

# AGE

## Effects of non-pharmacological interventions on cardiovascular risk factors in hypertensive elderly patients

--Manuscript Draft--

<b>Manuscript Number:</b>	
<b>Full Title:</b>	Effects of non-pharmacological interventions on cardiovascular risk factors in hypertensive elderly patients
<b>Article Type:</b>	Research Article
<b>Keywords:</b>	aging; blood pressure; cardiovascular disease; circuit training; endurance training; relaxing training.
<b>Corresponding Author:</b>	Fabio Esposito Milan, ITALY
<b>Corresponding Author Secondary Information:</b>	
<b>Corresponding Author's Institution:</b>	
<b>Corresponding Author's Secondary Institution:</b>	
<b>First Author:</b>	Massimo Venturelli
<b>First Author Secondary Information:</b>	
<b>Order of Authors:</b>	Massimo Venturelli Emiliano Cè Eloisa Limonta Federico Schena Barbara Caimi Stefano Carugo Arsenio Veicsteinas Fabio Esposito
<b>Order of Authors Secondary Information:</b>	
<b>Funding Information:</b>	
<b>Abstract:</b>	<p>Recommendations for prevention of cardiovascular diseases (CVDs) risk factors among older adults highlighted the importance of non-pharmacological interventions, including endurance training (ET). However, the evidence of efficacy of other interventions based on short-bouts of exercise (circuit training, CT), and the practice of breath-control and meditation (relaxing training, RT) is growing. The aim of this study was to elucidate if CT or RT are equally effective in CVD risk factors reduction compared to ET. To this purpose, in forty elderly participants, with clinically diagnosed grade 1 hypertension, resting blood pressure, blood glucose and cholesterol levels, maximum oxygen uptake ( ), mechanical efficiency, quality of life were evaluated before and after 12 weeks of ET, CT, and RT treatments. Resting blood pressure reduced significantly in all groups by ~11%. In ET, blood cholesterol levels (-18%), (+8%), mechanical efficiency (+9%), and quality of life scores (+36%) ameliorated. In CT blood glucose levels (-11%), (+7%), and quality of life scores (+35%) were bettered. Conversely, in RT the lower blood pressure went along only with an improvement in the mental component of quality of life (+42%). ET and CT were both appropriate interventions to reduce CVDs risk factors, because blood pressure reduction was accompanied by decreases in blood glucose and cholesterol levels, increases in , mechanical efficiency, and quality of life. Although RT is not an appropriate stimulus to reduce some CVD risk factors, the reduction in blood pressure</p>

suggests the utilization of this approach in patients with mobility limitation.

**ABSTRACT**

Recommendations for prevention of cardiovascular diseases (CVDs) risk factors among older adults highlighted the importance of non-pharmacological interventions, including endurance training (ET). However, the evidence of efficacy of other interventions based on short-bouts of exercise (circuit training, CT), and the practice of breath-control and meditation (relaxing training, RT) is growing. The aim of this study was to elucidate if CT or RT are equally effective in CVD risk factors reduction compared to ET. To this purpose, in forty elderly participants, with clinically diagnosed grade 1 hypertension, resting blood pressure, blood glucose and cholesterol levels, maximum oxygen uptake ( $\dot{V}O_2 \text{ max}$ ), mechanical efficiency, quality of life were evaluated before and after 12 weeks of ET, CT, and RT treatments. Resting blood pressure reduced significantly in all groups by ~11%. In ET, blood cholesterol levels (-18%),  $\dot{V}O_2 \text{ max}$  (+8%), mechanical efficiency (+9%), and quality of life scores (+36%) ameliorated. In CT blood glucose levels (-11%),  $\dot{V}O_2 \text{ max}$  (+7%), and quality of life scores (+35%) were bettered. Conversely, in RT the lower blood pressure went along only with an improvement in the mental component of quality of life (+42%). ET and CT were both appropriate interventions to reduce CVDs risk factors, because blood pressure reduction was accompanied by decreases in blood glucose and cholesterol levels, increases in  $\dot{V}O_2 \text{ max}$ , mechanical efficiency, and quality of life. Although RT is not an appropriate stimulus to reduce some CVD risk factors, the reduction in blood pressure suggests the utilization of this approach in patients with mobility limitation.

