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Effects of a short-term interval aerobic training program with recovery bouts on vascular function in sedentary aged 70 or over: A randomized controlled trial

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A R T I C L E I N F O

Keywords:
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Physical activity
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A B S T R A C T

Background: Interval aerobic training programs with active recovery bouts (IATP-R) are reported as being more adapted to seniors while improving cardiorespiratory and endurance parameters. Report of benefits on vascular function is still limited.

Purpose: To measure the impact of IATP-R on vascular function among seniors.

Methods: Sedentary volunteers (≥70 years of age) were randomly assigned to either IATP-R (n = 30) or control group (n = 30). The IATP-R consisted of 2 weekly sessions of 30-min (6 × 4-min at first ventilatory threshold (VT_1) intensity + 1-min at 40% of VT_1) cycling exercise over 9.5-week. Controls remained their sedentary life over the same period. In all participants, the endothelial function was measured by flow-mediated dilation (FMD) in brachial artery and arterial stiffness through the carotid/radial and carotid/femoral pulse wave velocity (PWV). Systolic (SBP) and diastolic blood pressure (DBP) were measured at baseline and 9.5 weeks later.

Results: Resulting from a planned interim analysis, IATP-R improved SBP (IATP-R: from 133.7 ± 9.8 to 122.6 ± 9.4 mmHg *vs.* Controls: from 128.9 ± 12.5 to 132.6 ± 14.7 mmHg), DBP (IATP-R: from 80.2 ± 7.0 to 74.1 ± 6.7 mmHg *vs.* Controls: from 77.1 ± 6.8 to 80.3 ± 7.5 mmHg), and FMD (IATP-R: from 6.7 ± 2.0 to 7.5 ± 2.7% *vs.* Controls: from 7.9 ± 2.7 to 7.5 ± 2.5%). No significant impact on PWV was measured.

Conclusion: Although these findings resulted from an interim analysis, IATP-R might be effective in regulating BP and improving endothelial function among sedentary seniors.

1. Introduction

Aging is an unavoidable part of life and, unfortunately, one of the highest risk factor for cardio-cerebrovascular disorders. Among the different major pathways by which aging and risk factors such as diabetes and/or adiposity affect cardiovascular and brain health is vascular dysfunction (*i.e.*, vascular stiffening and endothelial dysfunction) (Lakatta & Levy, 2003). The development of vascular dysfunction is largely attributable to two physiological changes: (i) the stiffening of the large elastic arteries (the aorta and carotid arteries) and (ii) the development of systemic vascular endothelial dysfunction (Franzoni et al., 2005; Lakatta & Levy, 2003). Importantly, endothelial dysfunction (particularly impaired endothelium-dependent vasodilation in both resistance and conduit arteries) has been linked to the pathogenesis of atherosclerosis and acute cardiovascular events (Tousoulis, Charakida, & Stefanadis, 2008). These alterations are primarily related to a worsening of mitochondrial function, and increased inflammatory profile and free radical production combine with a gradual loss of antioxidant

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capacity (Franzoni et al., 2005). Altogether, these mechanisms lead to an impairment of nitric oxide (NO) bioavailability (Taddei et al., 2000) with a reduced endothelium-dependent vasodilation that in turn contributes to diabetes, hypertension, dyslipidemia, and different types of cancer (Dow, Stauffer, Brunjes, Greiner, & DeSouza, 2017). In addition, increased blood pressure favors large artery stiffening, especially when other common vascular risk factors are also present. This in turn aggravates hypertension by increasing the systolic blood pressure (SBP) and contributes myocardial hypertrophy and arterial lesions (Safar, Levy, & Struijker-Boudier, 2003). Epidemiological data strongly suggests that subjects with artery stiffness have wider pulse pressure (PP = SBP-DBP (diastolic blood pressure)), and that stiffening of large arteries is associated with excess morbidity and mortality independently of other cardiovascular risk factors in general and aged population (Benetos et al., 1997; Protogerou et al., 2011).

Two recent systematic reviews and meta-analyses of randomized controlled trials have reported that aerobic training (AT) improved arterial stiffness and vascular function in adults (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014, 2015), and reinforced that among the different types of AT, interval AT program (IATP) was the most effective. Indeed, both short- (*i.e.,* < 12 weeks) and long-term (*i.e.,* ≥12 weeks) IATP were effective for improving cardio-metabolic health outcomes (Batacan, Duncan, Dalbo, Tucker, & Fenning, 2017). Although two trials have reported that regular IATP improved arterial stiffening and vascular function in sedentary seniors with and without chronic comorbid condition(s) (Wisloff et al., 2007; Vogel et al., 2013), this type of exercise training are often difficult to conduct in seniors (Bouaziz et al., 2018; Vogel, Lang, Schmitt, Kaltenbach, & Bouaziz, 2016). Indeed, sustaining such intensity over weeks is frequently associated with muscle pain, early exhaustion, and finally the withdrawal from programs (Biddle & Batterham, 2015). Recently, we reported the better tolerance, safety, and efficacy on maximal cardiorespiratory and endurance parameters of a lightweight IATP including recovery bouts (IATP-R) (Bouaziz et al., 2018). By analyzing the impact of IATP-R on vascular function in sedentary seniors that is a highly prevalent condition in this population, this randomized controlled trial, in a pragmatic way, would contribute to provide public health arguments to promote a type of physical activity that fits seniors' needs and capacities.

