in the analysis. Additionally, part of the pre-post data was collected but remains to be processed and therefore was not analyzed (n=13). This interim analysis was conducted in order to provide partial data for the construction of a doctoral thesis. Additionally, we reason that due to the recent operationalization of ultrasound vascular assessments in our group, an interim analysis could serve for data inspection regarding consistency among assessments. A flow diagram depicting the study design is presented in Figure 1. A total of 74 subjects were included in the FAS for the present study. Table 1 presents the sample clinical characteristics for FAS and COMP analysis.

Out of the 59 patients included in COMP analysis, 28 (47.4%) presented themselves in a different pharmacological condition for evaluations of FMD. In EXERCISE these cases accounted for 10 out of the 31 patients, representing 32.3% of the group sample, while in

EDUCATION this was the case for 18 out of 28, representing 64.4% of the group sample. A total of 31 patients (20 in EXERCISE and 10 in EDUCATION) were eligible to be included in SENS.

FMD values in the FAS analysis were non-significantly lower after EDUCATION and non-significantly higher after EXERCISE in all analyses. Systolic blood pressure was non-significantly lower for both EDUCATION and EXERCISE. Diastolic blood pressure changed less than 1 mm Hg after both interventions, except for EDUCATION in SENS. cIMT values were non-significantly lower after both interventions. No differences between the groups were observed in neither of the parameters evaluated ($P<0.05$). The results of baseline and change from baseline in MID and POST are presented in table 2. Figure 2 depicts a graphical representation of FMD FAS and figure 3 for cIMT assessments.

DISCUSSION

The present study explored the vascular responses of older adults with hypertension exposed to two different lifestyle interventions. In the selected sample, neither of the proposed interventions appear to significantly impact vascular health as assessed by FMD and ciMT measurements. Although our working hypothesis (superiority of exercise intervention) was not confirmed herein in such interim analyses, we reason that the generated evidence is a robust assessment on the effects of a combined exercise intervention compared to an active control group (health education) in a set of patients with key characteristics related to vascular health, such as the combination of hypertension and aging. Therefore, further assessments using active control groups and, possibly, exercise interventions more likely to be efficacious are warranted to build up on our findings in this specific population.

In both FAS and COM analysis the numeric behavior of pre-post FMD measurements were comparable, with lower values observed post exposure to EDUCATION and higher values

after EXERCISE. However, the magnitude of change and dispersion of the observed averages are such that no inference about the effects produced by the interventions can be made.

Increases of 1% in FMD values are associated with a 12% risk reduction for future cardiovascular events (22). In this regard, the FMD delta observed in the exercise completers group (0.5%) might bear clinical significance, although the presented results are not sufficient to make this inference. Improvements in FMD in relation to exposure to exercise are well described in the literature. A recent meta-analysis evaluating the effects of aerobic exercise interventions in FMD values of individuals with hypertension showed increases of 1.5% in this variable, with a borderline significance (95% confidence interval of -0.11% to +3.0%). Despite showing a potential benefit, the aforementioned study reviewed only 5 primary studies, denoting that this area of knowledge is still underexplored. Additionally, only one of the evaluated trials in Pedralli et al. was conducted exclusively in the older adult population (7), which differs from the overall adult population since endothelial function declines with age (17).

In the mentioned trial, Westhoff et al. evaluated the effects of a 3 days·week^{-1} treadmill-based walking interval training in various markers of cardiovascular health, including FMD, in older adults with hypertension (7). The authors found a significant t-test based difference in the delta of FMD between the groups, with the aerobic exercise group presenting an FMD increase of 2.3%. Of notice however, pre-post FMD values did not differ in the exercise group ($p=0.43$). However, in the referred work, training sessions were closely monitored for intensity assurance, including blood lactate tests, and medication changes were not permitted during the trial. These are key differences that put both trials on different ends of the explanatory-pragmatic continuum and that might explain the observed differences between the studies. Our results suggest that in less controlled scenarios, exercise training might not detectable changes in FMD values of older adults with hypertension, in comparison to an active control.

In relation to cIMT, neither interventions were effective in modifying this parameter, as the study sample did not present any significant changes in cIMT at any time point. Evidence of the association of cIMT with future cardiovascular events is compelling (18), but in the context of exercise training, there is conflicting evidence about the associations of exposure to such practices and changes in cIMT. Taylor et. al (10), in an observational study, showed no differences between cIMT of middle-aged marathon runners and their sedentary counterparts. When studying 137 subjects with type 2 diabetes and coronary artery disease randomized to either 12 months of exercise training or standard care, Byrkjeland et al. also found no differences in cIMT between the groups (19). On the other hand, Park et al. randomized 50 elderly women with sarcopenic obesity to 6 months of exercise or a control group, showing a significant regression from 0.68 mm to 0.67 mm in the exercise group, values that are similar to our findings, but with half the dispersion observed in our study (20). This fact might be a consequence of the exclusion of individuals with hypertension from the referred study sample, which could lead to a more homogenous sample in relation to cIMT measurements. Due to the heterogeneous presentation of our sample, our results suggest that observable changes in these parameters are not warranted in older adults with hypertension.

BP also did not change with time in both groups, despite both groups presenting lower systolic BP values after the interventions (between 3.6 and 7.8 mm Hg), no statistical difference was noted. Nonetheless, this was an ancillary analysis to better understand the impact of possible vascular adaptations in BP. However, the observed deltas in systolic BP of approximately 6-8 mm Hg in EXERCISE are consistent with the expected change observed in a meta-analysis on combined exercise effects on BP (12) and since no sample size calculation was performed for this analysis, we cannot rule out a lack of statistical power to unveil differences, since EDUCATION also numerically decreased systolic BP. Diastolic BP values were minimally

variable in both groups, which might be a function of lower baseline values for both groups (~80 mm Hg).

The presented results need to be interpreted in light of the limitations of this study. The HAEL trial was constructed with a more pragmatic approach than most of the exercise literature, and therefore we did not restrict treatment changes, lifestyle choices, and clinical decisions that might have brought confusion to the assessed variables (especially FMD). Further analysis controlling for confounder factors, such as weight change, are warranted. Additionally, FMD assessments were not conducted in full accordance with current guidelines (21). Since the trial was conducted prior to the publication of the referred guideline, it was not possible to include these recommendations in our FMD acquisition procedures (ie. avoidance of exercise 24h prior to testing, testing endothelial-independent dilatation, known coefficient of variation per sonographer, stereotactic probe holder, etc.).

CONCLUSIONS

Older adults with hypertension are characterized by long lasting endothelial dysfunction and poor overall vascular health. Our study indicated that a 3-month exercise intervention might be insufficient to produce detectable changes in their already impaired endothelial function and structure, when compared to a group receiving health education. Further studies, with longer periods of interventions and more robust sample sizes are needed to better comprehend vascular adaptations to exercise in the elderly.

ACKNOWLEDGEMENTS

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AUTHORS CONTRIBUTIONS

L. P. S. - was involved in the elaboration the study conception and design, data acquisition, analysis and interpretation and drafting the manuscript.

C. E. B - was involved in the elaboration the study conception and design, data acquisition, and in the revision of the manuscript for important intellectual content.

L. H. - was involved in the elaboration the study conception and design, data acquisition and in the revision of the manuscript for important intellectual content.

B. F. - was involved in data analysis and in the revision of the manuscript for important intellectual content.

T. A. - was involved in data analysis and in the revision of the manuscript for important intellectual content.

N. L. O. - was involved in the elaboration the study conception and design, data acquisition, and in the revision of the manuscript for important intellectual content.

H. T. - was involved in the elaboration the study conception and design, and in the revision of the manuscript for important intellectual content.

D. U. - as involved in the elaboration the study conception and design, data interpretation and in the revision of the manuscript for important intellectual content.

REPRODUCIBILITY STATEMENT

The HAEL Study Group supports the sharing of academic data and our intention is that the data from the trial may contribute to the scientific understanding on the topics explored. The trial has consent from participants as well as IRB approval to share de-identified data. Data sets, variables' dictionary and statistical analysis script will be made available online upon registration and acceptance of the data sharing terms and policy. Data usage will be under the PI's auspice.

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TABLES

Table 1 – Sample characteristics

	Full analysis set			Completers		
	Total Sample	**Education**	**Exercise**	**Total Sample**	**Education**	**Exercise**
N	74	38	36	59	29	30
Male, N(%)	35(47%)	18(47%)	17(47.%)	28(47%)	14 (48%)	14(47%)
Age, years±SD	67.3±5.9	67.7±6.3	66.9±5.8	67.7±6.0	67.7±6.1	67.7±6.0
SBP, mmHg±SD	138.0±22.0	138.6±23.6	137.4±20.5	140.0 ±21.6	142.3±22.9	137.9±20.5
DBP, mmHg±SD	80.3±13.0	81.1±14.1	79.5±11.8	80.4±12.4	81.5±13.7	79.3±11.3
AH medications, median(range)	2(1-4)	2(1-4)	2(1-3)	2(1-4)	2(1-4)	2(1-3)
Diabetes, N(%)	11(15%)	7(18%)	4(11%)	10(17%)	6(21%)	4(13%)
VO_{2peak} $ml.kg^{-1}.min^{-1}$±SD	22.8±6.1	22.4±6.5	23.3±5.7	23.3±6.4	23.2±7.0	23.5±5.9
BMI, kg/m^2 ±SD	30.4±5.0	30.2±4.8	30.6±5.2	30.1±5.4	29.9±5.3	30.2±5.6
Waist circumference, cm±SD	103.8±12.6	102.9±12.1	104.7±13.3	102.9±13.2	101.8±12.3	104.0±14.2

SBP= systolic blood pressure; DBP= diastolic blood pressure; AH= anti-hypertensive; BMI= body mass index;