**Effects of non-pharmacological interventions on cardiovascular risk factors in hypertensive elderly patients.**

Venturelli Massimo<sup>1</sup>, Cè Emiliano<sup>1</sup>, Limonta Eloisa<sup>1</sup>, Schena Federico<sup>2</sup>, Caimi Barbara<sup>3</sup>, Carugo Stefano<sup>3,4</sup>,  
Veicsteinas Arsenio<sup>1,5</sup>, Esposito Fabio<sup>1</sup>.

<sup>1</sup> Department of Biomedical Sciences for Health, University of Milan, Italy.

<sup>2</sup> Department of Neurological and Movement Sciences, University of Verona, Italy.

<sup>3</sup> ASP Pio Albergo Trivulzio, Division of Cardiology, University of Milan, Italy.

<sup>4</sup> Department of Clinical Sciences and Community Health, University of Milan, Italy.

<sup>5</sup> Center of Sport Medicine, Don Gnocchi Foundation, Milan, Italy.

**Running title:** Non-pharmacological treatment in hypertension

**Funding:** None

Corresponding author:

Fabio Esposito, M.D.

Department of Biomedical Sciences for Health, University of Milan, Via Colombo 71, 20133 Milano, Italy.

Email: [fabio.esposito@unimi.it](mailto:fabio.esposito@unimi.it)

1  
2 **ABSTRACT**

3  
4 Recommendations for prevention of cardiovascular diseases (CVDs) risk factors among older adults highlighted  
5 the importance of non-pharmacological interventions, including endurance training (ET). However, the evidence  
6 of efficacy of other interventions based on short-bouts of exercise (circuit training, CT), and the practice of  
7 breath-control and meditation (relaxing training, RT) is growing. The aim of this study was to elucidate if CT or  
8 RT are equally effective in CVD risk factors reduction compared to ET. To this purpose, in forty elderly  
9 participants, with clinically diagnosed grade 1 hypertension, resting blood pressure, blood glucose and  
10 cholesterol levels, maximum oxygen uptake ( $\dot{V}O_2 \text{ max}$ ), mechanical efficiency, quality of life were evaluated  
11 before and after 12 weeks of ET, CT, and RT treatments. Resting blood pressure reduced significantly in all  
12 groups by ~11%. In ET, blood cholesterol levels (-18%),  $\dot{V}O_2 \text{ max}$  (+8%), mechanical efficiency (+9%), and  
13 quality of life scores (+36%) ameliorated. In CT blood glucose levels (-11%),  $\dot{V}O_2 \text{ max}$  (+7%), and quality of  
14 life scores (+35%) were bettered. Conversely, in RT the lower blood pressure went along only with an  
15 improvement in the mental component of quality of life (+42%). ET and CT were both appropriate interventions  
16 to reduce CVDs risk factors, because blood pressure reduction was accompanied by decreases in blood glucose  
17 and cholesterol levels, increases in  $\dot{V}O_2 \text{ max}$ , mechanical efficiency, and quality of life. Although RT is not an  
18 appropriate stimulus to reduce some CVD risk factors, the reduction in blood pressure suggests the utilization of  
19 this approach in patients with mobility limitation.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

40 **Keywords:** aging; blood pressure; cardiovascular disease; circuit training; endurance training; relaxing training.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2 **INTRODUCTION**  
3

4 Cardiovascular diseases (CVDs) are the main cause of mortality and the most common reason of permanent  
5 disability in the western countries (Go et al., 2013). Several risk factors contribute to the development of CVDs,  
6 such as age, elevated levels of blood cholesterol, diabetes, obesity, tobacco use, and hypertension (HYP) (Najjar  
7 et al., 2005). In the view of this close correlation between CVDs risk factors and lifestyle, the updated  
8 recommendations for prevention of CVDs highlight the importance of physical activity among treatments of  
9 HYP (Aronow et al., 2011; Mancia et al., 2013). Specifically, hypertensives are encouraged to participate in  
10 endurance training (ET) programs to reduce both systolic and diastolic arterial blood pressure. This ET-induced  
11 reduction in arterial pressure is generally accompanied by improvements in central and peripheral hemodynamic  
12 factors (Gibala et al., 2012; Hood et al., 2011) Additional benefits of ET are the improvement of maximal  
13 aerobic capacity ( $\dot{V}O_2 \text{ max}$ ), that is highly correlated with longevity and independence of aged population  
14 (Venturelli et al., 2012; Venturelli et al., 2013), and the reduction of other CVDs risk factors, such as glucose  
15 and cholesterol levels, and obesity (Pescatello et al., 2004).  
16  
17