2. Materials and methods

2.1. Study design

The study was a prospective and open-label randomized controlled trial conducted in the frame of the consultation of Physical Aptitude Assessment for Health (CAPS in French language) of the University Hospitals of Strasbourg (France). It was originally designed to measure the impact of IATP-R on maximal cardiorespiratory and endurance parameters and the sample size was calculated for these primary outcomes as already published (Bouaziz et al., 2018). Initially scheduled from December 2014 to October 2017, the period of enrollment was finally restricted to one year (*i.e.,* from November 2016 to October 2017) because of logistical issues. Once recruited, sedentary seniors were then randomly assigned into the training (*i.e.,* IATP-R) or the control group using a computer-generated random numbers *via* the CleanWEB™ secure online-randomization platform. This was centralized and independently coordinated by one of the methodologists of the Clinical Investigation Centre of the University Hospitals of Strasbourg. The allocation was balanced by considering blocks of size 10. During the study, members of the CAPS team supervised all volunteers and trained specialists collected the outcome measures blind to the allocation group. All participants carried out an incremental maximal exercise test (IET), and were assessed for endothelial function, arterial stiffness, and SBP and DBP, at baseline and 9.5 weeks later (Fig. 1). All along the 9.5 weeks of the study course, in both groups, the physical activity level was measured on a weekly base according to the International Physical Activity Questionnaire (IPAQ) score (Hagströmer, Oja, & Sjöström, 2006). A sedentary lifestyle was defined with a score < 2. This experimental protocol included adherence to the declaration of Helsinki and was approved by the local ethic committee (IDRCB 2014-A00872-045/PRI 2013-HUS N°5830).

2.2. Population study and inclusion/non-inclusion criteria

Following a call of research subjects, seniors were invited to participate without financial incentives. A study announcement was broadcasted on local radio and newspapers in addition to flyers made available in local community centres, primary care physicians and physiotherapists' offices, and distributed by local senior meal delivery services. As detailed by Fig. 2, to be eligible, volunteers had to be aged 70 years or over, functionally independent but with a sedentary lifestyle (*i.e.,* IPAQ score < 2). All volunteers, thus selected, completed a medical visit including a physical examination with the measurement of anthropometric parameters, resting heart rate (HR), and blood pressure (BP), and an electrocardiogram (ECG). Body height was electronically measured (Soehnle®) and body composition (*i.e.*, total body weight, percentage of body fat, and fat-free mass) determined with bioelectrical impedance (Tanita®, TBF-300). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The waist circumference was measured in the horizontal plane midway between lowest rib and the iliac crest by using a flexible inch tape (Ma et al., 2013). The Charlson comorbidity index, which consists in a number scoring system based on 19-weighted comorbid medical conditions, was considered to evaluate the volunteers' level of comorbidities (*i.e.*, low level: 0 ≤ score ≤ 1, medium level: 2 ≤ score ≤ 4, and high level: score ≥ 5) (Quan et al., 2011) (Table 1). The Study of Osteoporotic Fractures (SOF) frailty index was considered to evaluate the frailty status of the volunteers (Ensrud et al., 2007). Frailty classified as the presence of ≥2 components out of list of three: weight loss (intentional/unintentional, > 5% in the last year), exhaustion (an answer of 'no' to the question 'do you feel full of energy?') and low mobility (inability to perform a chair rise five times) (Table 1). With the complete review of the current and past medical history, all conditions that contra-indicated IATP-R were identified (*e.g.*, uncontrolled hypertension, severe musculoskeletal/musculotendinous disorders or fibromyalgia). In addition, individuals with significant cognitive impairment, undergoing chemotherapy for cancer, or suffering from any acute infection were not enrolled. The medication list was also reviewed and participants taking beta-blockers or other anti-hypertensive and negative chronotropic drugs were also not included. During the medical interview, volunteers received instructions about the IATP-R and an informed consent was signed for final inclusion. At the time of inclusion volunteers were also asked to maintain their usual diet all along the duration of the study. Participants could be secondarily excluded in case of the occurrence of chest pain, high BP, rhythm disorder, ST segment deviation, and/or respiratory problems during the IET carried out at baseline (Table 2).

2.3. Vascular function assessment

Under standardized conditions and at the same time of day, in all participants, a trained member of the CAPS team blind to the group allocation supervised the vascular function assessment. Thus, pulse wave velocity (PWV), SBP and DBP, and brachial artery flow-mediated dilation (FMD) were measured before the two IET (*i.e.*, at baseline and 9.5 weeks later) in a quiet and controlled temperature room at 21 °C. All measures were performed after a 6-hour fast, 8-hour abstinence from caffeine, alcohol drugs, stimulants, and vasoactive medications, and at least 24 h after strenuous physical activity.

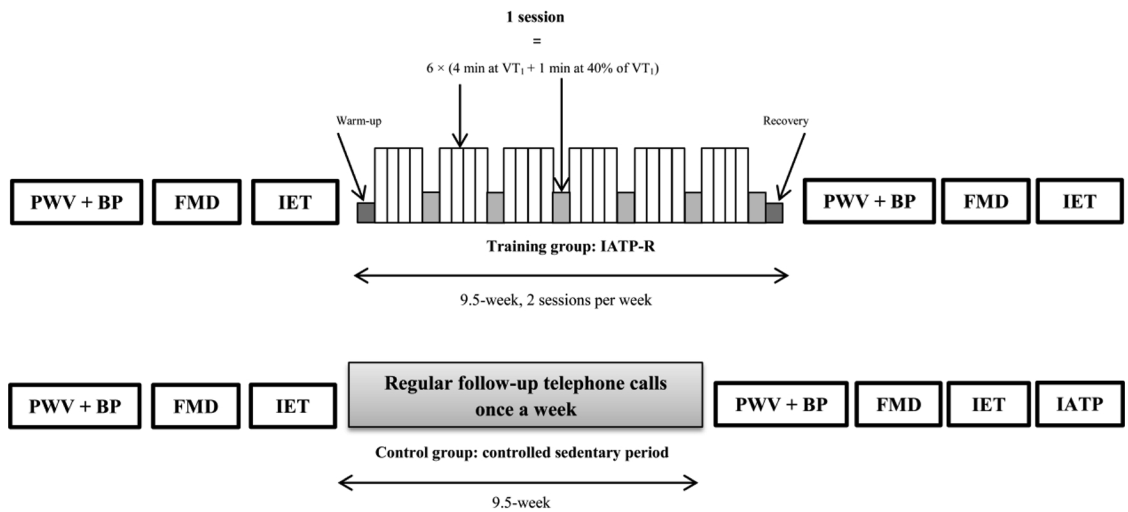

Fig. 1. Protocol design of the study.
Note: PWV: Pulse wave velocity; BP: Blood pressure; FMD: Flow-mediated dilation; IET: Incremental maximal exercise test; IATP-R: Interval aerobic training program with recovery bouts; IATP: Interval aerobic training program

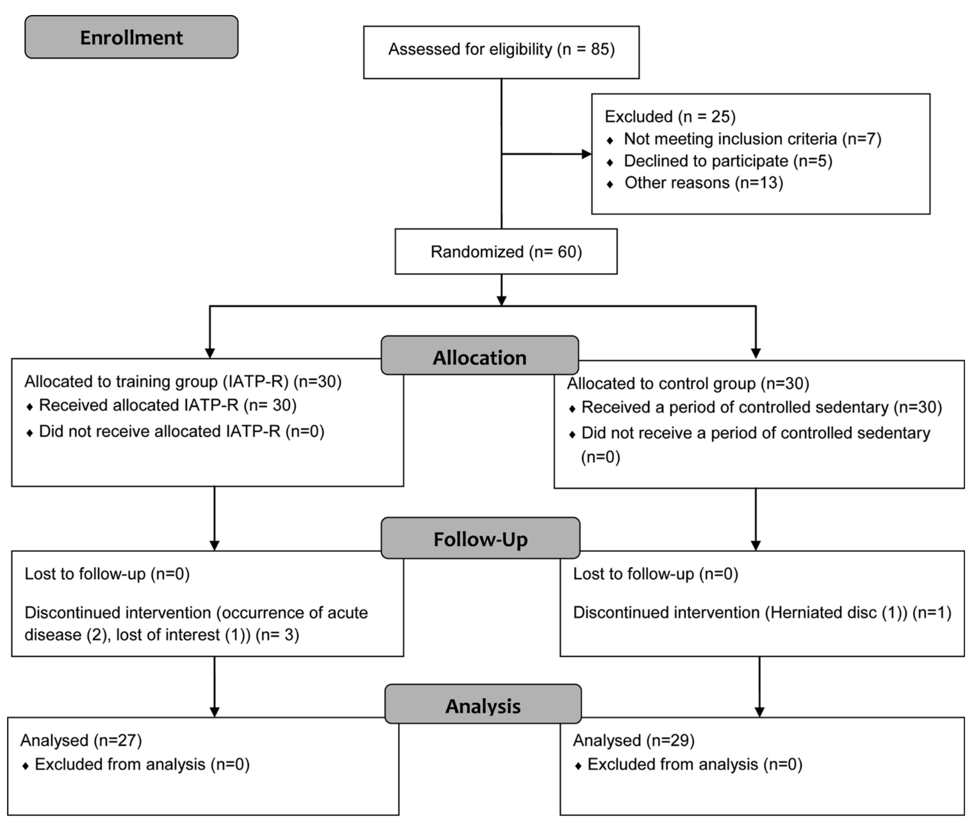

Fig. 2. Flow chart of the study.
Note: IATP-R: Interval aerobic training program with recovery bouts

2.3.1. *Pulse wave velocity (PWV) measurement*

PulsePen® device (DiaTecne s.r.l., Milan, Italy) was used to measure the carotid/radial PWV reflecting the upper limb arterial stiffness, and the carotid/femoral PWV for the aortic stiffness in accordance with the procedure previously described (Salvi et al., 2004). PulsePen® is a validated, easy-to-use, and high-fidelity tonometer. It consists of an applanation tonometer combined with an ECG unit. All measurements were preceded by 15-min of rest in supine position, with as much as possible control of the environmental noise and temperature. During the procedure, participants were continuously monitored with an ECG.

Carotid/femoral and carotid/radial PWV were measured by recording carotid and femoral, and carotid and radial waveforms respectively in rapid succession. PWV was defined as the distance between the measuring sites divided by the difference between the delayed rise of the distal pulse wave from the R-wave belonging to the immediately preceding ECG qRs complex, and the delayed rise of the proximal pulse wave from the R-wave belonging to the immediately preceding ECG qRs complex. The pulse wave delay was measured by calculating the time elapsed from the peak of the R-wave and the ‘foot’ of the immediately following pressure pulse contour. For the carotid/femoral measurement, the distance of the pulse wave transit represented the difference between the distance from the supra-sternal

Table 1
Baseline characteristics of the 60 study subjects.