Table 2 – Baseline and change from baseline of the evaluated parameters

		Education			Exercise			
	n	Baseline	Change from baseline in MID	Change from baseline in POST	Baseline	Change from baseline in MID	Change from baseline in POST	P-value*
FMD (%)								
FAS	74	6.1±3.9	-1.2 (-3.2 to +0.7)	-0.9 (-2.8 to +1.0)	5.3±3.5	-0.5 (-2.6 to +1.7)	+0.3 (-2.0 to +2.6)	0.24
COMP	59	6.8±4.1	-1.8 (-4.4 to +0.7)	-1.2 (-3.6 to +1.2)	5.4±3.6	-0.6 (-3.1 to +1.8)	+0.5 (-2.1 to +3.1)	0.18
SENS	31	7.2±4.3	-2.7 (-6.1 to +0.7)	-0.4 (-3.5 to +2.6)	5.1±3.7	-0.7 (-3.5 to +2.1)	+0.5 (-3.5 to +2.1)	0.53
SBP (mm Hg)								
FAS	74	138.6±23.6	-	-3.6 (-10.4 to +3.2)	137.4±20.5	-	-5.9 (-13.4 to +1.5)	0.55
COMP	59	142.3±23.3	-	-5.6 (-14.3 to +3.1)	138.3±20.3	-	-6.5 (-14.9 to +2.0)	0.86
SENS	31	140.9±26.8	-	-5.8 (-21.5 to +9.9)	139.9±21.3	-	-7.8 (-17.2 to +1.6)	0.78
DBP (mm Hg)								
FAS	74	81.1±14.1	-	-0.1 (-3.4 to +3.2)	80.6±13.9	-	-0.4 (-4.0 to +3.3)	0.88
COMP	59	81.8±13.8	-	-0.1 (-4.5 to +4.3)	79.6±11.2	-	+0.1 (-3.9 to +4.0)	0.93
SENS	31	87.1±16.0	-	-1.5 (-9.9 to +7.0)	79.4±12.4	-	-0.5 (-5.2 to +4.3)	0.79
cIMT (mm)								
COMP	61	0.69±0.11	-0.01 (-0.07 to +0.04)	-0.02 (-0.09 to +0.06)	0.71±0.15	-0.03 (-0.08 to +0.02)	-0.04 (-0.07 to +0.01)	0.38

*= for interaction term Group*Time in relation to Baseline-Post assessments. FMD= flow-mediated dilatation; FAS

FIGURES

FIGURE 1

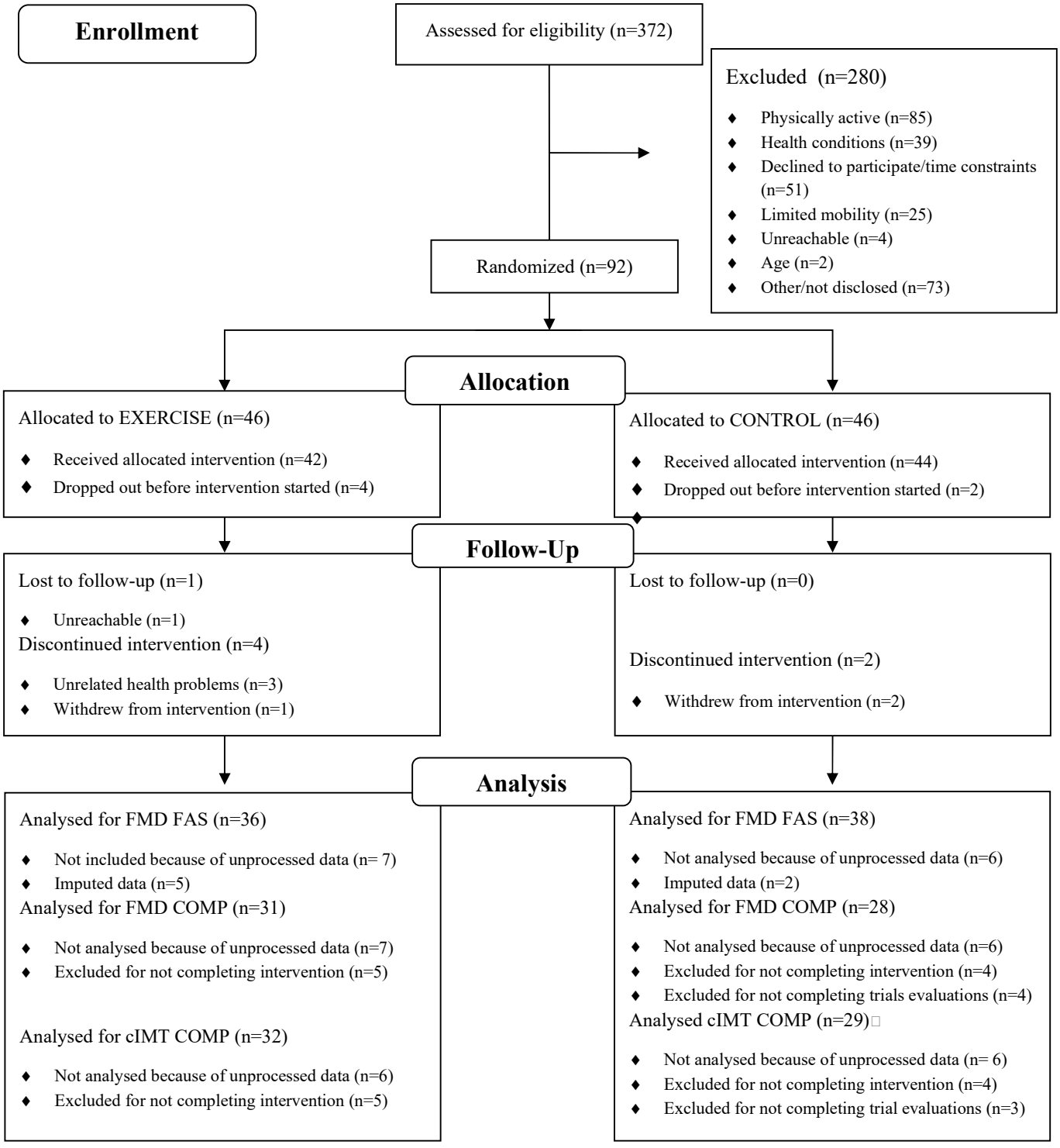

Figure 1 – Participants' flow-chart. FMD = Flow-mediated dilatation; FAS = Full analysis set; COMP = Completers set.

FIGURE 2

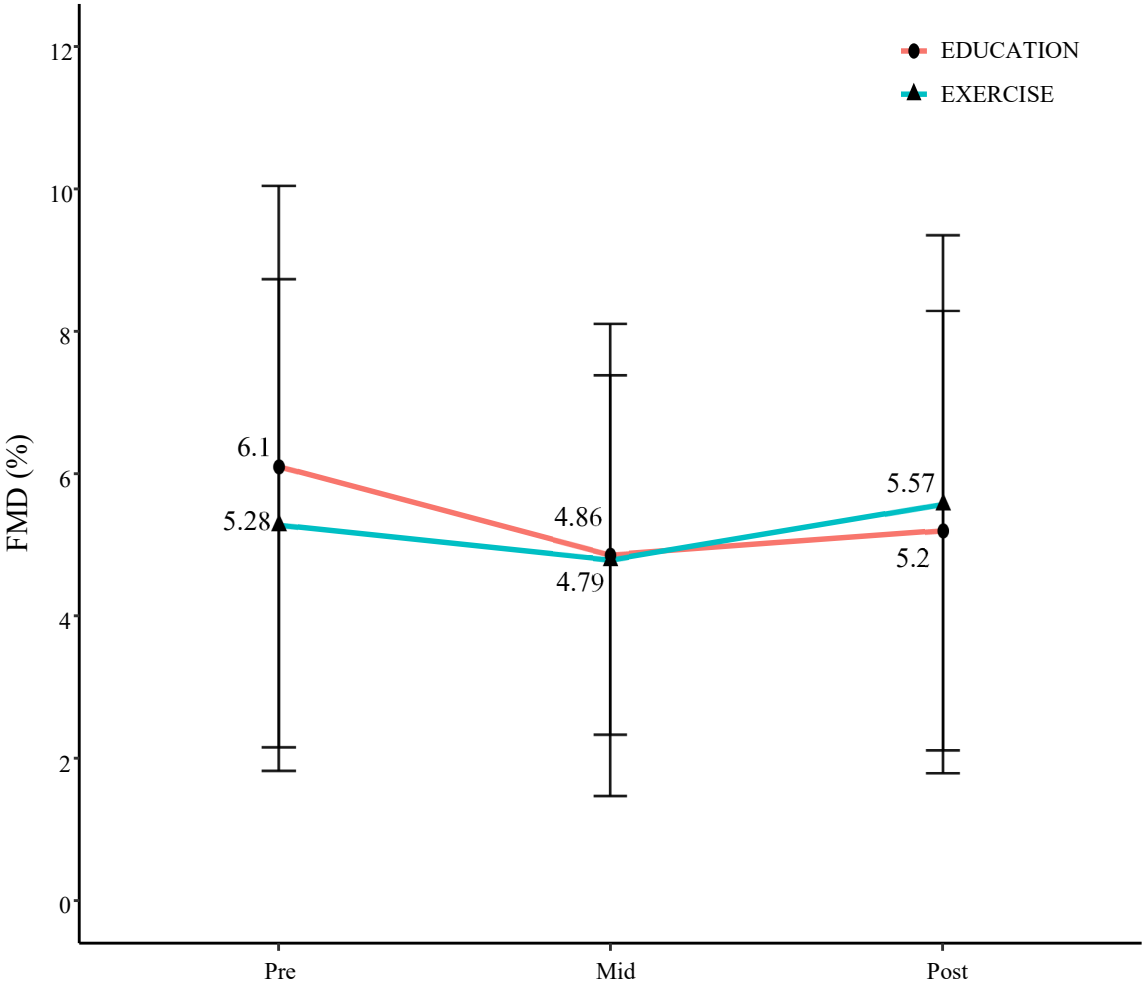

Figure 2 – Flow-mediated dilatation (FMD) responses in intervention groups.