18 Also other emerging non-pharmacological treatments for HYP may reduce resting arterial blood pressure (Pal et  
19 al., 2013; Sousa et al., 2013). Interestingly, circuit-training (CT) physical exercise is becoming one of the most  
20 popular fitness programs in healthy old individuals because of its greater enjoyment with respect to standard ET  
21 (Bartlett et al., 2011). However, limited data are available on the effectiveness of this exercise approach on the  
22 reduction of CVDs risk factors in old hypertensives (Guimaraes et al., 2010; Lamina, 2010). Besides the  
23 potential appeal of CT for the old population, it is important to note that the physiological mechanisms activated  
24 by CT are different to those involved in ET in terms of central hemodynamics stimulation (Zhang et al., 2014).  
25 The limited heart rate (HR) and cardiac output responses are indeed counterbalanced by high stimulation of the  
26 peripheral circulation as during small muscle mass exercise (Esposito et al., 2010; Esposito et al., 2011).  
27  
28

29 Remarkably, a reduction in arterial blood pressure has been observed also after an alternative healthcare practice,  
30 based on breath control and meditation (relaxing training, RT) (Patel, 1975; Santaella et al., 2006). RT is a  
31 simple method to improve autonomic balance, respiratory control, and, consequently, to reduce blood pressure in  
32 hypertensive individuals. However, whether this alternative treatment can also ameliorate other CVDs risk  
33 factors is still a matter of investigation.  
34  
35

36 Given the clear evidence of ET effectiveness on the amelioration of several CVDs risk factors, exercise capacity,  
37 and quality of life in elderly patients with HYP, the aim of this study was to elucidate if other emerging non-  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1 pharmacological interventions, based upon CT (mainly peripheral stimulation) or RT (no central or peripheral  
2 hemodynamic involvement), are equally successful with respect to ET (both central and peripheral stimulation).  
3  
4 To this purpose, resting blood pressure, blood glucose and cholesterol levels, maximal exercise capacity,  
5 mechanical efficiency, and quality of life were evaluated before and after 12 weeks of ET, CT, and RT  
6 treatments. We hypothesized that a similar positive effect on blood pressure will be retrieved in all conditions.  
7  
8 However, this expected outcome will be complemented with positive effects on blood glucose and cholesterol  
9 levels, maximal exercise capacity, mechanical efficiency, and quality of life only in ET and CT, but not in RT.  
10  
11  
12  
13  
14  
15

## 16 **METHODS**

17  
18 **Participants:** Forty elderly participants (20 males and 20 females), with clinically diagnosed grade 1  
19 hypertension, corresponding to a mean systolic and diastolic blood pressure of 140-159 mmHg, and/or 90-99  
20 mmHg, respectively, volunteered in the study and signed a written informed consent form. All procedures  
21 conformed with the standards set by the 1974 Declaration of Helsinki, and the Institutional Review Boards of the  
22 local University approved the study. Patients with beta-blockers were excluded from the study. Participants  
23 medications were not altered throughout the investigation. A complete list of medications, participants  
24 characteristics, and comorbidity is displayed in Table 1.  
25  
26  
27  
28  
29  
30  
31  
32  
33

34 **Experimental design and training protocols:** The experimental design, with the proposed interventions, is  
35 represented in Figure 1. All volunteers participated to a series of sessions to familiarize with the exercise  
36 protocols and interventions. During the last familiarization session, blood pressure was measured and fasting  
37 blood samples were taken. On a different day, participants performed a graded maximal cycle exercise test to  
38 assess  $\dot{V}O_2$  peak with indirect calorimetry. After the baseline evaluations (PRE), participants were randomly  
39 allocated with stratification for gender to four different groups (n=10, 5 males + 5 females each group): ET, CT,  
40 RT, and hypertensive controls (CTRL).  
41  
42  
43  
44  
45  
46  
47  
48

49 Training sessions for ET, CT and RT lasted 60 min each, for 3 times a week. ET group performed endurance  
50 exercise training on treadmill, elliptical, and stepper ergometers. Duration of twenty minutes at 70% of maximal  
51 exercise capacity, was set for each ergometer and maintained for the entire duration of ET program. CT group  
52 executed short bouts of dynamic exercises on knee extension, knee flexion, calf rise, and leg press ergometers.  
53 CT exercises were performed at 1 Hz at 70% of the maximal mechanical power. The duration of a single bout of  
54 CT exercise was 60 s, with 60 s of recovery in between. RT group participated to a relaxing training program  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2 characterized by breathing at 5-6 cycles/min and meditation (Hering et al., 2013). CTRL did not undergo a  
3 specific intervention, therefore their data were utilized as control group. Exercise training compliance was  
4 evaluated as a percentage of training sessions attended. All the baseline evaluations were then repeated after 12  
5 weeks of intervention (POST).  
6  
7  
8  
9

10 **Exercise modalities:** Cycle exercise was performed on an electromagnetically braked cycle ergometer (Bike-  
11 Race Technogym SpA, Gambettola, Italy). Treadmill walking exercise was performed on a motorized inclinable  
12 treadmill (Run-Race Technogym SpA, Gambettola, Italy). Elliptical exercise was performed on an elliptical  
13 ergometer (Sinchro Technogym SpA, Gambettola, Italy). Step exercise was performed on a stepper ergometer  
14 (Step-Race Technogym SpA, Gambettola, Italy). KE, KF, CR, and LP exercises were performed on  
15 commercially ergometers (Excite line, Technogym SpA, Gambettola, Italy). RT was performed in a soundproof  
16 room. This group of participants, remained supine for the entire duration of the relaxation session, and an expert  
17 trainer supervised the training session with verbal feedbacks on the breathing frequency.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

28 **Measurements and calculations:** Breath-by-breath O<sub>2</sub> and CO<sub>2</sub> expiratory airflow and HR were continuously  
29 recorded and digitized (Quark b<sup>2</sup>, Cosmed, Rome Italy) during PRE and POST graded maximal cycle exercise  
30 tests. During maximum test pedal rate was maintained at 60 revolutions per minute ( $\pm 3\%$ ) and work rate was  
31 progressively increased (15 W per min) until voluntary exhaustion. Pulmonary ventilation ( $\dot{V}E$ ) and gas  
32 exchange parameters were calculated as the average of the last 30 s of any given workload. Energy expenditure  
33 and power output were expressed in watts. Delta efficiency was calculated as the reciprocal of the slope of the  
34 linear relationship between power output and energy expenditure (3 data points corresponded to 80, 95, and 110  
35 W) (Poole et al., 1992). Maximal exercise capacity was determined for ET and CT ergometers with standard  
36 graded maximal tests as follows: on the treadmill both speed and slope were progressively increased until  
37 voluntary exhaustion (Bruce et al., 1973); on both elliptical and stepper ergometers, work rate was progressively  
38 increased (15 W per min), with a cadence at 60 per minute, until voluntary exhaustion. KE, KF, CR, and LP  
39 ergometers were instrumented with a commercially available electronic system (TGS-power control, Technogym  
40 SpA, Gambettola, Italy). Range of motion, velocity, and power output were continuously monitored and utilized  
41 as feedback for participants. Maximal exercise capacity for KE, KF, CR, and LP was assessed with a graded  
42 increased workloads protocol, with 1-min steps at a frequency of 60 contractions per min, until voluntary  
43 exhaustion. The 70% of the maximal workload achieved during these evaluations was utilized for ET and CT  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1 interventions. HR monitors (Polar RS400) were utilized to measure HR response during the interventions. HR  
2 response was assessed also in CTRL while sitting on a chair for a period of time similar to the duration of the  
3 intervention. HR reserve (HRR) was calculated as the difference between exercise and resting HR, divided by  
4 the difference of age-predicted maximal and resting HRs.  
5  
6

7  
8  
9  
10 **Blood analyses:** A fasted venous blood sample was analyzed for glucose, high- and low-density lipoprotein  
11 blood levels by standard techniques.  
12

13  
14  
15  
16 **Blood pressure:** Two different physicians measured blood pressure with standard auscultatory and mercury  
17 sphygmomanometer technique at about the same time of the day to minimize the effect of circadian rhythm on  
18 the measurement. Both operators repeated the blood pressure evaluations 2 times in blind before and after  
19 intervention. Data reported in the text are the average of the four evaluations.  
20  
21  
22

23  
24  
25  
26 **Health-related quality of life:** The Italian version of the SF-36 health survey (Apolone et al., 1998) was  
27 administrated before and after the interventions. Briefly, the first 4 items of the SF-36: physical functioning,  
28 role-physical, bodily pain, general health were assessed and categorized in the physical component of the SF-36.  
29 Similarly, the remnants 4 items: vitality, social functioning, role-emotional, and mental health were recorded and  
30 summarized in the mental component of the SF-36. The items scores were than calculated with the computer-  
31 based tool (<http://www.sf-36.org>; SF-36® Health Survey Health Assessment Lab, Medical Outcomes Trust, and  
32 QualityMetric Incorporated).  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 **Statistical analysis:** Raw data were analyzed using a statistical software package (IBM SPSS Statistics v. 19,  
43 Armonk, NY, USA). To check the normal distribution of the sampling, a Shapiro-Wilk test was applied. A two-  
44 way (time and group) ANOVA for repeated measures was applied on each variable before and after the  
45 interventions to assess the effects of training, and the interaction between the two factors. The location of  
46 possible differences was assessed by a Holm-Sidak post-hoc test. The level of significance was set at  $\alpha < 0.05$ .  
47  
48  
49  
50  
51  
52 Unless otherwise stated, the results are expressed as mean  $\pm$  standard error (SE).  
53  
54  
55

## 56 **RESULTS**

57  
58  
59  
60  
61  
62  
63  
64  
65

1 The participants' characteristics are summarized in Table 1. No difference was observed between ET, CT, RT  
2 and CTRL concerning anthropometrics, comorbidity, and pharmacological treatments ( $p = 0.8$ ).

3  
4 **Intervention compliance:** The small-group approach to the interventions with the supervision of expert operators  
5 resulted in  $92\pm 3\%$  compliance for ET,  $97\pm 2\%$  for CT, and  $95\pm 4\%$  for RT, without statistical difference between  
6 groups ( $p = 0.8$ ).

7  
8  
9  
10 **HR response during ET, CT, RT interventions:** HR response, recorded during a single session in the 1<sup>st</sup> week of  
11 the ET exercises, was 21% higher respect to CT. Similarly, the difference between CT and RT was 22% (Figure  
12 2; Panel A). Despite the exercise-intensity adopted for both ET and CT was 70% of maximal capacity, the lowest  
13 HR attained during CT was determined by the short intermittent exercise modality (1 min of exercise followed  
14 by 1 min of recovery) (Figure 2; Panel B) essential to the premise of the current experimental design.  
15 Interestingly, HR recorded during a session of the 12<sup>th</sup> week of intervention was significantly reduced only  
16 during the ET exercise, while was not changed during CT, and RT (Figure 2; Panel A). Data from CTRL are also  
17 provided.

18  
19  
20  
21  
22  
23  
24  
25  
26 **Resting HR and blood pressure:** Prior to training, no significant difference in HR, SBP, and DBP were found  
27 among ET, CT, RT, and CTRL groups (Figure 3; Panels A, B, and C). As a consequence of ET, CT, and RT  
28 training, the hypertensive subjects exhibited a significant and similar decrease in SBP and DBP. However resting  
29 HR was not changed after the interventions (Figure 3; Panel C).

30  
31  
32  
33  
34 **Blood analyses and health-related quality of life:** At baseline, glucose and cholesterol were not different in ET,  
35 CT, RT, and CTRL groups, (Table 2). The effect of CT was more pronounced in the reduction of glucose (-26  
36 mg/dl), while ET training, ameliorated both HDL (+9 mg/dl) and LDL (-14 mg/dl). Mental component of the  
37 SF-36 survey for health-related quality of life was equally increased for ET, CT, and RT. However, only ET and  
38 CT demonstrated a significant increase in the physical component of SF-36 (Table 2).

39  
40  
41  
42  
43  
44 **Maximal cycle exercise pre- and post- ET, CT, RT and CTRL:** Maximum work rate during cycle exercise  
45 increased significantly after the 12 weeks of intervention by ~30 W for both ET and CT, and by ~15 W for RT.  
46 No change was observed for the CTRL group. Pre-training, cycle  $\dot{V}O_{2peak}$  was  $1260\pm 104$ ,  $1199\pm 105$ ,  $1214\pm 111$ ,  
47 and  $1189\pm 131$  ml/min for ET, CT, RT, and CTRL respectively. Post-training cycle  $\dot{V}O_{2peak}$  was significantly  
48 increased in both ET (+8%) and CT (+7%), while in RT and CTRL was similar to pre-training values (Figure 4;  
49 Panel D). Pre-training  $\dot{V}CO_{2}$  attained during maximal cycling exercise was similar for all the 4 groups ~1390  
50 ml/min, however after the intervention peak of  $\dot{V}CO_{2}$  was increased by ~9% in RT, ~11% in CT, ~2% in RT, and  
51

1  
2  
3  
4  
5  
6  
7  
8  
9  
~1% in CTRL (Figure 4; Panel C). Pre-training, peak in  $\dot{V}_E$  was not different between groups ~47 l/min, but  
similar to the  $\dot{V}_{CO_2}$  results, was significantly increased in RT and CT after the interventions (Figure 4; Panel B).  
Pre-training HR peak reached during cycle exercise was similar ~150 BPM in the four groups. However, post-  
training maximum HR was significantly augmented only in ET ~7%, while CT ~3%, RT ~2%, and CTRL ~2%  
did not changed (Figure 4; Panel A).

10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
**Mechanical efficiency:** Twelve weeks of ET resulted in an attenuated oxygen uptake recorded at given  
submaximal work rates (80-95-110 W) of the maximal cycle exercise. This outcome indicates a significant  
increase in mechanical efficiency that was obtained only by the ET group (Figure 4; Panel D; Figure 5).  
Interestingly, patients in ET group exhibited a similar trend in the reduction of HR at submaximal work rates  
(Figure 4; Panel A), indicating an increased cardiac reserve induced by the ET intervention.

## 23 DISCUSSION

24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
With the intent to evaluate the effectiveness of different non-pharmacological treatments on the modification of  
CVDs risk factors, exercise capacity, and quality of life of old hypertensive individuals, we investigated the  
effects of three different interventional strategies (ET, both central and peripheral stimulation; CT, only  
peripheral stimulation; and RT, no central or peripheral hemodynamic involvement) in elderly patients with  
grade 1 of HYP. In agreement with our hypothesis, resting systolic and diastolic blood pressures were  
significantly reduced in all groups. This expected positive outcome was accompanied by different achievements  
in blood glucose and cholesterol levels, maximum aerobic power, mechanical efficiency and health-related  
quality of life scores. The reduction in blood pressure in ET was accompanied by a concurrent decrease in blood  
cholesterol levels and an increase in  $\dot{V}_{O_2\text{peak}}$ , mechanical efficiency and quality of life scores. Similarly, in CT,  
blood pressure amelioration was accompanied by a decrease in blood glucose levels and an increase in  
 $\dot{V}_{O_2\text{peak}}$  and quality of life scores. On the contrary, in RT the lower systolic and diastolic blood pressure went  
along only with an improvement in the mental component of quality of life.

60  
61  
62  
63  
64  
65  
**Non-pharmacological treatments and CVDs risk factors:** Despite the three different approaches were similarly  
effective in the reduction of HYP, other CVDs risk factors were affected differently by ET, CT, and RT.  
Specifically, HDL and LDL, two important CVDs risk factors, were significantly ameliorated after the ET  
treatment, while the effect on cholesterol was not significant for CT, and RT. This result is in agreement with the

majority of the literature, and it is likely caused by the predominant utilization of the free-fat acids derived from cholesterol during the ET (Braz et al., 2012).

Interestingly, while ET and RT exhibited a positive, but not significant, trend in the reduction of glucose, the effect of CT was more pronounced. These positive results on glucose reduction are in the range of outcomes usually retrieved in aerobic and resistance training (Short et al., 2003). Noticeably, this additional positive outcome reinforces the relationship between the positive effects of physical exercise and cardiovascular health (Guimaraes et al., 2010; Sousa et al., 2013). Collectively, it appears that non-pharmacological interventions based upon active exercise training, ET and CT, were both successful in the amelioration of several CVDs risk factors, while RT was less effective.

***Non-pharmacological treatments and quality of life:*** Quality of life is a relevant aspect of health in old patients with HYP. It is well established that physical exercise can positively change these psychological and health-condition factors in this population (Tolonen et al., 2013). Our data on the mental component of the SF-36 confirm and advance these results, underlining that also a RT approach can improve the psychological component of quality of life. However, the results of physical component of the SF-36 survey indicate that the patients' perception of his/her health status increased only after a period of active exercise training (ET or CT). This contrast can be explained by the additional, and assessed in the current study, positive health-related improvements (blood pressure, glucose and cholesterol levels, and exercise capacity) obtained by ET and CT interventions. Therefore, it appears that these additional health-related gains obtained by the employment of active exercise, may predispose old individuals with HYP to a better perception of their quality of life. Again, the overall better responses on the CVDs risk factors together with the improved quality of life observed in our study, indicate that the best choices in terms of non-pharmacological treatment for HYP reduction are ET and CT.

***Non-pharmacological treatments and maximal exercise capacity:*** Maximal exercise capacity, defined by  $\dot{V}O_2$  max, is a strong predictor of cardiovascular health and independence in older adults (Paterson et al., 2004) and hypertensives (Totsikas et al., 2011). Thus, the investigation of the effectiveness of non-pharmacological treatment has clear practical significance in terms of identifying the means by which the capacity for an independent lifestyle can be maintained (Mancia et al., 2013). Our data indicate that both ET and CT enhanced significantly the maximal exercise capacity assessed during cycle maximal test. According to the

1 maximal work rate,  $\dot{V}O_{2peak}$  increased significantly in both ET (+8%) and CT (+7%). Moreover, the lack of  
2 difference in maximal exercise capacity exhibited by the participants assigned to RT intervention suggests that  
3 this non-pharmacological approach for HYP reduction is not effective on the enhancement of  $\dot{V}O_{2peak}$  .  
4 Therefore, this additional result in favor of the ET and CT treatments suggests that the adoption of an active  
5 lifestyle characterized by the practicing of dynamic exercise has a remarkable effect not only on blood pressure,  
6 but also in maximal exercise capacity, and possibly in the independence of old hypertensives.  
7

8  
9  
10  
11  
12 Another important outcome exhibited by the ET group, was the significant increase in the HR recorded at  
13 maximum exercise. It is important to note that this positive gain of ~7% was not obtained by the other groups,  
14 implying that only after an ET intervention a positive effect on the heart hemodynamics could be retrieved.  
15  
16 Several studies emphasized the importance of cardiovascular stimuli, such as ET, that increase maximal cardiac  
17 output and HR, by which maximal exercise capacity can be enhanced (Carrick-Ranson et al., 2014). However,  
18 our data suggest that even with CT, characterized by a very limited cardiovascular stimulus, the  $\dot{V}O_{2peak}$  was  
19 positively increased. This equal response in the maximal aerobic capacity obtained by the employment of these  
20 different approaches suggests that different factors affected this result. Indeed, the positive effect of ET on  
21  $\dot{V}O_{2peak}$  was likely caused by both central and peripheral adaptation, such as a better heart hemodynamics  
22 (Rodrigues et al., 2012), an increased skeletal muscle capillarization (Hansen et al., 2010), a higher nitric oxide  
23 bioavailability (Blanco-Rivero et al., 2013), and an increased mitochondrial density (Pesta et al., 2011). On the  
24 contrary, the increased maximal exercise capacity demonstrated after CT was primarily induced by peripheral  
25 adaptations (Gibala et al., 2012; Hood et al., 2011), predominantly related to a preserved response of  
26 mitochondrial function to this short-intermittent training.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43

44 ***Non-pharmacological treatments and mechanical efficiency:*** The  $\dot{V}O_{2max}$  is certainly one of the best  
45 predictors of independence. However, the metabolic demands obtained during the everyday tasks, such as  
46 walking, stairs climbing, and housekeeping, are only a fragment of the maximal aerobic capacity measured  
47 during a maximal test (Astrand, 2003). On the contrary, mechanical efficiency at submaximal intensity is more  
48 representative of the work economy by which the activities of daily life can be executed, and, in turn, has a clear  
49 consequence on the independence and quality of life of this old population (Venturelli et al., 2012; Venturelli et  
50 al., 2012; Venturelli et al., 2013). In this scenario, it has been demonstrated that mechanical efficiency is  
51 significantly reduced in sedentary patients with pulmonary and heart dysfunctions (Perrault, 2006; Richardson et  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2 al., 2004; Riescher et al., 2004). Moreover, the recent literature reports that non-pharmacological interventions,  
3 based upon high intensity exercise, are effective for the enhancement of mechanical efficiency (Hoff et al., 2007;  
4 Karlsen et al., 2009). Interestingly, our data revealed that mechanical efficiency was significantly ameliorated  
5 only after ET (Figure 5). Conversely, mechanical efficiency after CT and RT treatments was unchanged,  
6 suggesting that in old hypertensive individuals the stimulation of both central and peripheral factors is required  
7 to obtained a significant gain in mechanical efficiency. This positive finding was likely the consequence of: (i)  
8 an increased heart economy, exhibited by a reduction in cardiac output and HR, with a concomitant increase in  
9 stroke volume during exercise at given submaximal work-rates; and (ii) a peripheral adaptation to a slower  
10 skeletal muscle fiber phenotype (Gibbs et al., 1972; Hunter et al., 2001).  
11  
12  
13  
14  
15  
16  
17  
18  
19

## 20 **CONCLUSION**

21  
22 The choice of non-pharmacological treatments for the reduction of CVDs risk factors has to take into account not  
23 only the direct effects on cardiovascular health, but also other accessory outcomes that can affect the  
24 independence and quality of life of old hypertensive individuals. Moreover, personal psychological and  
25 economical barriers need to be accounted for the efficacy of the treatment. Therefore, it appears that the  
26 employment of an active lifestyle characterized by the execution of ET is the best choice to reduce CVDs risk  
27 factors, because the amelioration of HYP is accompanied by decreases in blood glucose and cholesterol levels,  
28 increases in maximal exercise capacity, mechanical efficiency, and quality of life. Other workouts characterized  
29 by short intermittent dynamic exercises are equally effective in the reduction of HYP and improvement  
30 of  $\dot{V}O_{2peak}$ . However, CT appears less effective in the enhancement of mechanical efficiency. Alternative  
31 healthcare practices, based on breath control and meditation, are equally successful in the reduction of HYP.  
32 However, the latter approach is not an appropriate stimulus to reduce other CVDs risk factors and to enhance  
33 indicators of independence. Therefore, the choice of this non-pharmacological treatment has to be recommended  
34 in persons that are not predisposed to commence a dynamic exercise program, such as patients with mobility  
35 limitations.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

## 50 **ACKNOWLEDGMENTS**

51  
52 The authors greatly appreciate the time and effort of the patients that participated to this study. We wish to thank  
53 Stefano Zucca and Alessio Sollima for their valuable assistance with patients' coordination, during the  
54 evaluations and exercise interventions.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2 **REFERENCES**  
3  
4

5  
6 Apolone G and Mosconi P (1998) The Italian SF-36 Health Survey: translation, validation  
7 and norming. *J Clin Epidemiol* 51(11):1025-36.  
8  
9

10  
11 Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea  
12 MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW,  
13 Schocken DD, Weber MA, Wesley DJ, Harrington RA and Force AT (2011) ACCF/AHA  
14 2011 expert consensus document on hypertension in the elderly: a report of the American  
15 College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents.  
16 *Circulation* 123(21):2434-506. doi: 10.1161/CIR.0b013e31821daaf6  
17  
18  
19  
20  
21  
22  
23  
24  
25

26  
27 Astrand P-O (2003) Textbook of work physiology : physiological bases of exercise. Human  
28 Kinetics, Champaign, IL  
29  
30  
31

32  
33 Bartlett JD, Close GL, MacLaren DP, Gregson W, Drust B and Morton JP (2011) High-  
34 intensity interval running is perceived to be more enjoyable than moderate-intensity  
35 continuous exercise: implications for exercise adherence. *J Sports Sci* 29(6):547-53. doi:  
36 10.1080/02640414.2010.545427  
37  
38  
39  
40  
41  
42

43  
44 Blanco-Rivero J, Roque FR, Sastre E, Caracuel L, Couto GK, Avendano MS, Paula SM,  
45 Rossoni LV, Salaices M and Balfagon G (2013) Aerobic exercise training increases neuronal  
46 nitric oxide release and bioavailability and decreases noradrenaline release in mesenteric  
47 artery from spontaneously hypertensive rats. *J Hypertens* 31(5):916-26. doi:  
48 10.1097/HJH.0b013e32835f749c  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

Braz NF, Carneiro MV, Oliveira-Ferreira F, Arrieiro AN, Amorim FT, Lima MM, Avelar NC, Lacerda AC and Peixoto MF (2012) Influence of aerobic training on cardiovascular and metabolic parameters in elderly hypertensive women. *Int J Prevent Med* 3(9):652-9.

Bruce RA, Kusumi F and Hosmer D (1973) Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 85(4):546-62.

Carrick-Ranson GC, Hastings JL, Bhella PS, Fujimoto N, Shibata S, Palmer MD, Boyd K, Livingston S, Dijk E and Levine BD (2014) The Effect of Lifelong Exercise Dose on Cardiovascular Function During Exercise. *J Appl Physiol.* doi: 10.1152/jappphysiol.00342.2013

Esposito F, Mathieu-Costello O, Shabetai R, Wagner PD and Richardson RS (2010) Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. *J Am Coll Cardiol* 55(18):1945-54. doi: 10.1016/j.jacc.2009.11.086

Esposito F, Reese V, Shabetai R, Wagner PD and Richardson RS (2011) