

Case Report

Effects of isometric handgrip training in patients with cardiovascular disease: rationale and design of the ISOPRESS network

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Abstract — Meta-analytical studies have indicated that isometric handgrip training promotes significant reduction in blood pressure in hypertensive patients with similar or greater decreases in blood pressure than observed after aerobic and dynamic resistance training. However, several gaps in the literature still need to be addressed. Thus, we designed the ISOPRESS network group, which consists of a task force of different research groups aimed at analyzing the effects of isometric handgrip training on different contexts, parameters, and populations. Thus, the aim of this study was to describe the rationale and design behind the ISOPRESS, presenting the methods employed. The ISOPRESS questions involve whether isometric handgrip training is effective in hypertensives in different settings (ISOPRESS 1 – unsupervised training and ISOPRESS 2 – public health system), whether it works in patients with other cardiovascular diseases (ISOPRESS 3 – obstructive sleep apnea and ISOPRESS 4 – peripheral artery disease) and what are the mechanisms underlying the effects of isometric handgrip training in hypertensives (ISOPRESS 5 – neural mechanism). The study will yield information on the effectiveness of isometric handgrip training in different settings and patients with other cardiovascular diseases. Finally, it will help to understand the mechanisms involved in reducing blood pressure in hypertensives.

Keywords: research methods; hypertensive; isometric training; blood pressure; exercise

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide. It is estimated that 30% of deaths worldwide are a consequence these diseases¹. The total direct and indirect cost of CVD in the United States for 2010 was estimated to be \$315.4 billion². It is known that there is a strong, independent relation between CVD morbidity, and mortality and hypertension², with more than 50% of all CVD directly associated to hypertension¹. Hypertension affects more than 1 billion people³, and in 2025, it is estimated that hypertension will affect more than 1.5 billion people worldwide⁴. Therefore, interventions to reduce blood pressure are sorely needed in order to reduce cardiovascular risk and the costs associated with high blood pressure.

Lifestyle modification programs are considered a cornerstone in therapeutic approach of CVD patients⁵⁻⁷, and a key recommendation is exercise. Aerobic exercises have been widely recommended for lowering blood pressure and they are complemented by dynamic resistance exercises⁵⁻⁷. Recently, meta-analytical studies⁸⁻¹³ demonstrated that isometric training, especially the handgrip¹³, decreases the office blood pressure, and a recent estimate showed reductions of approximately 7 mmHg for systolic and 5 mmHg for diastolic in hypertensives¹⁴. These decreases are similar or greater than those observed after aerobic and dynamic resistance training¹⁰. Interestingly, isometric handgrip training is performed with a portable device, is easy

to perform, requires less than 35 min per week⁵⁻⁷, and avoids important barriers for physical activity practice in patients with cardiovascular disease^{15,16}. These aspects have piqued the interest of the scientific community to understand the potential of isometric handgrip training in the therapeutic approach of patients with CVD. However, the studies were performed only in hypertensive and normotensive patients, and analyzed only a few variables^{17,18}.

In this context, we designed the ISOPRESS network group, which consists of a task force of different research groups in Brazil that aim to understand the effects, applicability and mechanisms of isometric handgrip exercise. For this, we will analyze the effects of isometric handgrip training on different populations (hypertensive, peripheral artery disease patients and obstructive sleep apnea patients) and contexts (ie clinical, unsupervised and laboratory). Thus, the aim of this study was to describe the rationale and design behind the ISOPRESS network, presenting the methods employed.