FIGURE 3

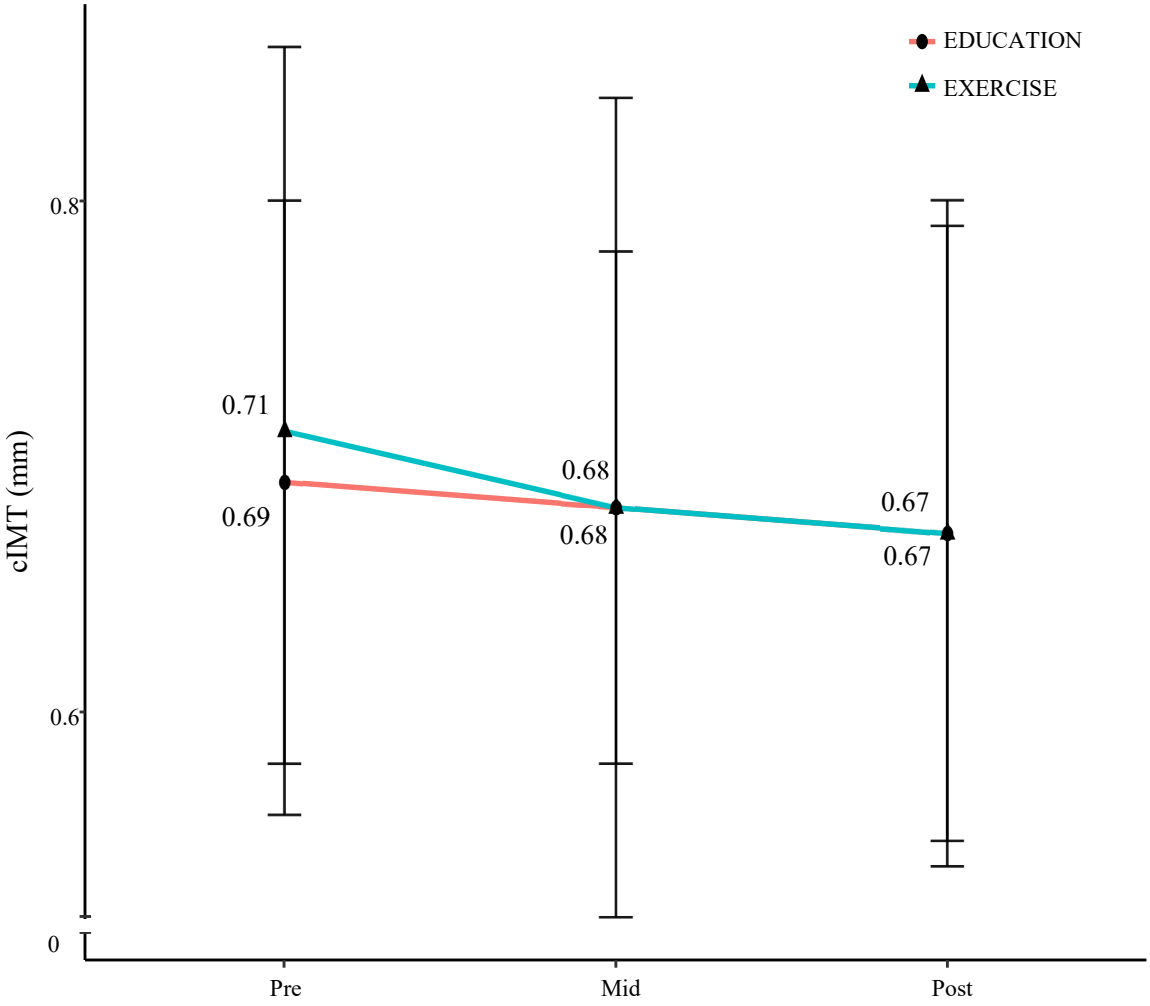

Figure 3 – Carotid intima-media thickness (cIMT) responses in intervention groups.

6. Final remarks

From ancient Greece, China, and India, to the present day, physical education as the intentional and systematic practice of physical activity is deemed not only a necessary but a smart measure to improve one's health. The present work aimed to explore some of the effects of lifestyle modification through exercise training in cardiovascular health parameters related to the development of atherosclerosis.

The review of literature herein presented explored the strengths and weaknesses of exercise-related literature in the context of positive modifications in cardiovascular health, more specifically focused on dyslipidemia, hypertension and endothelial function. It is apparent that the knowledge within this field has much to improve, especially in relation to the conduction of robust and methodologic sound trials, very common in the area of pharmacology, but rare in the exercise literature. Despite this gap, exercise is now recognized as an efficient lifestyle tool in the management of hypertension, and the mechanisms behind these reductions are partially uncovered. However, evidence of the potential effects within specific populations, such as the elderly, still need to be strengthened.

With this idea in mind, our group is conducting the multicenter randomized controlled trial partially represented here, the HAEL Study. In what we believe to be a solid methodological design, this trial aims to improve the knowledge in areas related to the cardiovascular effects of exercise training in older adults with hypertension. The methodological characteristic of pragmatism of this trial, albeit a potential source of bias, is completely focused on real-world settings.

The two original papers described inside this volume were focused on two key clinical characteristics of older adults with hypertension: sympathetic hyperactivity and endothelial dysfunction. Our proposed interventions did not seem to differ in respect to responses in the chosen variables. Although the findings in both studies contradicted the operational hypothesis

that exercise would be superior to health education in positively altering the assessed parameters, it has to be underscored that the HAEL Study was conducted with an active comparator and in a much more pragmatic setting than most of the related literature. Much of the exercise studies have control groups based on waitlists, usual care or the ethically sub-optimal sedentary groups, in experiments with drug-naive individuals or with the withdrawal of standard-of-care pharmacological treatments. While such studies are indeed important for the physiological understanding of exercise responses, in real-world settings the patients present themselves for healthcare providers in a much different way. The proximity to real-world settings might be both the strength and the weakness of the trial, however, studies like the ones presented here and the others that will come from the HAEL project are needed in the exercise science.

In realistic conditions, older adults with hypertension do not seem to present detectable changes in baroreflex sensitivity, autonomic control and vascular health. These findings suggest a possible resistance to positive adaptations seen in other scenarios, that might be influenced by the characteristics of the selected population and facts related to the ambulatory conditions of the individuals. Our team has extensive data on other variables that could be useful in establishing robust statistical approaches, controlling for possible confounders observed here. Due to time constraints and the ongoing status of the project, these data were not explored within this document. Therefore, it is expected, with the subsequent development of the project, further understanding of the underlying mechanisms behind the observed responses.

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APPENDICES
APPENDIX 1 – Ethical approval for the project

UFRGS - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE DA UNIVERSIDADE FEDERAL

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Treinamento físico combinado e educação em saúde para idosos com hipertensão arterial: um ensaio clínico randomizado e multicêntrico

Pesquisador: Daniel Umpierre de Moraes

Área Temática:

Versão: 1

CAAE: 62427616.0.1001.5327

Instituição Proponente: Hospital de Clínicas de Porto Alegre

Patrocinador Principal: Hospital de Clínicas de Porto Alegre

DADOS DO PARECER

Número do Parecer: 1.882.621

Apresentação do Projeto:

A hipertensão arterial sistêmica é uma condição de saúde com alta prevalência na população brasileira, especialmente em idosos. Diversas evidências demonstram eficácia do exercício físico crônico, principalmente o exercício aeróbico, no tratamento da hipertensão arterial. Porém, embora a combinação de estímulos aeróbicos e de força seja amplamente recomendada para induzir benefícios neuromusculares e cardiorrespiratórios frente ao envelhecimento, evidências sólidas para a população hipertensa são escassas. Trata-se de um ensaio clínico randomizado, para avaliar os efeitos de um programa de treinamento combinado pragmático, com pouca necessidade de maquinário específico, comparado a um programa de educação em saúde, nos níveis de pressão arterial ambulatorial de idosos hipertensos.

Objetivo da Pesquisa:

OBJETIVO GERAL

Estudar a eficácia de um programa de treinamento combinado (exercícios aeróbicos e de força), comparado a um programa de educação em saúde, sobre os níveis ambulatoriais de pressão arterial e marcadores de saúde em indivíduos idosos com hipertensão arterial.

Endereço: Rua Ramiro Barcelos 2.350 sala 2227 F
Bairro: Bom Fim **CEP:** 90.035-903
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3359-7640 **Fax:** (51)3359-7640 **E-mail:** cephcpa@hcpa.edu.br

OBJETIVOS ESPECÍFICOS

1. Avaliar os efeitos de 12 semanas de um programa de treinamento combinado ou programa de educação em saúde sobre a PA sistólica e PA diastólica nos períodos de vigília, sono noturno, e ao longo durante 24 horas (MAPA, Space Labs 90207);
2. Avaliar os efeitos de 12 semanas de um programa de treinamento combinado ou programa de educação em saúde sobre capacidades funcionais de ênfase cardiorrespiratória (teste de caminhada de 6 minutos – TC6) ou neuromuscular (tarefas funcionais, Short Physical Performance Battery- SPPB e teste de preensão manual);
3. Avaliar os efeitos de 12 semanas de um programa de treinamento combinado ou programa de educação em saúde sobre a qualidade de vida e sintomas depressivos avaliados e aderência à medicação por questionários (Short Form 36, SF-36; Geriatric Depression Scale 15, GDS-15; Morinsky Medication Adherence Scale – 8 item, MMAS-8; respectivamente);
4. Avaliar os efeitos de 12 semanas de um programa de treinamento combinado ou programa de educação em saúde sobre o perfil lipídico (colesterol total, triglicerídeos e HDL).
5. Em participantes de um dos centros de intervenção (Porto Alegre), analisar os efeitos de 6 e 12 semanas de um programa de treinamento combinado ou programa de educação em saúde sobre a função vascular mensurada com uso de ultrassonografia.

Avaliação dos Riscos e Benefícios:

Riscos:

Haverá registro formal de eventos adversos leves, moderados, ou graves, relacionados ou não com as intervenções do presente projeto de pesquisa, bem como com ocorrência durante ou fora dos procedimentos de estudo. Para minimizar o risco dos participantes, o estudo contará com procedimentos padronizados pela equipe de pesquisa, e previamente discutidos/treinados na equipe de pesquisa (a qual contará, no mínimo, com um médico cardiologista e uma médica endocrinologista). Além disso, haverá exames pré-participação para caracterização adequada de potenciais riscos na participação neste estudo.

Benefícios:

Durante os acompanhamentos, resultados clínicos disponíveis no estudo serão disponibilizados a outros profissionais que atuem na assistência clínica dos sujeitos de pesquisa. Ao final do estudo, os participantes de cada centro de execução serão recebidos pelos pesquisadores para apresentação final de resultados adaptada ao público leigo e orientações gerais sobre hipertensão

arterial, prática de atividades e cuidados gerais em saúde (por exemplo, redução do risco de quedas).

Comentários e Considerações sobre a Pesquisa:

Projeto vinculado ao PPG Ciências da Saúde: Cardiologia e Ciências Cardiovasculares.

Estudo multicêntrico,com dois centros: HCPA e Pelotas.

Amostra: 184 indivíduos > 60 anos, hipertensos, alcança um poder de 79% e 92% para detectar variações de 2,5 mmHg e 3,0 mmHg na PA sistólica de 24 horas, com desvio padrão de 6,0 mmHg e nível alfa de 0,05 em uma análise por modelo de efeitos mistos e 15% de perdas.

Considerações sobre os Termos de apresentação obrigatória:

Apresente TCLE.

Recomendações:

Nada a recomendar.

Conclusões ou Pendências e Lista de Inadequações:

O projeto apresenta as seguintes pendências:

1. No item de riscos e benefícios, especificar os potenciais riscos relacionados ao teste de esforço máximo considerando o risco cardiovascular basal dos participantes, e quais os critérios para não realização do teste.