Subjects' characteristics	Control group (N = 30)	IATP-R group (N = 30)
Demographic data		
Age (years ± SD)	74.3 ± 3.4	72.9 ± 2.5
Female, n (%)	23 (76.6)	21 (70.0)
Anthropometric parameters		
Total body mass (kg ± SD)	77.8 ± 13.9	77.4 ± 15.4
Body fat (kg ± SD)	37.6 ± 8.3	35.1 ± 8.4
Waist circumference (cm ± SD)	99.6 ± 17.3	98.1 ± 16.4
Free-fat mass (kg ± SD)	46.0 ± 6.7	47.0 ± 9.2
Body mass index (kg/m^2 ± SD)	28.8 ± 5.1	28.7 ± 5.6
Normal (18.5 - 24.9), n (%)	6 (20.0)	7 (23.3)
Overweight (25.0 - 29.9), n (%)	12 (40.0)	10 (33.3)
Obesity (30.0 - 40.0), n (%)	12 (40.0)	13 (43.3)
Comorbidities		
Charlson Comorbidity Index (mean ± SD)*	3.8 ± 1.3	4.0 ± 1.7
Hypertension, n (%)	11 (36.7)	12 (40.0)
Type 2 diabetes, n (%)	3 (10.0)	6 (20.0)
Dyslipidemia, n (%)	9 (30.0)	9 (30.0)
Osteoporosis, n (%)	4 (13.3)	6 (20.0)
Osteoarthritis, n (%)	4 (13.3)	3 (10.0)
Depression, n (%)	2 (6.6)	4 (13.3)
Smoking, n (%)	1 (3.3)	1 (3.3)
Frailty		
Non-frail (SOF Index score = 0), *n (%)*	23 (76.6)	25 (83.3)
Pre-frail (SOF Index score = 1), *n (%)*	7 (23.3)	5 (16.6)
Medications		
Perindopril, n (%)	2 (6.6)	2 (6.6)
Enalapril, n (%)	1 (3.3)	0 (0.0)
Candesartan, n (%)	1 (3.3)	1 (3.3)
Olmesartan, n (%)	1 (3.3)	2 (6.6)
Telmisartan, n (%)	1 (3.3)	1 (3.3)
Irbesartan, n (%)	1 (3.3)	0 (0.0)
Valsartan, n (%)	2 (6.6)	3 (10.0)
Hydrochlorothiazide, n (%)	1 (3.3)	1 (3.3)
Lercapidine, n (%)	1 (3.3)	1 (3.3)
Triamterene, n (%)	0 (0.0)	1 (3.3)
Glibenclamide, n (%)	1 (3.3)	1 (3.3)
Sitagliptine, n (%)	1 (3.3)	1 (3.3)
Gliclazide, n (%)	0 (0.0)	2 (6.6)
Metformine, n (%)	1 (3.3)	2 (6.6)
Statins, n (%)	9 (30.0)	9 (30.0)
Cardiorespiratory parameters at baseline		
Measured FVC / theoretical FVC	95.24	96.52
Measured FEV_1 / theoretical FEV_1	97.28	98.00
Measured MTP / theoretical MTP	93.24	96.52
Measured VO_{2peak} / theoretical VO_{2peak}	98.93	97.11
Measured HR_{max}/ theoretical HR_{max}	88.5	94.4

Note: SD: standard deviation; IATP-R: Interval Aerobic Training Program with Recovery bouts; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; IET: incremental exercise test; MTP: maximal tolerated power; VO_{2peak}: peak of oxygen uptake; HR_{max}: maximal heart rate; SOF: study of osteoporotic fractures; *: the Charlson index was considered to define three levels of burden of co-morbidity: low (0–1), medium (2–4), and high (5 or over).

notch and the femoral point of application of the tonometer, and the distance from the carotid point of tonometer application and the supra-sternal notch. For the carotid/radial measurement, distance of the pulse wave transit represented the difference between the distance from the supra-sternal notch and the radial point of application of the tonometer, and the distance from the carotid point of tonometer application and the supra-sternal notch. The device did not validate measurements if BP or HR differences between the carotid and femoral artery or between the carotid and radial artery recordings were > 10%. In each patient, two successive measures of carotid/radial and carotid/femoral PWV values were averaged and used for subsequent analyses. The arterial stiffness measurement was repeated a third time if the difference in the 2 measurements was > 0.5 m/s using the median value. A PWV value higher than 10 m/s was considered as the cutoff point for arterial stiffness (Mancia et al., 2013). Globally, the examination was completed within 10 min.

2.3.2. Blood pressure measurement

SBP and DBP were measured at brachial artery level with an automatic oscillometric sphygmomanometer (Dinamap; GE Pro 300V2) after 20-min of rest in supine position. The values were then introduced in the PulsePen® software and were used for the calibration of pressure wave. The pulse pressure (PP) was defined as the difference between SBP and DBP, and mean BP (MBP) as DBP + (1/3) × PP. According to current cutoff values (Flack, Calhoun, & Schiffrin, 2018), stage I hypertension was defined as 130–139 mmHg for SBP and/or 80–89 for DBP and stage II hypertension as ≥140 for SBP and/or > 90 mmHg for DBP.

2.3.3. Measurement of the brachial artery flow-mediated dilation (FMD)

Endothelial function was estimated through the FMD of the brachial artery using a validated procedure (Gokce et al., 2003). This was applied in all participants after 15-min of rest in supine position with the right arm extended and immobilized with foam, supported at an angle of ~80° from the torso to allow access to the brachial artery for image acquisition.

HR and mean BP were determined from an automated sphygmomanometer (Dinamap; GE Pro 300V2) on the contralateral arm. During the procedure, participants were also continuously monitored with an ECG. The brachial artery diameter and flow velocity were imaged using a 7.5-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (5000 Phillips-HDI-system) placed 1–2 cm above the antecubital fossa. Pictures were then carefully obtained in longitudinal B-mode images to maximize the vessel diameter and provide the optimal blood-vessel wall definition. Continuous pulsed wave Doppler velocities were obtained using the ultrasound machine, and data were collected using the lowest possible insonation angle (always < 60°), which did not vary during each study.

After a baseline scans recorded over 1 min assessing resting vessel diameter and flow, a sphygmomanometer cuff placed around the forearm at 10 cm distal to the brachial artery segment for the echo imaging was inflated to > 200 mmHg for 5 min. Diameter and flow recordings resumed 30 s before cuff deflation and continued for 3 min thereafter, leading to reactive hyperemia with increasing brachial artery blood flow and resulting in the FMD. Thus, peak artery diameter and flow, and the time taken to reach these peaks after the release of the occlusion, were recorded. The FMD was expressed as the maximal percentage change in vessel diameter after reactive hyperemia relative to the baseline scan. A reduced percentage of FMD (< 8.1%) was considered as a predictive factor for major vascular complications (Gokce et al., 2003).

2.4. The incremental exercise test (IET)

In both study groups and blind to the participants' group allocation, a cardiologist conducted an incremental maximal exercise tests (IET) at baseline and 9.5 weeks later (Fig. 1). The IET were performed on an upright electronically braked cycle ergometer (Ergoselect 2, MSE®) in the air-conditioned room (22.0 ± 0.5 °C), two hours after a light breakfast. Minute ventilation, O_2 uptake and CO_2 output were measured on a breath-by-breath basis by means of an open-circuit metabolic chart with rapid O_2 and CO_2 analyzers (MEDGRAPHICS, MSE®). The pneumotachograph was calibrated with a 3-l calibration syringe, and the gas analyzers with reference gases. The breath-by-breath data were averaged over 20-second periods. HR was monitored continuously during the test with an ECG (T12, Mortara®). Each participant performed a maximal effort according to the criteria of the American

Table 2
Metabolic outcomes in control and training groups before and after the study.

Parameters	Control group (N = 29) Before	After	%Change	IATP-R group (N = 27) Before	After	%Change
LDL-C (mmol/l ± SD)	3.48 ± 1.01	3.37 ± 0.84	−3.2%	3.29 ± 0.90	3.27 ± 0.85	−0.6%
HDL-C (mmol/l ± SD)	1.66 ± 0.44	1.64 ± 0.48	−1.2%	1.59 ± 0.39	1.73 ± 0.40*	8.8%#
Total cholesterol (mmol/l ± SD)	5.71 ± 0.99	5.67 ± 1.03	−0.7%	5.46 ± 1.03	5.59 ± 0.97	2.3%
Fasting blood glucose (mmol/l ± SD)	5.74 ± 0.74	5.79 ± 0.90	0.9%	6.11 ± 1.37	5.86 ± 1.13*	−4.1%#
Total body mass (kg ± SD)	77.7 ± 13.8	77.8 ± 14.0	0.1%	77.2 ± 15.2	76.7 ± 14.7	−0.6%
Body fat (kg ± SD)	37.6 ± 8.3	37.9 ± 8.6	0.8%	35.1 ± 8.4	35.3 ± 7.1	0.6%
Free-fat mass (kg ± SD)	46.0 ± 6.7	45.8 ± 7.1	−0.4%	47.0 ± 9.2	46.8 ± 8.4	−0.4%
BMI (kg/m^2 ± SD)	28.8 ± 5.0	28.8 ± 4.8	0%	28.7 ± 5.3	28.7 ± 5.2	0%
Waist circumference (cm ± SD)	98.8 ± 15.7	98.7 ± 15.5	−0.1%	99.5 ± 14.3	99.3 ± 14.1	−0.2%

Note: SD: standard deviation; IATP-R: Interval Aerobic Training Program with Recovery bouts; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; *: significantly different from inclusion; #: significantly different from the control group.

Thoracic Society and the American College of Chest Physicians (American Thoracic Society & American College of Chest Physicians, 2003) to determine maximal tolerated power (MTP) (Watts – W), peak of oxygen uptake ($\dot{V}O_{2peak}$) (L. min^{-1}), maximal ventilation ($\dot{V}_E$) (L. min^{-1}) and maximal HR (HR_{max}) (bpm). The first ventilatory threshold (VT_1) (W) was determined graphically using the $\dot{V}O_2$ (L. min^{-1}), $\dot{V}CO_2$ (L. min^{-1}) and $\dot{V}_E$ (L. min^{-1}) curves. It was confirmed by the method of Beaver, Wasserman, and Whipp, (1986) based on computerized regression analysis of the $\dot{V}CO_2$ *versus* $\dot{V}O_2$ slopes. After a 3-min warm-up at 20 W, charge increments of 10 W.min^{-1} were monitored up to exhaustion (10–15 min). Additional spirometric parameters were obtained *via* a body plethysmograph, and included maximal minute ventilation (L.min^{-1}), forced vital capacity (FVC – L), forced expiratory volume in one second (FEV_1 – L) and the FEV_1/FVC ratio.

2.5. The interval aerobic training program with recovery bouts (IATP-R)

The IATP-R was performed on an upright electronically braked cycle ergometer (Ergoselect 2, MSE®) in an air-conditioned room (22.0 ± 0.5 °C). It consisted of a 30-min cycling workout twice a week over 9.5-week (*i.e.*, 19 sessions in total). As depicted by Fig. 1, each session involved six 5-min bouts of exercise combining 4-min cycling at the measured pre-intervention VT_1 workload (called "BASE") and 1-min cycling at 40% of the pre-intervention VT_1 workload (called "RECOVERY"). Every session started with a 3-min warm-up and finished with a 3-min recovery. During exercise, HR was continuously recorded (Suunto T6c, Vantaa, Finland). The mean HR value was calculated every 3-min of each series of 4-min and taken as the "target value" for the entire training program. When the exercise tolerance improved with training, for each HR decrease of 10 beats/min a 10% increase in the "BASE" was done, while the "RECOVERY" bouts values remained constant (Bouaziz et al., 2018).

2.6. Control group

Participants assigned to the control group were requested to keep a sedentary lifestyle and current food habits. This was controlled on a weekly base by telephone call during which participants were also detailed their level of activities according to the IPAQ questionnaire. They had also to confirm that they were not engaged in any exercise or training programs. At the end of the study protocol, controls were offered to engage a supervised training program (Bouaziz et al., 2018).

2.7. Statistical analysis

Statistical analyses were performed under Bayesian paradigm and computed with R (version 3.2.2) and WinBUGS (version 1.4.3) software. The study powerful was initially calculated for primary outcomes (cardiorespiratory fitness and endurance parameters – MTP, VO_{2peak} and HR_{max}, VT_1 and HR at baseline VT_1) (Bouaziz et al., 2018) and was estimated to be 81%, with a type I error rate of 5%. The expected sample size was 65 participants per study group. In the experimental protocol it was planned an interim analysis at the time when 60 volunteers were recruited with possibility of study discontinuation according to the direction and amplitude of the results.

For the descriptive analyses, results were expressed for numerical data as means ± standard deviations; for categorical variables as number and percentage. Normality of the distributions was tested using the Shapiro-Wilk test, and assessed graphically (Q-Q plot). The analyses were computed for the secondary outcomes (SBP, DBP, MBP, PP, carotid/femoral PWV, carotid/radial PWV, and FMD) with a hierarchical model with fixed and random effect. The model used was:

$$Y_{ijk} = \beta_0 + \beta_1 \times treatment_i + \beta_2 \times time_j + \beta_3 \times (treatment_i \times time_j) + \beta_4 \times subject_k + \varepsilon_{ijk}.$$

The effect of the intervention was estimated by the interaction term β_3. For the computation, low informative prior probabilities (*i.e.*, a β mean equal to 0 and its variance equal to 1000) then more informative prior probabilities were considered for a sensibility analysis. For the posterior probability distributions, 95% credibility intervals were calculated and posterior probabilities of a difference given the data, written down P or probability, were given. This probability should not be confused with the usual *p-value* (*i.e.*, the probability, under the null hypothesis of obtaining a result equal to or more extreme than what was actually observed which commonly set at $p = 0.05$). For significance, a probability $P > 0.975$ or < 0.025 was considered in Bayesian paradigm where there is also no inflation of the alpha type I error with interim analyses.

3. Results

The presented data resulted from the interim analysis planned in the study protocol when 30 volunteers were enrolled in each group (mean age 73.8 ± 3.2 years). Characteristics at baseline are presented in Table 1. No significant difference was measured between the two groups in terms of anthropometric parameters, comorbid conditions, and cardiorespiratory parameters. Among them, 56/60 successfully completed the study protocol and were considered for subsequent per-protocol analyses (Fig. 2).

3.1. Adherence rate and adverse events

As presented in Fig. 2, withdrawals in both groups were related neither to the training program nor to the sedentary period. Among controls, 29/30 volunteers have completed the sedentary period, and 1 participant has left because of herniated disc. With respect to the IATP-R, 27/30 volunteers have completed 19/19 training sessions; 2, 10/19 and 5/19 sessions respectively. One participant 1 has left the training program just after the consent form was signed. With an adherence rate

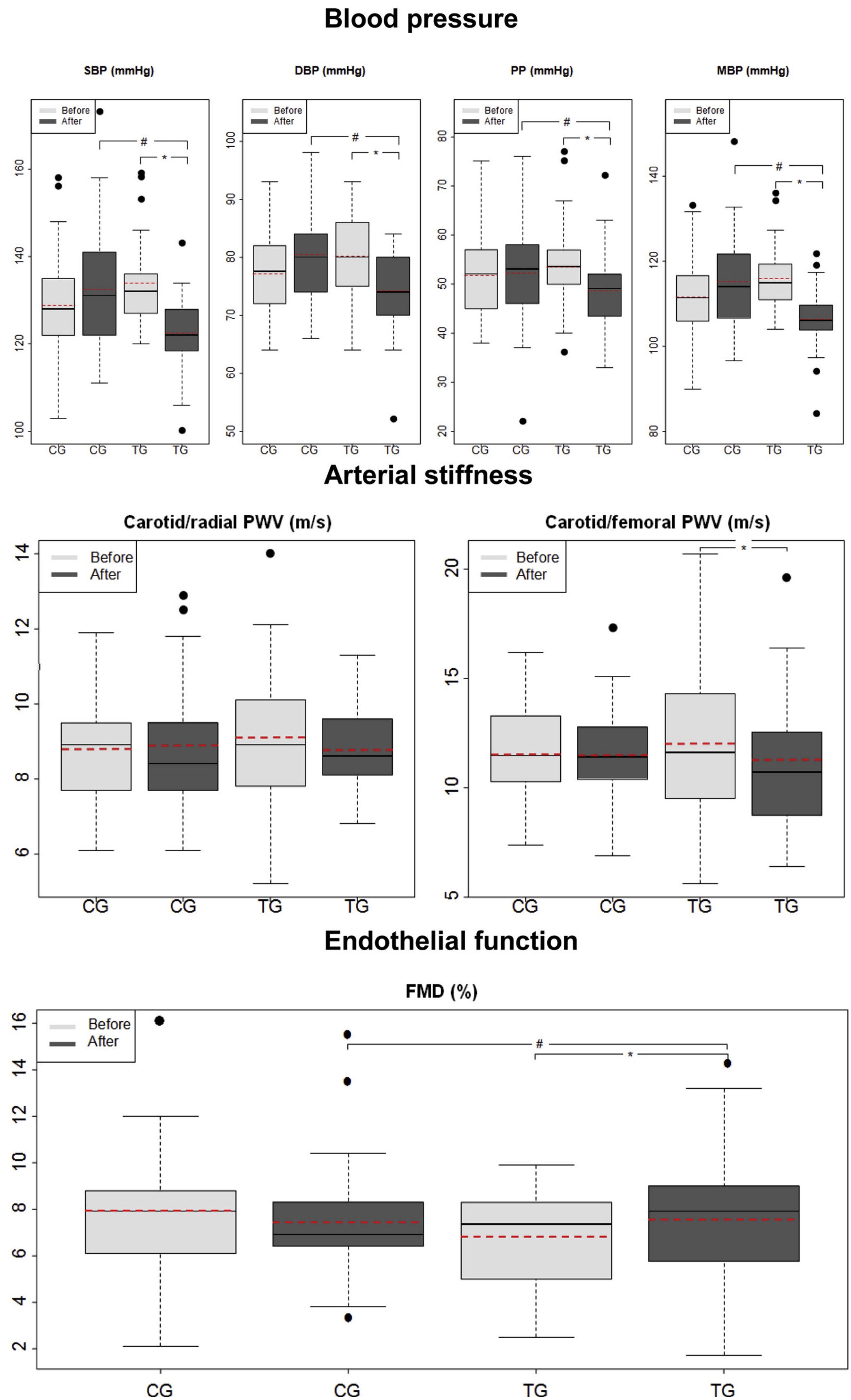

Fig. 3. Box plot of blood pressure, arterial stiffness and endothelial function in control and training groups before and after the study.
Note: CG: Control group; TG: Training group; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: Pulse pressure: MBP: Mean blood pressure: PWV: Pulse wave velocity; FMD: Flow-mediated dilation; *: significantly different from inclusion #: significantly different from the control group.

of 94.7% (defined as mean percentage of the exercise prescription) and during the 555 sessions, no adverse events or health problems directly attributable to the IATP-R was reported.

3.2. Effects of the IATP-R

The effects of the IATP-R on BP, PWV and FMD are presented in Fig. 3. After 9.5-week, SBP (IATP-R group: from 133.7 ± 9.8 to 122.6 ± 9.4 mmHg *vs.* control group: from 128.9 ± 12.5 to 132.6 ± 14.7 mmHg) and DBP (IATP-R group: from 80.2 ± 7.0 to 74.1 ± 6.7 mmHg *vs.* control group: from 77.1 ± 6.8 to 80.3 ± 7.5 mmHg) were lowered in the IATP-R group compared to controls. The PP also decreased significantly after the IATP-R (IATP-R group: from 53.6 ± 8.9 mmHg to 48.5 ± 8.3 mmHg *vs.* control group: from 51.8 ± 9.4 mmHg to 52.3 ± 11.7 mmHg). A similar effect was finally also reported with the MBP. A non-significant improvement was observed between the two groups for the carotid/femoral PWV (IATP-R group: from 12.01 ± 3.5 to 11.26 ± 3.3 m/s; control group: from 11.50 ± 2.2 to 11.45 ± 2.2 m/s). A significant increase in the FMD was measured with the training program (IATP-R group: from 6.7 ± 2.0 to 7.5 ± 2.7% *vs.* control group: from 7.9 ± 2.7 to 7.5 ± 2.5%).

4. Discussion

The interim analysis of this randomized controlled study reports the benefits of IATP-R on vascular function in sedentary seniors. After 19 sessions of training over 9.5 weeks, the IATP-R was associated with significant reduction of BP values and increase in FMD. These findings should be considered of particular interest regarding the increasing risk of cardiovascular morbidity and mortality with advancing age, which is in part due to vascular dysfunction. Benefits of AT on BP are supported by robust evidence in the general population (Hanssen et al., 2017; Whelton, Chin, Xin, & He, 2002) which are less consistent among seniors. The latter results, for the most, resulted from long-term training programs (*i.e.,* ≥12 weeks) (Bouaziz et al., 2017). Although numerous epidemiological studies suggest that IATP may prevent cardiovascular (CV) diseases, considerable evidence now indicates that cardiovascular events, including acute myocardial infarction, sudden death, stroke, and aortic dissection can be also triggered by vigorous physical activity. Indeed, older individuals who are sedentary and unaccustomed to sudden bursts of vigorous activity are at increased risk of acute CV events during vigorous exercise. Accordingly, exercise progression of lower intensity may be initially required in less well controlled environments and may still place considerable stress on the cardiovascular systems of unfit individuals (Franklin, 2014; Thompson, 2007). Thus, despite a reduced volume of total physical activity compared to programs without recovery bouts and after only 9.5-week, IATP-R improved BP values of a similar extend to which reported previously with IATP (Braith, Pollock, Lowenthal, Graves, & Limacher, 1994; Huang, Thompson, & Osness, 2006; Vogel et al., 2013). Thus, in normotensive seniors, Braith et al. (1994) reported after 24 weeks of IATP a significant decrease in SBP (-9 mmHg) and DBP (-8 mmHg). Vogel et al. (2013) showed, after 9 weeks of IATP, a significant lowering in SBP (-7.3 mmHg) and DBP (-7.5 mmHg); and Huang et al. (2006), after 10-week of IATP, a significant reduction in resting SBP (-7.8 mmHg) and DBP (-9.6 mmHg).

In addition, IATP-R has resulted in a significant improvement in the endothelial function. This is in the line with the study of Johnson, Padilla, and Wallace, (2012) in which FMD was improved in trained men following energy expenditure equivalent to 30-min at 50% of VO_{2peak} only and this regardless of intensity or duration. In sedentary seniors, similar improvements were also reported (DeSouza et al., 2000; Pierce, Eskurza, Walker, Fay, & Seals, 2011). Such interventions improving FMD may have important clinical implications for the prevention of age-associated CV diseases. Importantly, 9.5 weeks of IATP-R improved brachial artery FMD to 7.5%, which is close to the average normal values (*i.e.,* 8.1%). Thus our aerobic exercise intervention essentially restored brachial artery FMD in previously sedentary older adults to almost normal values. We hypothesis that this improvements were independent of changes among other factors, suggesting a direct physiological impact of the training program, as already reported (DeSouza et al., 2000; Green, 2009; Moreau, Donato, Seals, DeSouza, & Tanaka, 2003). Along with the impact of AT on increasing forearm blood flow responses to acetylcholine (DeSouza et al., 2000), the present results provide evidence that IATP-R improves endothelium-dependent dilation in both conduit arteries and resistance vessels of originally sedentary seniors.

This study has also investigated the impact on arterial stiffness. While prior works in healthy younger counterparts reported a reduction of the arterial stiffness (Hanssen et al., 2017; Hayashi, Sugawara, Komine, Maeda, & Yokoi, 2005), we found no significant change. This result is however in the line with those reported by Vogel et al. (2013) and Aizawa and Petrella (2008) respectively after 9 and 20 weeks of AT in sedentary pre-hypertensive. This result could be also explained by the low exercise frequency of the IATP-R and the short interval between the pre- and post-training measurement of PWV which is probably too short to counterbalance the profound remodeling associated with the vascular aging process (Ashor et al., 2014; Hays et al., 2018).

Different reasons have contributed to the benefits of the IATP-R on vascular function among seniors. First, with its tailored and personalized design according to the VT_1 obtained during the pre-training IET, the physical intensity of the IATP-R probably fitted the real capacities of the seniors. Furthermore, the workload of the “BASE” was regularly adapted session after session according to the impact of the IATP-R on HR. Workload and intensity were thus adjusted all along the program to the progress of the participant. Second, the interval rather than continuous design, as reported in the literature, explains the health benefits (Ciolac, 2012; Hanssen et al., 2017; Wisloff et al., 2007). This was illustrated by the great adherence rate (94.7%) that was much higher than those usually reported with usual AT (Bouaziz et al., 2018, 2019) and the good tolerance among this population of seniors previously sedentary (IPAQ score < 2). Finally, IATP-R was also in the line of the physical activity recommendations edited by the European society of cardiology concerning healthy sedentary seniors (Piepoli et al., 2016).

This study has however some limitations. First, the generalization of the findings is limited by the voluntary character of the participants. Second, volunteers were also selected as sedentary on the base of the self-reported IPAQ. Although widely considered in epidemiological studies for physical activity surveillance, and slight divergence in the translation, difference in the compliance rates with established study protocols, and/or using of diverse method for data analysis, concordance between studies in the measurement of health-related physical activity in populations with the IPAQ seems to be high (Bauman et al., 2009). However, this declarative sedentary life style could be secondarily and *a posteriori* confirmed with the comparison of the endurance and cardio-respiratory parameters collected during the two IET (*i.e.* at baseline and 9.5 weeks later). After 9.5 weeks, no significant change was measured, which confirmed that controls remained effectively sedentary and even the bias thus created would have just reduced the measured benefit of the IATP-R reported in the present study. Finally, participants under vasoactive medications were included. While this may have underestimated the benefits of IATP-R, some reports have confirmed that vascular functions were also improved after exercise training even in populations under cardiovascular medications (Hambrecht et al., 2003).

5. Conclusion

Although conducted over a relatively short period, the study shows that IATP-R might be effective in regulating BP and improving endothelial function. The intrinsic characteristics of the IATP-R have certainly contributed to these benefits but have to be confirmed in larger populations.

Author contributions

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WB, ES, BG, GK and TV involved in the conception and design of the study. All authors involved in acquisition, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. WB, PML and POL were drafted the manuscript. WB, FL, PML and POL were statistically analyzed the study. TV involved in funding. WB, ES, CM and TV supervised the study. All authors approved the final and submitted version.

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Conflict of interest

None.

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