Methods

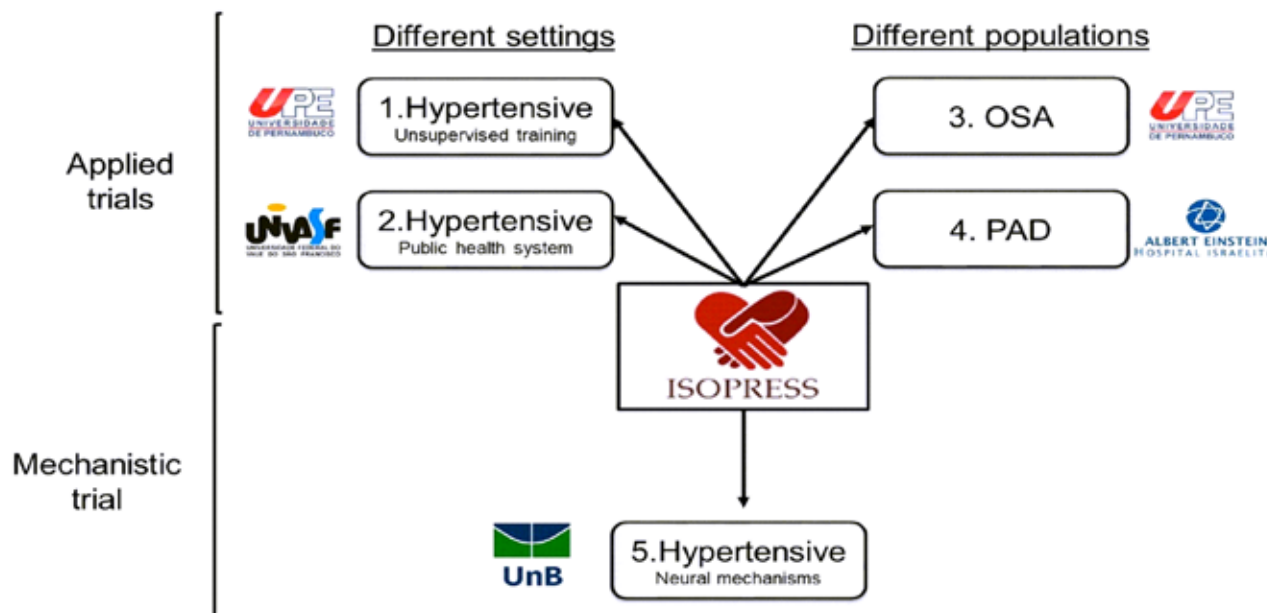
Rationale

The ISOPRESS network was developed to analyze the effects of isometric handgrip training on cardiovascular variables in

different contexts and populations. The ISOPRESS network includes four Brazilian institutions that will address five different questions regarding handgrip exercise training. The questions involve whether isometric handgrip training is effective in different

settings (ISOPRESS 1 and 2), whether it works on patients with other cardiovascular diseases (ISOPRESS 3 and 4) and what are the mechanisms underlying the effects of isometric handgrip training (ISOPRESS 5). These aspects are clarified in the figure 1.

Figure 1. Rationale of ISOPRESS network. OSA - Obstructive Sleep Apnea. PAD – Peripheral artery disease.



The importance of ISOPRESS 1 and 2 studies are that all studies using isometric handgrip training used the supervised training at laboratory. However, given that the handgrip is portable, easy to perform and requires short period of time to perform the exercise, the unsupervised training seems to be an interesting option of training at low cost. The ISOPRESS 3 and 4 are designed to analyze the effects of isometric handgrip training on patients with comorbid conditions, which are prevalent in adults (obstructive sleep apnea)¹⁹ and the elderly (peripheral artery disease)²⁰. Thus, the design will allow the understanding of isometric

handgrip training on subjects with different severities of cardiovascular disease.

The mechanisms underlying the effects of isometric handgrip exercise are still unclear. Although some evidence has suggested the possible role of the autonomic nervous system^{21,22} and oxidative stress²³, several pieces of the puzzle are missing. The purpose of ISOPRESS 5 is to analyze autonomic and vascular parameters as some of them were not previously described (baroreflex sensitivity). The characteristics of the studies developed in ISOPRESS project, as well as the guiding questions, sample involved, and settings are presented in Table 1.

Table 1. Characteristics of studies developed in ISOPRESS project.

	Question	Sample	Setting
Isopress 1	Are the effects of unsupervised isometric handgrip training similar to supervised training?	Hypertensive	Unsupervised
Isopress 2	Can isometric handgrip training decrease blood pressure in patients attended in public health system?	Hypertensive	Public health system
Isopress 3	Can isometric training reduce blood pressure in patients with obstructive apnea syndrome?	Obstructive Sleep Apnea	Clinical
Isopress 4	Can isometric training reduce blood pressure in patients with vascular disease?	Peripheral arterial disease patients	Clinical
Isopress 5	Does the autonomic modulation is involved in the reduction in blood pressure with handgrip training?	Hypertensive	Laboratory

Inclusion criteria:

The inclusion and exclusion criteria vary between studies, depending on the specific aim of the study, as well as the specific characteristics of the studied sample. For example, peripheral artery disease patients present higher prevalent rates of cognitive impairment²⁴ and this could affect the unsupervised training. Patients with hypertension associated with diabetes or other cardiovascular diseases or neurological/cognitive diseases will not be included in studies with hypertensives (ISOPRESS 1, 2 and 5) in order to avoid chronic complications of these diseases. In all studies, patients will be excluded if they change their medication.

ISOPRESS 1: Age > 18 years old, both sexes, non-participation in exercise program: use of antihypertensive medication, availability to participate in any group.

ISOPRESS 2: Age > 18 years old, both sexes with controlled hypertension from antihypertensive medication. All subjects will be recruited individually in the family health centers.

ISOPRESS 3: Age from 30 to 65 years old, both sexes, with mid to moderate obstructive sleep apnea (apnea-hypopnea index 5-29 events/hour) and uncontrolled blood pressure (e.g. systolic blood pressure > 130 mmHg and diastolic > 80 mmHg in ambulatory blood pressure monitoring).

ISOPRESS 4: Age > 50 years old, if female, post-menopausal without hormone therapy replacement, ankle brachial index < 0.90, in one or both lower limbs, insufficiently active, non-smoker, no diagnosis of neurological/cognitive diseases.

ISOPRESS 5: Age > 18 years old, both sexes, non-participation in exercise program, not using antihypertensive, and non-smoking.

Similarities and differences in exercise protocol

All efforts were made to standardize the methodology among different studies. In all studies patients will be allocated in their groups according to random numbers generated on the website www.randomizer.org. In addition, the evaluators will be will not be seen by the group of the patients. All groups will perform four two minute' sets with 30% of maximum

voluntary contraction. The training period will last between eight and twelve weeks.

In some cases, the standardization was violated to attend some specific aim of the study. For example, in ISOPRESS 4, which includes peripheral artery disease patients, the understanding of local effects of training is important due to the systemic atherosclerotic process in these patients. Therefore, in this specific study, an unilateral exercise training will be performed, while in the other studies a bilateral protocol will be used. Although this difference may impact the comparisons, previous studies with unilateral training reported results similar to bilateral training²⁵⁻²⁷.

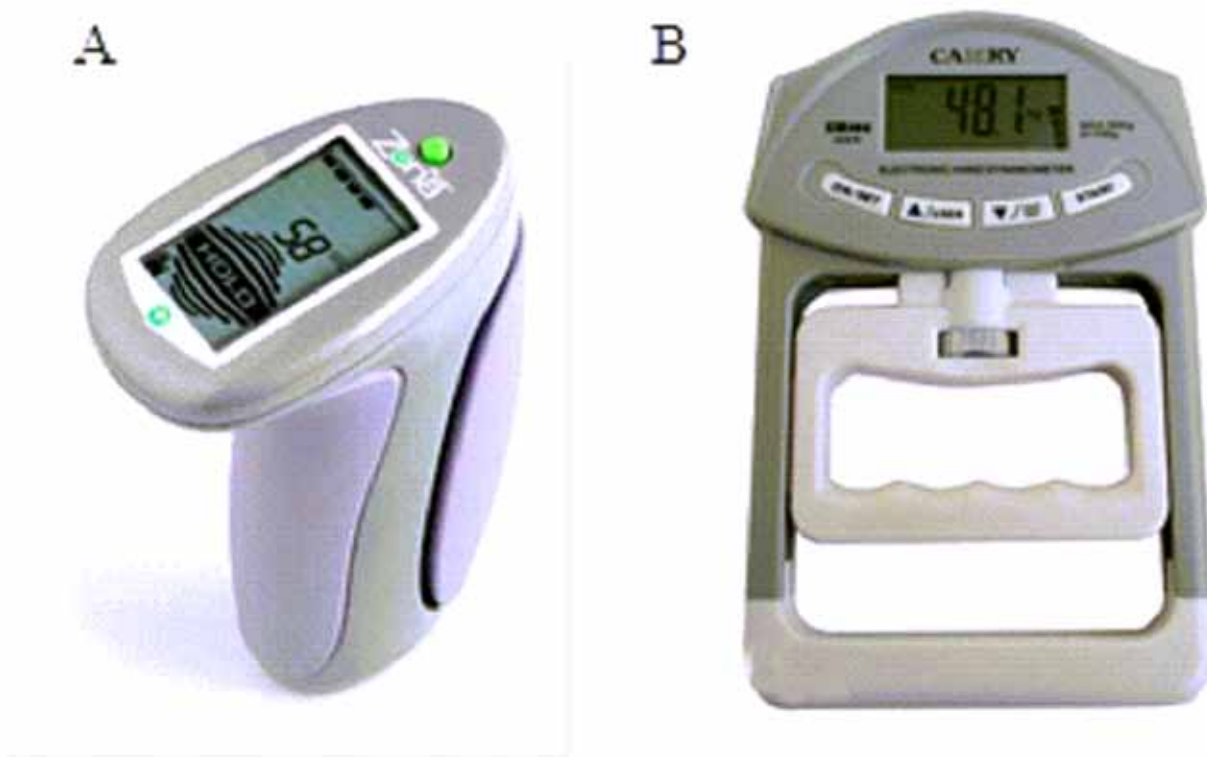
Another difference is the device used to perform training programs. The use of two devices will allow understanding the influence of different devices during isometric handgrip training on cardiovascular variables. The devices that will be used are: a) Zona Plus (Zona Health, Boise, Idaho, USA) and, b) Camry device (Zhongshan Camry Electronic Co. Ltd. Zhongshan Guangdong, China). There Zona plus is a digital dynamometer that was developed specifically for isometric handgrip training. In each session it records the maximal voluntary contraction, and then sets the load that need to be achieved in each set. The screen in the device provides an instantaneous feedback of the amount of force indicating if the amount of force applied is adequate. In addition, the device has a timer that provides information regarding the duration of exercise and the rest intervals. On the other hand, the Camry is a simple device that provides information regarding the amount of force supplied. Thus, the determination of the amount of strength, duration of the set and rest intervals should be actively performed by the volunteers. Figure 2 presents the two devices used in this study.

Finally, the control group will differ in some points between studies. In all studies patients randomized for the control group will be encouraged to increase their physical activity level and to have healthy eating habits. However, for ethical reasons, the patients attended in public health system (including peripheral artery disease patients) will receive specific recommendations to increase their amount of physical activities, as a way to improve their health. In all studies, the experimental group will receive the same lifestyle recommendations as the control group. Table 2 presents the details of interventions between studies.

Table 2. Details of interventions between studies in the ISOPRESS project.

	Protocol	Supervision	Device	Control
Isopress 1	Bilateral	No	Camry	Improve lifestyle habits
Isopress 2	Bilateral	No	Zona Plus	Achieve 5000 steps/day
Isopress 3	Bilateral	Yes	Camry	Improve lifestyle habits
Isopress 4	Unilateral	No	Zona Plus	Achieve 5000 steps/day
Isopress 5	Bilateral	Yes	Zona Plus	Improve lifestyle habits

Figure 2. Devices will be used in the ISOPRESS project. A - Zona Plus device; B - Camry device.



Variables analyzed

Table 3 lists the variables obtained in the studies. The measures are standardized between all studies. Prior to all cardiovascular

variables measurements, the patients will be instructed to avoid physical exercise for at least 24 hours prior to the visit, avoid smoking, alcohol and caffeine ingestion for at least 12 hours and to eat a light meal before arriving at the laboratory.

Table 3. Outcomes assessments of ISOPRESS project.

Variables	ISOPRESS 1	ISOPRESS 2	ISOPRESS 3	ISOPRESS 4	ISOPRESS 5
Office blood pressure	X	X	X	X	X
Ambulatory blood pressure	X	X	-	-	-
Central blood pressure	X	-	X	X	-
Ankle brachial index	X	-	-	-	-
Cardiac autonomic modulation					
Heart rate variability	X	-	-	X	-
Blood pressure variability					X
Central sympathetic activity	-	-	-	-	X
Baroreflex sensitivity					
Non-pharmacological approach	-	-	-	-	X
Pharmacological approach	-	-	-	-	X
Arterial stiffness measures	X	-	X	X	-
Vascular measures	X	-	X	X	-
Biomarkers	X	-	-	-	-

Office blood pressure

Office blood pressure will be performed through the Omron HEM 742 device. For this, individuals remain for ten minutes in the supine position. Three consecutive measurements will be performed with one-minute intervals at higher arm pressure and with the proper cuff size to arm circumference. The value used is the average of the last two measures⁶.

Ambulatory blood pressure monitoring (ABPM)

The ambulatory blood pressure readings over a 24-hour period will be obtained using the oscillometric device (Dyna-MAPA, Cardios, Brazil) programmed to take measurements every 15 minutes during the daytime and every 30 minutes at night time. The individual will be oriented to log on a specific form any abnormal occurrence (daily or nightly), during the use of the device. Additionally, the person will be instructed to not drink alcoholic beverages, to not practice physical exercise and to not sleep during the day on the 24 hours under evaluation. The exam through the MABP will only be considered acceptable for the study if at least 85% of the possible measures for the 24 hours of monitoring are successfully obtained. Thus, the average and the standard deviation of the 24 hours of systolic, diastolic and mean blood pressure will be obtained, which also will be subdivided into waking and sleeping periods. The nocturnal drop in blood pressure will be calculated in absolute terms (mean waking – mean sleeping blood pressure), which will be obtained by the mean of the values reported in the period that the patients will be awake and sleep, respectively; while the morning surge will be calculated as the difference between the mean blood pressure during the last two hours of sleep and that of the first two hours after waking. The 24-hour awake and asleep pressure loads will be calculated by the percentage of measurements with values greater than 125/75, 130/85 and 110/70 mmHg, respectively⁶.

Central blood pressure

Central systolic and diastolic blood pressure will be obtained by pulse wave analysis recorded in the left radial artery using applanation tonometry (SphygmoCor, AtCor Medical, Australia) and the validated transfer function algorithm provided by the Sphygmocor® software will obtain the central values of systolic, diastolic, and mean blood pressures, equivalent to the pressure wave measured by an invasive catheter²⁸. To enhance the accuracy of measurements, only those values that had a quality index over 90% will be used.

Ankle brachial index

The ankle brachial index will be measured as the highest systolic blood pressure in the posterior tibial artery or dorsalis pedis artery divided by the highest systolic blood pressure in the brachial artery²⁹. The measurement of blood pressure in the ankle and arm

will be measured in triplicate, using Doppler vascular (Medmega DV160, Brazil) and a mercury sphygmomanometer, respectively.

Cardiac autonomic modulation

Blood pressure variability

Continuous beat-to-beat arterial blood pressure will be measured using finger photoplethysmography (Human NIBP Controller, AD instruments, Australia). After at least ten minutes of resting, ten minutes of consecutive beats will be recorded. Spectral analysis of blood pressure will be performed employing the CardioSeries v2.4 software, which uses Fourier transformation to calculate spectral power systolic blood pressure variability. Blood pressure variability will be calculated after appropriate spline interpolation and equidistant representation of systolic blood pressure data. The very low frequency (VLF) band will be defined in the range of 0.02-0.07 Hz, the low frequency (LF) band in the area of 0.07-0.15 Hz, and the high frequency (HF) band between 0.15 and 0.40 Hz. The LF component of blood pressure variability will be used as a proxy of the sympathetic modulation of the vascular tone³⁰.

Heart rate variability

Heart rate variability (HRV) will be assessed from the RR intervals obtained by a heart rate monitor (RS800CX, Polar Electro, Finland). Patients will remain in the supine position for 10 minutes and, after approximately 30 minutes at rest, next, at least five minutes of the stationary period will be used for analysis. All analysis will be performed with Kubios HRV software (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland) by a single evaluator blinded to the other study variables. The intraclass correlation coefficient of this measure in our lab ranged 0.990 to 0.993³¹, following the recommendations of the Task Force of HRV³².

The time-domain parameters, such as: standard deviation of all RR intervals (SDNN), root mean square of the squared differences between adjacent normal RR intervals (RMSSD), and the percentage of adjacent intervals over 50ms (PNN50) will be obtained. The frequency-domain parameters will be analyzed using the spectral analysis of HRV. Stationary periods of the tachogram will be broken down into bands LF and high HF frequencies, using the autoregressive method with a fixed model order of 12 by Akaike's information criterion. Frequencies between 0.04 and 0.4 Hz were considered as physiologically significant, where the LF component was represented by oscillations between 0.04 and 0.15 Hz and HF was represented by oscillations between 0.15 and 0.4 Hz. The power of each spectral component was normalized by dividing the power of each spectrum band by the total variance, minus the value of very low frequency band (< 0.04 Hz), and multiplying the result by 100.

Non-linear parameters, such as: Poincare plot (SD1 and SD2), Recurrence plot (Mean line length - Leman, Max line length – L_{max}, Recurrence rate - REC, Determinism – DET,

Shannon Entropy – ShanEn) and other parameters such as approximate entropy (ApEn), Sample entropy (SampEn), α_1 , α_2 and correlation dimension (D2) will be obtained.

Central sympathetic activity

Postganglionic multiunit muscle sympathetic nerve activity (MSNA) will be obtained using a unipolar tungsten microelectrode inserted in the peroneal nerve of the right leg at the fibular head, and a reference electrode will be placed subcutaneously 2–3 cm distal. The recording electrode will adjust until a site is found where nerve unit activity displays a pulse-synchronous pattern of spontaneous bursts, with a signal-to-noise ratio of 3:1, are increased during an end-expiratory breath-hold or Valsalva maneuver, and are unresponsive to an unexpected loud noise or skin stroking³³. The raw signal will be amplified ($\times 100,000$), filtered (bandwidth 700–2,000 Hz), rectified, and integrated (time constant 0.1 s) to obtain a mean voltage neurogram (Iowa Bioengineering, Iowa City, IA). Sympathetic bursts will be identified using a fully automated program³⁴. The mean voltage neurogram will be normalized by calibrating the height of the largest set of bursts during baseline to a value of 1,000 arbitrary integration units (AU). MSNA will be quantified as burst incidence (bursts/100 heart beats), burst frequency (bursts/min), and MSNA total activity (AU).

Baroreflex sensitivity

Non-pharmacological approach

Continuous beat-to-beat arterial blood pressure will be measured using finger photoplethysmography (Human NIBP Controller, AD instruments, Australia). After at least ten minutes of resting, ten minutes of consecutive beats will be recorded.

Beat-to-beat time series of systolic blood pressure and RR intervals will be analyzed using the sequence technique for estimating spontaneous cardiac baroreflex sensitivity (cBRS; CardioSeries v2.4, Brazil). Briefly, sequences of three or more consecutive beats with corresponding increases or decreases in systolic blood pressure and RR interval will be identified as arterial baroreflex sequences. Sequences will be detected only when the variation in RR intervals is greater than 1.0 ms, and when systolic blood pressure changes are greater than 1 mmHg, and longer than 3 consecutive cardiac cycles. A linear regression will be applied to each individual sequence and only those sequences in which R^2 was > 0.85 will be accepted. The slopes of the systolic blood pressure and RR interval relationships are then calculated and averaged for a measure of spontaneous cBRS. The sequence technique is based on the identification of sequences of consecutive beats in which progressive increases in systolic BP are followed by a progressive lengthening in RR intervals or vice versa; progressive decreases in systolic blood pressure are followed by a progressive shortening in RR intervals.

In addition, the baroreflex effectiveness index (BEI) will be calculated³⁴. BEI is defined as the ratio between the number of

systolic blood pressure ramps followed by the respective reflex RR interval ramps and the total number of systolic blood pressure ramps observed in a given time window.

Pharmacological approach

The baroreflex sensitivity sequence technique will also be evaluated during episodes of rise and fall in blood pressure. The rapid and abrupt change in blood pressure will be induced using a pharmacological model. In this procedure transient hypotension and hypertension (always in this order) will be induced by intravenous bolus injections of sodium nitroprusside (150 to 300 μg) and phenylephrine hydrochloride (200 to 400 μg).

Arterial stiffness measures

Pulse wave velocity will be measured using high-fidelity applanation tonometry (Sphygmocor, ATCOR Medical, Australia) following the guidelines of the Clinical Application of Arterial Stiffness, Task Force III³⁵. For the central pulse wave velocity, the distance between carotid artery to the suprasternal notch and femoral artery to the suprasternal notch will be measured using a standard tape. Then, the distance between the two arteries will be divided by the time difference. Simultaneous EKG will be assessed to obtain heart rate and, according to a “foot-to-foot” method, the time difference between the points will be measured.

Aortic blood pressure and reflected wave indicators – augmentation index, augmentation index 75bpm, and aortic pulse pressure – will be estimated in the radial artery using the applanation tonometry technique (Sphygmocor, ATCOR Medical Australia), and the validated transfer function provided by the Sphygmocor® software. Pulse pressure will be obtained by the difference between the systolic and diastolic pressure in the radial artery using the applanation tonometry technique.

The ambulatory arterial stiffness index which will be defined as 1 minus the regression slope, from individual 24-hour recordings, and it will be computed the regression slope of diastolic pressure on systolic blood pressure.

Vascular measurements

Blood flow and flow-mediated dilation measurements will be obtained by ultrasound according to recent recommendations^{36,37}. A two-dimensional ultrasound machine will record images of the brachial artery with spectral Doppler and linear transducer (Ultra-0122, Philips, The Netherlands).

For that, each patient should lie comfortably in the supine position for at least 20 minutes of rest with the arm slightly abducted. After locating the brachial artery, the transducer will be placed on the distal third of the arm (2–12 cm above the antecubital fossa). To confirm to the good location and the quality of the arterial pulse obtained, the Doppler sound will be activated. The contrast resolution, depth, and gain will be adjusted to optimize the longitudinal images of the lumen/arterial

wall interface. Brachial artery diameter and insonation angle-corrected at 60°, blood velocity spectra will be simultaneously recorded via the pulsed-wave mode at linear frequencies of 13 and 6.0 MHz, respectively.

Baseline diameter and blood velocity waveforms will be continuously recorded over 120 s. After that, a cuff, placed on the forearm, will be inflated with a pressure above 50 mm Hg of the systolic blood pressure measured before the examination. The occlusion will be maintained for five minutes, and, after this period, rapidly released. The Doppler recordings will be resumed 30 s before deflation and will maintain for 180 s after. The diameter of the brachial artery and post-occlusion of blood flow velocity will be measured after the release. The vasodilatory capacity will be calculated by the flow-mediated dilation, the percentage of increase in diameter of the brachial artery post occlusion compared to their baseline values.

In addition, the carotid intima-media thickness will be obtained. For this, the ultrasound will be used in accordance with previous recommendations³⁸. A two-dimensional ultrasound machine will record images with spectral Doppler and linear transducer (Ultra-0122, Philips, The Netherlands). The contrast resolution, depth (3-4 cm), frequency (> 15 Hz) and gain will be adjusted to optimize the longitudinal images of the arterial wall interface. The measures will be carried out in triplicate, before the carotid artery bifurcation and at the end of diastole.

The intima-media thickness of carotid artery is given by the average thickness of the selected image.

Biomarkers

Blood samples (4 ml) will be collected in tubes containing EDTA, homogenised by inversion, and then will be centrifuged at 1500 rpm for 15 min. Thereafter, the plasma will be separated, placed in Eppendorf tubes, and kept at -80°C until analysis. Blood will be analyzed for oxidative stress and inflammation markers. The oxidative stress marker will be analyzed as advanced oxidized protein products (AOPP), which reflects protein oxidation of inflammatory nature and malondialdehyde (MDA), a final product of the lipoperoxidation reaction. The inflammation markers will be analyzed are: interleukin-1 β (IL-1 β), interleukin-10 (IL-10), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), C-reactive protein (CRP) will be performed in plasma samples using available commercial kits, following the manufacturers' instructions (Invitrogen, California USA).

Schedule

In table 4 is described the schedule for execution of each study ISOPRESS network.

Table 4. Schedule of each study of ISOPRESS network.

	ISOPRESS 1				ISOPRESS 2				ISOPRESS 3				ISOPRESS 4				ISOPRESS 5			
	2015	2016	2017	2018	2015	2016	2017	2018	2015	2016	2017	2018	2015	2016	2017	2018	2015	2016	2017	2018
Staff training	X					X				X				X			X			
Recruitment	X	X				X	X			X				X			X	X		
Intervention	X	X				X	X	X			X			X			X	X		
Data analysis		X	X				X	X			X	X		X	X	X		X	X	
Submission of manuscripts		X	X	X			X	X			X	X		X	X	X		X	X	X

Ethical issues

All procedures of the ISOPRESS network were approved by the Institutional Review Board at each institution in which the studies will be developed. All procedures followed the Brazilian National Research Ethics System Guidelines and with the Helsinki Declaration of 1975 (revised in 1983). A written informed consent form was obtained from each patient before participation.

Statistical issues

Analysis

Normality and homogeneity of variance of data will be confirmed by Shapiro-Wilks and Levene tests, respectively. The analysis

of the effects of isometric handgrip training on cardiovascular variables (table 1) will be made in line with the intention-to-treat principle through comparison of the changes in the main outcomes between experimental and control groups. If the data does not meet the parametric premises, a nonparametric equivalent test will be used. An α -level of < 0.05 will be used to establish statistical significance in all analyses.

Power calculation

To determine sample size, previously published data on the mean reduction and standard deviation of systolic blood pressure (our primary endpoint) following isometric handgrip training³⁹ will be used. From this work, we anticipated the smallest meaningful difference and standard deviation in systolic blood pressure

following isometric handgrip training to be 6 ± 4.6 mmHg. Based on an assigned α of 0.05 and β of 0.2, an estimate of the least nine participants per group was deemed sufficient. However, depending on the objective of each study larger sample sizes may be required.

Discussion

Isometric handgrip training has been considered a promising intervention to reduce cardiovascular risk in adults, given the positive effects on cardiovascular variables. Recent meta-analytical study showed a reduction in systolic blood pressure of 5 mmHg in hypertensives¹³. Another advantage of the handgrip exercise is its easy implementation that allows it to be carried anywhere, including at home.

However, the following gaps have not been measured: the mechanisms responsible for the reduction of blood pressure after isometric handgrip training in hypertensives; the effects of unsupervised training in clinical and public system settings; the effects this type of exercise in other populations with hypertension and associated diseases. These gaps will be addressed in the ISOPRESS network, including five studies performed in different research groups.

The main challenges of the ISOPRESS project are: (i) the feasibility of unsupervised handgrip training is unknown, and an attenuation of the effects of training is expected; (ii) the lack of effects in obstructive sleep apnea and peripheral artery disease symptoms may also make the adherence to training difficult; (iii) the methods used for the mechanical approach is invasive and some individuals may refuse to carry out the study

The ISOPRESS network is an innovative way to understanding the potential of handgrip exercise to control cardiovascular risk in CVD patients. The evaluation of neural and vascular mechanisms provide an important to elucidate the range of options that isometric handgrip training can reduce blood pressure. In practical terms, the results will facilitate the understanding of whether this promising mode of exercise that requires only 33 minutes a week of practice is effective in clinical settings. These aspects can be an interesting strategy for application in public health.

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