2. Revisar o TCLE:

a) TCLE completo, mas um pouco complexo para entendimento do paciente. Por exemplo, parece pouco provável que o participante entenda o que significa rastreamento em pesquisa.

b) Devem ser especificados todos os exames que serão realizados com as amostras de sangues dos participantes.

c) A informação que "Primeiramente seu braço será colocado em um manguito e terá o fluxo sanguíneo interrompido por alguns momentos" deve ser melhor explicada em termos de desconforto ocasionado pelo teste.

d) Na frase "Em caso de emergência, o serviço médico será imediatamente contatado, os pesquisadores darão assistência de primeiros socorros, e seu contato para emergência será informado" sugere-se substituir a última oração por "e a pessoa que o Senhor(a) informou para o caso de emergência será avisada".

e) Um modelo de TCLE pode ser consultado na página do HCPA na internet – Pesquisa – Área do Pesquisador - Normas – Normas para elaboração de TCLE. Após sua adequação ao modelo, o

mesmo poderá ser verificado em consultoria à UARP/GPPG (8304).

A UARP/GPPG encontra-se à disposição dos pesquisadores para auxiliar na resposta às pendências, na revisão de Termos de Consentimento e para quaisquer outros esclarecimentos, se necessário.

Considerações Finais a critério do CEP:

A análise foi realizada com base em todos os documentos apresentados, incluindo o projeto em sua íntegra.
O projeto deverá estar cadastrado também no sistema WebGPPG, em função dos aspectos logísticos e financeiros.
Os pesquisadores deverão responder a todos os questionamentos indicados na lista de pendências apontadas no campo Conclusões ou Pendências e Lista de Inadequações deste parecer, identificando claramente as respostas de acordo com a numeração das pendências, através de uma carta ao CEP (em documento editável/word), que deverá ser adicionada à Plataforma Brasil. Quando a resposta alterar os documentos anteriormente submetidos, como, por exemplo, o projeto ou o TCLE, adicionar na carta de respostas claramente a identificação do item que foi modificado e nova versão dos documentos.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_798319.pdf	28/11/2016 11:09:18		Aceito
Outros	Atestado_prof_Daniel_Umpierre.pdf	25/11/2016 11:20:13	Lucas Porto Santos	Aceito
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Pendente

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 27 de Dezembro de 2016

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APPENDIX II

PROTOCOL ARTICLE FOR HAEL STUDY

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STUDY PROTOCOL Open Access

The "Hypertension Approaches in the Elderly: a Lifestyle study" multicenter, randomized trial (HAEL Study): rationale and methodological protocol

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Abstract

Background: Hypertension is a clinical condition highly prevalent in the elderly, imposing great risks to cardiovascular diseases and loss of quality of life. Current guidelines emphasize the importance of nonpharmacological strategies as a first-line approach to lower blood pressure. Exercise is an efficient lifestyle tool that can benefit a myriad of health-related outcomes, including blood pressure control, in older adults. We herein report the protocol of the HAEL Study, which aims to evaluate the efficacy of a pragmatic combined exercise training compared with a health education program on ambulatory blood pressure and other health-related outcomes in older individuals.

Methods: Randomized, single-blinded, multicenter, two-arm, parallel, superiority trial.
A total of 184 subjects (92/center), ≥60 years of age, with no recent history of cardiovascular events, will be randomized on a 1:1 ratio to 12-week interventions consisting either of a combined exercise (aerobic and strength) training, three times per week, or an active-control group receiving health education intervention, once a week. Ambulatory (primary outcome) and office blood pressures, cardiorespiratory fitness and endothelial function, together with quality of life, functional fitness and autonomic control will be measured in before and after intervention.

Discussion: Our conceptual hypothesis is that combined training intervention will reduce ambulatory blood pressure in comparison with health education group. Using a superiority framework, analysis plan prespecifies an intention-to-treat approach, per protocol criteria, subgroups analysis, and handling of missing data. The trial is recruiting since September 2017. Finally, this study was designed to adhere to data sharing practices.

Trial registration: NCT03264443. Registered on 29 August, 2017.

Keywords: Older, Aged, Aging, Exercise, Physical activity, Clinical trial

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Backgrounds

Hypertension is a leading risk factor for disability-adjusted life years globally [1] and contributes to chronic diseases with low quality of life and high mortality rates. Advanced age and elevated blood pressure (BP) exponentially increase mortality risk, which underscore the importance of BP control in the older population [2]. Among nonpharmacological interventions, structured exercise programs are strongly recommended for adults with elevated BP or essential hypertension [3]. In older subjects, exercise interventions are cornerstone due to multiple effects that may benefit not only vascular disease markers [4] but also other outcomes related to physical function [5, 6].

Meta-analyses of several controlled intervention studies have generated estimates that, individually, aerobic or resistance exercise training can reduce systolic BP levels by 6 to 8 mmHg in patients with hypertension [7, 8]. However, two main aspects limit extended evidence extrapolation. First, trials have mostly used either aerobic or resistance exercise training alone in young or middle-aged individuals without hypertension. Second, given that the combination of aerobic and resistance training has become a recommended mode of exercise training, it is relevant to investigate the efficacy of combined training in older individuals with hypertension. Although combined exercise programs can enhance the nonpharmacological treatment of hypertension in the elderly, such sample has been scarcely addressed in clinical trials [9, 10]. Moreover, inferences are considerably constrained by only a minority of studies examining BP as a primary outcome together with a high risk of bias indicated by lower-to-median scores of methodological quality [9].

We aim to evaluate the efficacy of a combined aerobic and resistance exercise training program on reducing BP levels compared with an attention control group undergoing health education in older patients with hypertension (≥ 60 years old). Herein, we will describe the HAEL Study, which is a parallel, randomized (1:1 allocation ratio), controlled by active intervention, blinded for outcome assessors and data analysts, multicenter, superiority trial, using ambulatory BP as the primary outcome. The choice of the active comparator group aims to reach a principle of equipoise and partially account for research participation effects (Hawthorne effect). Our main hypothesis is that the exercise training program will lead to greater reduction in systolic ambulatory BP in comparison to the control group. Secondary outcomes related to cardiovascular, mental, and physical function were chosen due to their relevance for the elderly. Based on the design of interventions and variables of interest, we hypothesize that the combined exercise training program will lead to superior changes in secondary outcomes when compared to the health education.

Methods

Study setting

This multicenter trial takes place in Porto Alegre and Pelotas, cities located in southern Brazil. Porto Alegre is the coordinator center, at the Hospital de Clínicas de Porto Alegre, and centralizes most of the methodological procedures discussed below. The research teams for each center have similar sizes and identical structures of investigator roles (Additional file 1). The equipment and space used for interventions at both centers are similar and will be detailed in the *Interventions* topic. The present study protocol follows as closely as possible the SPIRIT Statement 2013 [11]. The World Health Organization Trial Registration Dataset is provided herein (Additional file 2).

Eligibility criteria

Inclusion and exclusion criteria for subjects are defined as follows. Study centers were chosen by convenience and no eligibility criteria was defined a priori for care-providers:

Inclusion criteria

1. Diagnosis of hypertension as assessed by a previous ambulatory BP monitoring (no later than six months) or current use of anti-hypertensive drugs.
2. Age ≥ 60 years old.
3. Unchanged pharmacological scheme for four weeks prior enrollment.
4. Willingness to participate in either intervention group.

Exclusion criteria

1. Inability or unwillingness to give informed consent for participation.
2. Myocardial infarction, revascularization procedures, deep vein thrombosis, cerebrovascular events or pulmonary embolism within the last 12 months.
3. Presence of chronic heart failure with NYHA classes III or IV or unstable arrhythmia.
4. Presence of chronic lung disease requiring use of corticosteroid or oxygen therapies.
5. Consumption of more than 14 alcoholic drinks per week.
6. Presence of kidney disease requiring dialysis.
7. Language, hearing or cognitive issues limiting communication.
8. Plans to move outside the areas of HAEL study sites during the period of participation.
9. A friend or relative living in the same household is a study participant.
10. Presence of progressive neurological disorders (Parkinson's disease, multiple sclerosis, etc.)
11. Cancer requiring treatment within the past two years.

12. Medical report indicating moderate or high risk for exercise-related event [12], based on the initial maximal exercise test and clinical evaluation.

Interventions

The HAEL participants are randomly allocated either to a combined exercise training program or to a health education intervention, each lasting 12 weeks. Detailed description on both interventions is provided below:

Combined exercise training

In Porto Alegre, exercise sessions take place at a communitarian exercise facility external to the teaching hospital. In Pelotas, exercise sessions take place at an exercise facility within the School of Physical Education, Universidade Federal de Pelotas.

Supervised exercise sessions lasting approximately 60 min, 3 days per week. The session consists of an initial warm-up (< 5 min), followed by 20–30 min of aerobic exercise in moderate intensity, 4–5 exercises, 2–3 sets of resistance training (lasting from 15 to 20 min), and 5–10 min of cool-down. The intensity of walking/running is based on the original Borg rating at 12–14 of perceived exertion [13], whereas resistance exercises are based on OMNI rating of 4–8 (out of 10) of perceived exertion scale [14]. Prescribed movements are identical for both centers and consist of multi-joint resistance exercises emphasizing major muscle groups and daily-life activities like sitting, standing up, pushing and pulling. To achieve greater external validity and applicability in environments with limited resources, the exercises are based on bodyweight and elastic band resistance, which require low complexity for setting up, are affordable and can be performed in limited space. The last 5–10 min of each session serve as the cool-down period, during which subjects perform stretching and mobilization exercises. During this time, the exercise supervisor addresses one of hypertension-related topics, based on the same contents planned to the health education group, however, with a brief informative approach lasting 2 to 5 min. Progression for resistance training sessions is based on more intense and faster contraction speed (Table 1). BP measurements are carried out before every exercise session to ensure that subjects BP are below 180 and 100 mmHg for systolic and diastolic BP, respectively. These pre-exercise BP values are documented once a week in subject's records.

Health education

In Porto Alegre, this intervention takes place at the Center of Clinical Research at the Hospital de Clinicas de Porto Alegre. In Pelotas, the intervention takes place at the School of Physical Education, Universidade Federal de Pelotas. The intervention consists on educational program with weekly lectures of approximately 60 min of duration. Each lecture is led by health professionals who follow a content script unified for both centers. By using expositive and interactive approaches, topics cover basic knowledge related to hypertension and therapeutic management. Table 2 shows all topics addressed in the health education group. Before the weekly education sessions, participants' BP levels are measured and documented.

Hypertension management

For safety reasons, some criteria are implemented to manage participants with uncompensated BP along the study (Fig. 1). Participants allocated to any intervention arm presenting sustained pre-session systolic or diastolic BP equals to or greater than 180 mmHg or 100 mmHg, respectively, at two subsequent sessions must undergo a medical appointment. Such values are defined by at least two measurements per session for participants in both groups. In addition, participants in combined exercise training are invited to walk for 5 min at light intensity to reduce a possible anticipatory BP elevation prior the exercise; in these cases, measurements occur after due rest after such short walk episode.

Therefore, participants with elevated BP according to the cutoff values mentioned above should be examined within seven days through consultation carried out by participants' physicians or study cardiologists. In consultations provided by study cardiologists, an algorithm will be followed (Fig. 1). In brief, whenever a consultation occurs, participants should receive medical clearance to continue to participate. In appointments conducted by study cardiologists, no pharmacological adjustment will be made at a first appointment for participants receiving medical clearance. Therefore, such consultations will be based on reinforcing measures of antihypertensive

Table 1 Resistance training prescription within the combined exercise program

Resistance training variable	Initial prescription (weeks)	Progression (weeks)
Number of sets	2 (1–3)	3 (4–12)
Intensity[a]	Light to moderate (1–3)	Moderate to high (4–12)
	Target: 4 to 6, out of 10	Target: 6 to 8, out of 10
Number of exercises	4 (1–6)	5 (7–12)
Contraction speed[b]	Moderate (1–6)	High (7–12)

[a]assessed by OMNI rating of perceived exertion scale. [b]concentric contraction performed as fast as possible

Table 2 Topics covered in the health education intervention

Topics in health education for hypertension
1.Getting to know hypertension
2. Hypertension and risk
3. Signs, symptoms and urgencies
4. General treatment for hypertension
5. Medication and adherence
6. Diet-sodium intake
7. DASH diet
8. Alcohol and tobacco
9. Psychological stress
10. Weight loss and risk reduction
11. Physical activity
12. Wrap-up and celebration

DASH: Dietary Approaches to Stop Hypertension

management. Whenever a second medical appointment is necessary, pharmacological adjustments will be considered to ensure BP control and risk reduction. Such cases may fulfill criteria for discontinuation and will only be kept in interventional under medical recommendation.

Criteria for discontinuing allocated interventions

A participant may be discontinued from the study at the investigator's discretion for safety reasons. For subjects allocated to any group, an incident cardiovascular event, hospitalization or severe health event during the intervention period are considered criteria to discontinue study participation. Examples of a severe health event may include: sustained uncompensated BP for 2–3 times during the protocol (systolic BP ≥ 180 mmHg or diastolic BP ≥ 100 mmHg, respectively), and medical illness that precludes attendance to intervention sessions. In addition, muscular or joint injuries (e.g., muscular, joint) impairing the participant to follow the intervention are considered exclusion criteria for participants allocated to combined exercise training.

Strategies for trial retention

During weekends, participants allocated to both groups receive text messages with Institutional Review Board (IRB)-approved content to reinforce time and place of intervention sessions. For the health education group, the message content is based on the topic that will be covered at the next class, whereas the exercise training group receives four slightly different messages along each month of intervention (three monthly cycles of four messages). We use phone calls to inquire for any adverse events if a participant misses a session of any intervention arm. The phone calls schedule is ceased for participants declaring their withdrawal from the study.

Outcomes

In each center, both randomized groups are assessed for the outcomes listed below by standardized methodological procedures and a similar schedule (Table 3). Outcomes are measured for all randomized participants, irrespective of attendance or completion status. For participants who drop out of the study at any time after the randomization, research personnel use contact information to invite such individuals to undergo the end-study outcome assessments (12 weeks after intervention onset).

Primary outcome

The primary study outcome is systolic BP assessed by 24 h ambulatory BP monitoring measured before and after three months of intervention. Systolic BP was chosen as the primary outcome due to its linear rise in relation to age and powerful prediction of cardiovascular events in older adults [15, 16]. The study timeframe was chosen to allow an adequate time range to effects (if any) take place, while optimizing trial logistics and participants adherence to interventions [7].

The ambulatory BP values will be treated as individual values for diurnal (from device placement to 10 PM, within the evaluation day), nocturnal (from reported sleep time to reported waking time) and 24 h periods, aggregated as group means at baseline and 12 weeks (trial end). Baseline measurements are carried out no longer than 30 days before the first intervention session whereas post-intervention assessment occurs within 10 days after the last session.

Main secondary outcomes

A set of secondary outcomes clinically relevant for the elderly populations was established, including diastolic BP, endothelial function, and cardiorespiratory fitness. Together with systolic BP, the diastolic BP will be assessed through ambulatory and 'at office' measurements. Endothelial function is determined by flow-mediated dilatation measured by high resolution ultrasonography at baseline, mid-intervention (6 weeks), and post-intervention (12 weeks), in agreement with published guidelines [17]. Due to resource availability, this outcome is assessed only in participants allocated at the coordinator center. Cardiorespiratory fitness is determined by peak oxygen consumption (VO_2peak) obtained by maximal cardiopulmonary exercise testing at baseline and 12 weeks. Data regarding both main secondary outcomes will be aggregated as group means at the measurement timepoints.

Other outcomes

Other outcomes include complementary measures of physical function, habitual physical activity, adherence to pharmacological therapy, quality of life, and autonomic function. Physical function is evaluated by: (1) total walking

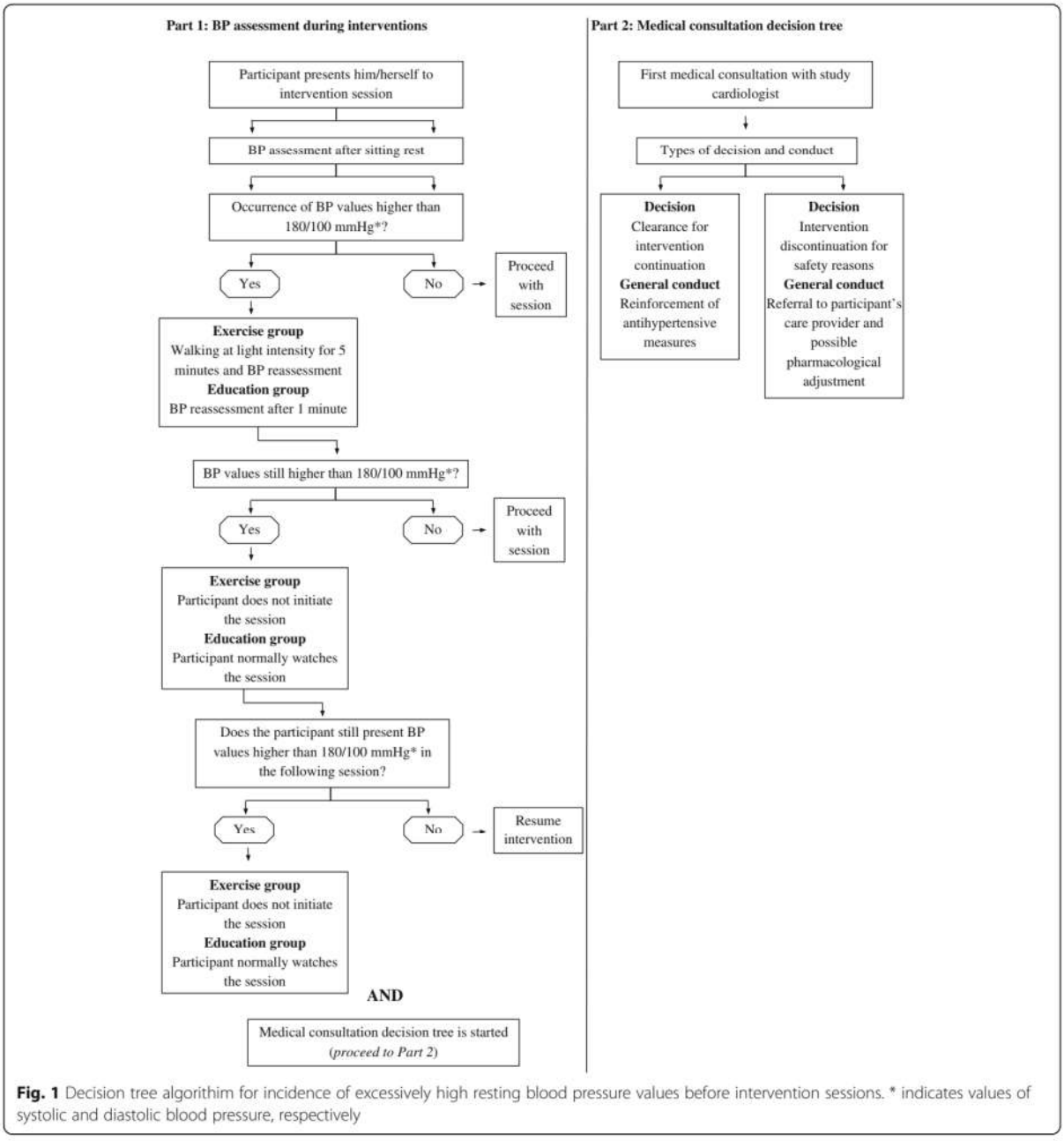

Fig. 1 Decision tree algorithim for incidence of excessively high resting blood pressure values before intervention sessions. * indicates values of systolic and diastolic blood pressure, respectively

distance, as assessed by the six-minute walk test [18], expressed as the longest distance walked at baseline and 12 weeks; (2) lower-limb functional capacity assessed by the Short Physical Performance Battery (SPPB), expressed by scores from 0 (worst performance) to 12 (best performance) based on 3 standing balance tests of increasing difficulty, five sit-to-stand attempts, and a 3-m walk test; and (3) handgrip strength, measured by a hand dynamometer. Self-reported physical activity is measured by the International Physical Activity Questionnaire (IPAQ) [19]. Medication adherence is assessed by Morisky's 8-item adherence scale (MMAS-8) [20–23]. Quality of life (QoL) outcomes are evaluated by: (1) geriatric depression symptoms, as assessed by the total score on the 15-item geriatric depression symptoms scale (GDS-15) [24, 25]; and (2) scores of QoL, as assessed by the World Health Organization Quality of Life questionnaire (WHOQo-L-OLD) [26]. In addition, participants allocated at the coordinator center undergo an autonomic modulation assessment by beat-to-beat BP variability and heart rate

Table 3 Time scheme for study conduction

	Study period							
	Enrolment	Baseline measures	Allocation and run-in*	Post-allocation			Close out	
TIMEPOINT➔	t-1	t0	t1	t2	t3	t4†	t5†	t5†
Timepoint description	Interviews	Occurs in 2 or 3 evaluation visits	–	Intervention Start	Evaluation visit (6th week)	Intervention end	Final evaluation visit 1	Final evaluation visit 2
ENROLMENT:								
Eligibility screening	x							
Informed consent	x							
Allocation			x					
INTERVENTIONS								
Combined exercise program				x	x	x		
Health education program				x	x	x		
ASSESSMENTS								
Primary outcome								
Ambulatory blood pressure		x					x	
Main secondary outcomes								
Office blood pressure		x					x	
Endothelial function‡		x			x		x	
Cardiorespiratory fitness§		x						x
Other outcomes								x
6-min walking test distance		x						x
SPPB		x						x
Quality of life questionnaires		x					x	
Autonomic function‡		x					x	
Additional measurements								
Anthropometric measurements		x					x	
Medication adherence scale (MMAS-8 Questionnaires)		x					x	
Blood variables collection		x					x	
Self-reported physical activity		x			x		x	
Grip strength		x			x			x

SPPB Short physical performance battery; *MMAS* Morisky Medication Adherence Scale. * = run-in period will be no longer than 2 weeks. † = time between t4 and t5 will be no longer than 2 weeks. ‡ = analysis of blood pressure and heart rate variability, exclusive for data collected at the coordinator center; § = cardiorespiratory fitness assessment occurs in a third separate visit at the participating center. Use of the©MMAS is protected by US copyright and registered trademark laws. Permission for use is required. A license agreement is available from Donald E. Morisky, 294 Lindura Court, Las Vegas, NV 89138–4632; dmorisky@gmail.com

variability analysis at rest sympathetic stimulation with the Stroop Color-Word Conflict Test.

Safety outcomes

The harms occurring over the period of participation in the trial are defined as adverse events as established by the National Institutes of Aging [27]. Such events are classified according to their severity (mild, moderate, severe), predictability (expected or unexpected), and potential relation with study procedures (definitely related, possibly related, or unrelated). We collect and manage solicited and spontaneously reported adverse events. There is no fixed collection schedule for assessment of harm outcomes, however, spontaneous reports have been documented, communicated to the IRB and managed at demand. In addition,

triggers for inspection include absence to one intervention or measurement sessions.

There is no formal adjudication committee, but adverse events are discussed and, if necessary, adjudicated by at least four (50%) out of the following investigators: principal investigator. (D.U), study director (S.S.P), study medical director (B.D.S), study managers (L.P.S, E.N.W, C.E.B), and expert consultants (C.A.P, L.S.P).

Sample size

Sample size for the primary outcome was calculated using estimates of effect sizes from (i) a meta-analysis of exercise training interventions and (ii) an randomized clinical trial based on a behavioral intervention for middle-aged patients with hypertension, evaluated by ambulatory BP monitoring, and analyzed in an intention-to-treat approach [7, 28]. We estimated that 184 participants would provide power values of 0.79 and 0.92 to detect differences of 2.5 mmHg and 3.0 mmHg between the two group mean values for the 24-h systolic BP, with an expected standard deviation of 6.0 mmHg. Such power calculation comprises: (1) an excess of 22 subjects due to the expected dropout rate (10–15%), (2) intraclass correlation of 0.1 in order to account the proportion that the center-to-center variance may affect the response variance, and (3) a two-sided significance level of 0.050 obtained from a mixed effects model fit without the treatment-by-center interaction.

Recruitment

The recruitment period for the HAEL Study is planned to range from September 2017 to March 2019. Recruitment phase began from September 2017 to December 2017. During this period, screening questionnaire was administered to 111 individuals (98 of those were not included due to exclusion criteria) and the total enrollment comprised 13 individuals. This was the initial phase to implement the processes for trial conduction in both centers.

From January 2018 on, we have established recruitment targets by center for participant inclusion.

To accomplish such targets, a multifaceted approach is used according to each center resources and comprises screening of electronic medical records as well as advertising means based on recruitment-billboards, newspaper releases, e-flyers in social media, word of mouth, and personal references. In addition, we developed a web site for the HAEL Study (www.ufrgs.br/hael) by which we present study relevant information and contact details. All communication and publicity materials have received IRB approval.

Assignment of interventions and blinding

Once included in the study, the participant receives an internal number to be de-identified. Sequence of allocation is based on computer-generated random numbers (www.random.org; randomness via atmospheric noise), 1:1 ratio, with permuted blocks of random sizes that are not disclosed to ensure concealment. Allocation concealment is implemented through a central randomization routine conducted by investigators with access to the randomized list (list holders: D. U, S.S.P, C.L.A.) and investigators charged with requesting the code to place subjects to their intervention group. In brief, assigners fill an online request whenever one or more subjects should enter an intervention arm. Thereafter, one of the list holders consult the code in consecutive order and uncover the code relative to the requested subject(s). Such requests are documented and archived for further accountability. To ensure intervention blinding, communication with participants is not carried out by the investigators involved in outcome assessments.

Blinding is implemented for outcome assessors and data analysts (double masking) of primary and secondary outcomes listed in this protocol. Due to the nature of interventions, the study staff conducting or supervising exercise or educational sessions as well as participants are not blinded. To ensure masking of the assessor, subjects are asked to omit their assigned group and not to talk about their interventions during outcome evaluation sessions. In the case of unintentional unblinding due to any reason, it is mandatory for involved researchers to notify the center coordinator. In such cases, participant ID, date, and unblinding circumstance are documented for internal control.

Data collection

A manual of operating procedures (MOP) was written to increase the consistency for implementation of assessments and interventions across the two study centers. In addition, standard operating procedure (SOP) documents are available for each assessment. Outcome assessors were trained and the handling of a SOP short version is mandatory during each data collection. A data collection committee formed by members of the two centers gathered before the trial onset to consolidate data collection procedures between centers. Periodic meetings and written communication are established to promote internal transparency and consistency.

All variables are assessed at baseline (prior randomization) and at study completion, whereas endothelial function, self-reported physical activity and handgrip strength are additionally assessed at the 6th week of intervention. A participant timeline for the study is presented in Table 3.

Measurement of primary outcome

Ambulatory BP In the assessment of 24-h BP, subjects wear an ambulatory BP monitor (90,207, SpaceLabs,

Redmond, WA, USA) on the non-dominant arm for 24 h. Participants are asked to refrain from exercise the day prior to and during the recording period. While wearing the monitor they are also asked to maintain a diary of daily activities to record any abnormal activities (such as highly stressful situations, increased physical exertion, etc.) and sleep hours. Data on self-reported sleep times will be used to analyze daytime and nighttime patterns of ambulatory BP monitoring. Ambulatory BP exams are considered valid when at least 70% of the expected readings are available, otherwise, an additional measurement is necessary [29]. Subjects allocated to the combined training intervention undergo the ambulatory BP assessment at least 24 h and no later than 10 days after the last exercise session.

Measurements of secondary outcomes

Office BP After sitting the subjects in a calm environment for 5 min, a researcher measures the subject's BP using calibrated and automated oscillometric devices (OMRON Healthcare Inc., Bannockbur, IL, USA), according to hypertension guidelines [30]. Three measurements, 1–2 min apart, are performed in the arm with the highest initial value. The average of the three measurements is considered the subject's office BP.

Cardiorespiratory fitness Subjects undergo a maximal cardiopulmonary test on a treadmill. Rates of oxygen uptake, carbon dioxide and volume of expired air are recorded breath-by-breath during an incremental walking/running protocol, with VO_2peak determination when criteria for test termination is reached [31]. All tests are supervised by a trained exercise physiologist and a physician, using a ramp protocol with rate of increments (both speed and elevation) implemented at their discretion, based on participants' clinical history, aiming a test lasting from 8 to 12 min. Subjects are asked to take their medications normally and refrain from caffeine consumption prior testing. Due to different gas analyzers between study centers (Porto Alegre: Cortex Metalyzer 3B, Leipzig, Germany; Pelotas: VO2000 MedGraphics, Ann Arbor, MI, USA, respectively), VO_2peak average values and CI 95% will be checked at the study completion. If a difference is identified between centers, VO_2peak will be reported accordingly.

Walking distance Subjects undergo a six-minute walking test conducted in a flat 30 m course, in which the total distance walked "as fast as possible" is assessed. Researchers are not allowed to give verbal encouragement other than standardized neutral cues each minute.

Lower limbs functional capacity Subjects complete the SPPB which is a 3-step testing that assesses balance, walking speed, and lower limbs muscular endurance [32, 33]. The balance stage of the test is comprised of three balance challenges of increased difficulty. The walking speed test assesses the 3-m regular-pace walking speed. The muscular endurance assessment involves standing-up five times from a chair as fast as possible without using the arms. The final test score is calculated as a sum of the scores obtained in the three tests. Each test has a maximum score of 4 points.

Geriatric depression symptoms Participants are asked to complete a version of the Geriatric Depression Scale 15 (GDS-15) validated for Brazilian Portuguese [25]. This questionnaire is comprised of 15 questions and is validated to assess depressive symptoms in the Brazilian elderly population. Due the personal nature of the provided information, questionnaires are answered by the participant alone and assisted by researchers only if needed.

Quality of life Participants answer the WHOQOL-OLD questionnaire, translated and validated forBrazilian elderly population [26]. This questionnaire is comprised of24 questions and is an estimate for QoL in 6 different domains. As justified in the procedure above, questionnaires are answered by the participant alone and researchers provide help only if requested.

Autonomic function Autonomic function is assessed by BP and heart rate variability (MP150, Biopac Systems, USA). Phalangeal beat-to-beat BP is recorded (in a sampling rate of 1000 Hz) at supine rest for 10 min and during a 5-min application of a variation of the Stroop Color-Word Conflict test [34]. This test is a mental stress challenge to sympathetically stimulate the subjects. We calculate the BP and heart rate variability based on a spectral analysis of systograms and tachograms. This method provides three frequency band components (Very Low Frequency, Low Frequency and High Frequency) from which autonomous control can be inferred.

Endothelial function To determine the flow-mediated dilatation (FMD), longitudinal images are obtained with the use of high-resolution ultrasonography (HD7XE, Phillips, USA). To do so, a high frequency transducer (3-12 MHz) records the dilatation of the brachial artery for 120 s immediately after the release from a 5-min total occlusion maneuver. The subjects are asked to fast for at least 6 h prior to the procedures. Brachial Analyzer Software (Vascular Tools, Medical Imaging Application, USA) is used to quantify changes in arterial diameter from baseline to post-cuff occlusion. Flow-mediated dilation will be calculated as the percentage change in arterial dimeter fromaverages of 10 baseline diastolic diameters and 3 maximum, systolic diameters post-cuffocclusion. In addition to the pre-and

post-trial measurements, a mid-term FMD assessment is conducted during the 6th week of intervention.

Control variables

Anthropometric assessment The subject is weighted on a calibrated scale, with light clothes and no shoes. Height is assessed through an analogic stadiometer, during a light inhale and with the head positioned in the Frankfurt plane. Waist circumference is assessed in the midpoint between the iliac crest and the 10th rib.

Adherence to pharmacological plan Subjects answer a validated Brazilian version of the MMAS-8 [20–23], which is comprised of eight self-reported items related specifically to adherence to anti-hypertensive medication scheme. This scale's score is divided into three categories: high adherence, moderate adherence and low adherence.

Blood variables Blood samples are collected for quantification of total cholesterol, HDL-cholesterol, creatinine, and glycated hemoglobin (HbA1c). In brief, after 12 h of fasting, an experienced technician collects 4 mL of blood from the antecubital fossa. In the coordinator center, blood samples are taken directly to the clinical pathology laboratory (central laboratory) where they are centrifuged and subsequently analyzed. In the participant center, blood samples are centrifuged and stored in a − 80 °C freezer. After 10–20 participants are sampled either at t0 or t5 (Table 3), the samples are transported in a thermic container filled with dry ice to the central laboratory for analysis.

Physical activity levels subjects answer a validated Brazilian version of the IPAQ [35]. The IPAQ long version is used, which assesses physical activity in five independently domains, namely: (a) job-related, (b) transportation, (c) housework, (d) recreational and (e) time spent sitting.

Handgrip strength isometric handgrip strength is measured in both arms with an analogic hand dynamometer (Jamar Sammons Preston Rolyan, Bolingbrook, IL, USA). After one research team member demonstrates proper device and body positioning, the subject keeps an upright standing posture and position his/her evaluated arm with the forearm parallel to the ground (elbow flexed at 90°). Thereafter, the subject is instructed to perform a maximal squeezing contraction with sustained (isometric) effort lasting 5 s. Three attempts are carried out in each arm with one-minute rest intervals.

Adherence assessments

Measures of adherence to interventions will be reported as group averages and operationalized as attendance and compliance. Attendance is monitored through session's frequency recording and will be treated as the percent of intervention sessions experienced by a participant given the total number of scheduled sessions (36 sessions for the exercise program or 12 sessions for the education program). Adherence will be treated as the percent of intervention sessions fully accomplished without protocol deviations given the total number of scheduled sessions. For example, this may include either: (i) a participant allocated to the exercise program that, for any reason, walked less than the prescribed duration for a given session; or (ii) a participant allocated to the education program that only partially watched a lecture.

Data management

At the two study centers, data are collected on standardized paper forms identified by subject number and trial ID and containing instructions for standardized operational procedures. From these forms, we proceed with double data entry for primary, secondary, and additional outcomes. Data entry is carried out at each study center, however, data are centrally stored and managed through the use of REDCap electronic data capture tools hosted at the Hospital de Clínicas de Porto Alegre. REDCap (Research Electronic Data Capture) is a secure, web-based application that will provide us with (1) an intuitive interface for validated data entry; and (2) audit trails for tracking data manipulation and export procedures [36]. Audition for missing or inaccurate data is conducted at the coordinator center. Data are backed up daily by automated export procedures from secure servers of the Hospital de Clínicas de Porto Alegre.

In addition, brachial artery images for endothelial function assessment will be analyzed at an external laboratory (Cardiovascular Aging Research Laboratory, Austin, Texas). To do so, we will share image files over a secure cloud-based sharing platform (Box Inc., USA) hosted by the University of Texas at Austin.

Statistical considerations

For primary and secondary outcomes, we will adhere to the intention-to-treat (ITT) principle and analyze all randomized participants, irrespective of attrition. The primary hypothesis will be tested on a superiority framework. Variables from ambulatory BP will be treated as diurnal, nocturnal and 24-h for both systolic and diastolic BP. Mixed effects models will be used to determine differences between groups using final values for systolic and diastolic ambulatory BP, adjusted for baseline values (pre-intervention). If these data present low linear fit, we will compare groups using generalized estimating equations with an independence model as the covariance matrix.

Two analysis sets will be established as follows: (1) a full analysis set (FAS) including all randomized subjects, therefore allowing ITT analyses; and (2) a per-protocol (PP) analysis set including all subjects that completed the trial (completers) with adherence to at least 70% of the intervention sessions (≥ 25 sessions for participants allocated in the exercise program, and ≥ eight sessions for participants allocated to the education program). Participants that drop out of the study due to safety concerns or other outcomes will not be censored in PP analysis. Additionally, we plan to carry out a subgroup analysis stratifying both groups by individuals with non-controlled BP before the intervention versus individuals with well-controlled BP before the intervention. Such stratification will be based on tertiles of systolic BP at baseline, with a primary interest in the comparison of interventions on ambulatory BP using the lowest and highest thirds.

Incomplete data will be explored in sensitivity analyses by pattern mixture model. This procedure will describe whether there is an interaction between the main missing patterns and other variables (e.g., group, time, group by time, BP status, BP status by group). We expect two main missing data patterns based on an indicator of completers versus non-completers (defined as randomized subjects without 12-week data). Because withdrawals may occur due to specific harms or other non-anticipated reasons, we will assess whether additional grouping (indicator) should be made due to different patterns of missing data. Therefore, we will qualitatively document reasons and details of withdrawals on a case-by-case basis. In the case of identifiable patterns indicating that missing data are non-ignorable, the interpretation of related findings should take missingness into account. No interim analyses other than monitoring of demographic data are planned.

Continuous variables will be summarized according to intervention groups at baseline, if applicable, and end of trial using arithmetic or geometric means, standard deviations, ranges, and interquartile ranges as appropriate. Change from baseline will be summarized descriptively accompanied by its 95% CI. In descriptive summaries, last observation carried forward (LOCF) will be employed to impute missing values. Categorical variables at baseline and end of trial (if applicable) will be summarized as absolute number and proportion of subjects (%) according to intervention groups.

Monitoring

Data monitoring

The HAEL Study does not have a data monitoring committee due to limited resources. We reason this committee would not be mandatory due to the characteristics of interventions and outcomes, despite its highly value for the overall quality of the trial.

Harms

The identification, possible solutions, and documentation of adverse events are based on a study management algorithm requested and approved by the Institutional Review Board from the coordinator center.

Auditing

If necessary, auditing will be conducted by the Hospital de Clínicas de Porto Alegre through defined protocols implemented by an independent monitoring team adjunct to the IRB structure.

Ancillary, post-trial care and harm from trial participation

After enrollment in the HAEL Study, each participant receives a brief report of health status prepared by a researcher not involved in intervention implementation and data assessments. If requested, punctual tests information can be given to participants for treatment matters. For harms suffered during trial enrollment related to the study (after adjudication by the committee), we planned contingency actions to assist the participant through care provided either at primary health care units or at the Hospital de Clínicas de Porto Alegre (tertiary care). Finally, the HAEL Study staff has Basic Life Support training and an algorithm for major adverse events is available if necessary.

Dissemination policy

We aim to disseminate the methods and findings of the HAEL Study to as many stakeholders as possible. Therefore, our dissemination plan after trial completion encompasses the following: (1) breakfast meeting with study participants by which we will present a layman-friendly explanation about the study design, findings, and interpretation; (2) press releases written by journalists and directed towards the general public, and (3) scientific manuscripts. For the latter, criteria for authorship on HAEL Study publications will adhere to the recommendations by the International.

Committee of Medical Journal Editors [37] and those defined by the destination journals. Because we have established a relatively large multi-author group, some publications will carry authorship by a group name designated the HAEL Study Group. When submitting a manuscript authored by HAEL Study Group, byline authors will be mostly defined by full-time equivalents of workload in trial activities. To this end, we do conduct monitoring of all investigators workload on a weekly basis. To ensure reporting completeness, manuscripts written by the HAEL Study Group must adhere to the CONSORT Statement [38], or, if applicable, more suited reporting guidelines.

Discussion

The HAEL Study presents features which are relevant to be highlighted. First, we established our research question towards the elderly population. Beyond a justification of scantiness of large exercise studies in samples exclusively composed by older individuals, elderlies represent our population of interest primarily because they yield a high prevalence of hypertension and present an exponentially increased risk of death [2]. Therefore, assessing the efficacy of lifestyle interventions that may positively influence BP control in this population is desirable, particularly because older individuals are common polypharmacy users and present reductions in both physical and psychological and/or cognitive domains. Second, we chose to implement a combined training intervention as the candidate method to provide superior effects in BP reduction, vascular adaptation, and functional measures. Importantly, this type of intervention has been recommended in several position stands of exercise to maximize health benefits because both cardiovascular and neuromuscular stimuli occur in parallel. Moreover, we simplified the choice of aerobic and resistance exercises so that the program may be more feasibly implemented in public health settings or low-resource scenarios. Third, we designed the comparator intervention to minimize possible differences due to participation (Hawthorne) effects as well as provide participants with information on varied topics related to hypertension management. Although the interventions differ in weekly frequencies, equating the frequencies of both programs in three times a week would make education meetings more repetitive and probably reduce attrition rates.

Finally, we point out that the HAEL Study is confirmatory trial by nature. Therefore, we have designed this trial establishing methodological standards as high as possible for both outcome measurements and trial management. In this regard, we emphasize some aspects such as the (i) use of 24-h ambulatory systolic and diastolic BP, which is scarcely available from previous trials; (ii) a standardized management plan for participants with uncompensated BP; and (iii) open research practices that will likely make the trial more useful and reproducible.

Additional files

Additional file 1: Roles of investigators. (DOCX 13 kb)

Additional file 2: World Health Organization Trial Registration Dataset. (DOCX 13 kb)

Additional file 3: Amendments chronology. (DOCX 12 kb)

Abbreviations

BP: Blood pressure; FMD: Flow-mediated dilatation; IPAQ: International Physical Activity Questionnaire; IRB: Institutional review board; ITT: Intention-to-treat; LOCF: Last observation carried forward; MOP: Manual of operating procedures; QoL: Quality of life; SPPB: Short Physical Performance Battery; VO2peak: Peak oxygen consumption

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CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).

FIPE (Fundo de Incentivo à Pesquisa e Eventos, Hospital de Clinicas de Porto Alegre).

Availability of data and materials

We support the reuse of scholarly data and intend that the data to be collected in this trial may contribute beyond our actions to the knowledge on exercise, elderly population and hypertension. We have obtained ethical consent from participants as well as IRB approval to share deidentified data after trial completion. Data sets, variables' dictionary and statistical analysis description will be made available online upon registration and acceptance of the study team's data sharing terms and policy. Data usage will be under the PI's auspices, but restrictions or screenings will not be imposed upon data requests. Ambulatory BP monitoring data and any deemed relevant support information (sociodemographic, clinical history and allocated groups) will be shared through a public repository no later than six months after the first study publication, with data access being available as long as deemed necessary by the study coordination. Data on other outcomes may be requested by contacting the PI. The public repository for data sharing is not yet defined, however, it will be presented in the study website and scientific publications.

Authors' contributions

DU, LPS and SSP generated the operating hypothesis for the study. DU, LPS, CEB, EN, LH, CAP, HT, LSP, RSM, BDS, CLA and SSP made major contributions for the study's rationale and protocol manuscript. LH, GZS, GDF, ATDN, LOP, ADS, GFM, LA, LG, MLB, PMB, PC and MRD contributed in intellectual, organizational and logistic frameworks for data collection, interventions' rationale and implementation, allocation concealment, data assessors blinding and other important aspects of study workflow, together with critically reviewing the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The study procedures were approved by the Ethics Committee/IRB from the Hospital de Clínicas de Porto Alegre (CAAE: 62427616.0.1001.5327) and Federal University of Pelotas (CAAE: 62427616.0.2001.5313), and adhered to Good Clinical Practices. The informed consent document includes the objectives of the study, a description of the testing procedures, explanation about interventions and its randomized allocation nature, the potential risks and benefits involved in the study, the costs to the participants, information on anonymized data sharing, and liabilities of the particular participating center. A copy of the consent form is given to the participant (or legal guardian), and this fact is documented in the subject's record. The investigator charged of providing study clarifications and seeking the participant's ethical consent must allow the subject sufficient time to decide whether or not to participate in the trial. Once a subject decides to participate, a signed and personally dated informed consent is obtained from the subject before any trial-related procedure.

Any modifications to the protocol which may impact relevant changes to study procedures (e.g., changes in eligibility criteria, assessments, information on risk/benefit) or to administrative routine require a formal amendment to

the protocol. Although such protocol changes may be applicable to only one center (e.g., inclusion of an assessment procedure for a given center), any amendment should have the approval of both centers coordinators and be approved by the Ethics Committee/IRB prior to implementation. This manuscript is accompanied by a description of existing amendments (Additional file 3).

Consent for publication
Not applicable.

Competing interests
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Publisher's Note

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APPENDIX III

Candidate's production during the doctorate period October 2015 – October 2019

Original studies

BRENTANO, M.A. ; UMPIERRE, DANIEL ; SANTOS, LUCAS PORTO ; LOPES, ANDRÉ LUIZ ; KRUEL, LUIZ FERNANDO MARTINS . Supersets do not change energy expenditure during strength training sessions in physically active individuals. Journal of Exercise Science and Fitness, v. 14, p. 41-46, 2016.

BRENTANO, MICHEL ARIAS ; UMPIERRE, DANIEL ; SANTOS, LUCAS PORTO DOS ; RADAELLI, REGIS ; PINTO, RONEI SILVEIRA ; KRUEL, LUIZ FERNANDO MARTINS . Muscle Damage And Muscle Activity Induced By Strength Training Super-Sets In Physically Active Men. JOURNAL OF STRENGTH AND CONDITIONING RESEARCH, v. 31, p. 1847-1858, 2016.

SANTOS, LUCAS P.; MORAES, RUY S. ; VIEIRA, PAULO J.C. ; ASH, GARRETT I. ; WACLAVOWSKY, GUSTAVO ; PESCATELLO, LINDA S. ; UMPIERRE, DANIEL . Effects of aerobic exercise intensity on ambulatory blood pressure and vascular responses in resistant hypertension. Journal of Hypertension, v. 34, p. 1317-1324, 2016.

FERRARI, RODRIGO ; UMPIERRE, DANIEL ; VOGEL, GUILHERME ; VIEIRA, PAULO J.C. ; SANTOS, LUCAS P. ; DE MELLO, RENATO BANDEIRA ; TANAKA, HIROFUMI ; FUCHS, SANDRA C. . Effects of concurrent and aerobic exercises on postexercise hypotension in elderly hypertensive men. Experimental Gerontology, v. 98, p. 1-7, 2017.

ZALESKI, A. ; TAYLOR, B. A. ; SANTOS, L. P. ; PANZA, G. A. ; KRAMARZ, M. ; MCCORMICK, K. ; THOMPSON, P. D. ; FERNANDEZ, A. B. ; CHEN, M. ; BLISSMER, B. ; GANS, K. M. ; PESCATELLO, L. S. . Using the immediate blood pressure benefits of exercise to improve exercise adherence among adults with hypertension. JOURNAL OF HYPERTENSION, v. 37, p. 1-12, 2019.

UMPIERRE, DANIEL ; SANTOS, LUCAS PORTO ; BOTTON, CÍNTIA EHLERS ; WILHELM, EURICO NESTOR ; HELAL, LUCAS ; SCHAUN, GUSTAVO ZACCARIA ; FERREIRA, GUSTAVO DIAS ; DE NARDI, ANGÉLICA TREVISAN ; PFEIFER, LUCINÉIA ORSOLIN ; DA SILVEIRA, ANDERSON DONELLI ; POLANCZYK, CARISI ANNE ; MENDES, GRACIELE FERREIRA ; TANAKA, HIROFUMI ; ALVES, LEONARDO ; GALLIANO, LEONY ; PESCATELLO, LINDA S. ; BRIZIO, MARIA LAURA ; BOCK, PATRÍCIA MARTINS ; CAMPELO, PAULA ; MORAES, RUY SILVEIRA ; DOMINGUES, MARLOS RODRIGUES ; SCHAAN, BEATRIZ D. ; ALBERTON, CRISTINE LIMA ; PINTO, STEPHANIE SANTANA . The -Hypertension Approaches in the Elderly: a Lifestyle study- multicenter, randomized trial (HAEL Study): rationale and methodological protocol. BMC PUBLIC HEALTH, v. 19, p. 1-13, 2019.

CILHOROZ, B. T. ; SCHIFANO, E. D. ; ASH, GARRETT I. ; PANZA, G. A. ; CORSO, L. ; CHEN, M. ; DESHPANDE, V. ; ZALESKI, A. ; FARINATTI, P. ; SANTOS, L. P. ; TAYLOR, B. A. ; ONEILL, R. J. ; THOMPSON, P. D. ; PESCATELLO, LINDA S. . FURIN variant associations with postexercise hypotension are intensity and race dependent. PHYSIOLOGICAL REPORTS, v. 7, p. e13952, 2019.

Book chapters

PESCATELLO, LINDA S. ; CORSO, L. ; SANTOS, LUCAS P. ; Livingston, J ; TAYLOR, B. A. . Angiotensin Converting Enzyme and the Genomics of Endurance Performance. In: J. Timothy Lightfoot; Monica J. Hubal; Stephen M. Roth. (Org.). Routledge Handbook of Sport and Exercise Systems Genetics. 1ed.: , 2018

International presentations

66th ACSM's Annual Meeting - SANTOS, L. P.; DE NARDI, ANGÉLICA TREVISAN ; PFEIFER, LUCINÉIA ORSOLIN ; OLIVEIRA, N. L. ; WU, Y. ; UMPIERRE, D. ; PESCATELLO, LINDA S. . Aerobic Exercise Training and Blood Lipids-Lipoproteins Among Healthy Adults: A Methodological Umbrella Review, 2019

66th ACSM's Annual Meeting - ZALESKI, A. ; TAYLOR, B. A. ; PARK, C. ; SANTOS, L. P. ; PANZA, G. A. ; KRAMARZ, M. ; MCCORMICK, K. ; THOMPSON, P. D. ; FERNANDEZ, A. B. ; CHEN, M. ; BLISSMER, B. ; DELUCA, K. ; PESCATELLO, LINDA S. . Using the Immediate Blood Pressure Benefits of Exercise to Improve Exercise Adherence. 2019.

International Symposium: Cardiovascular Effects of Exercise - SANTOS, L. P.; BOTTON, CÍNTIA EHLERS ; OLIVEIRA, N. L. ; FICO, B. ; ALHALIMI, T. ; TANAKA, HIROFUMI ; UMPIERRE, D. Endothelial function in older adults treated for hypertension: an exploratory analysis using an arbitrary cutoff for flow-mediated dilatation, 2019.

EBM Live - DANIEL UMPIERRE; ANGÉLICA T DE NARDI; CÍNTIA E BOTTON; LUCAS HELAL; LUCINÉIA O PFEIFER; LUIZA IC RICARDO; LUCAS P SANTOS; NÓRTON L OLIVEIRA. Strengthening the evidence in exercise sciences initiative (SEES initiative): a prospective project based on openness, surveillance, and feedback. 2019

Peer Review Congress. DANIEL UMPIERRE, LUCAS HELAL, PATRÍCIA BOCK, AND LUCAS PORTO SANTOS. Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guideline Items in Randomized Trials of Physical Activity Published in 5 Sports Medicine Journals. 2017

National level talks

XXII Brazilian Congress of Nutrology – High-intensity interval training, weight loss and metabolic profile modifications. 2018

74th Brazilian Congress of Cardiology – Exercise and hypertension. 2019

Local level talks

Rio Grande do Sul Cardiology Society Congress – Oral free communication evaluation. 2019

Rio Grande do Sul Cardiology Society Congress – Exercise and hypertension. 2019

Ongoing collaborations

Aerobic Exercise Training and Blood Lipids-Lipoproteins Among Healthy Adults: A Methodological Umbrella Review. (CRD42018102663) – Data extraction finished. Project in collaboration with UConn.

Impact of aerobic exercise on circulating endothelial progenitor cells. – Ongoing project, ending data collection. Hospital de Clínicas de Porto Alegre.

Health outcomes in children and adolescents exposed to physical activity interventions: overview of systematic reviews and meta-analyses. (CRD42019120334) – Ongoing data extraction. Hospital de Clínicas de Porto Alegre.

Health situation analysis of elderly users participating in public programs of physical activity in Porto Alegre, Brazil: a cross-sectional study. Data collection finished. Hospital de Clínicas de Porto Alegre.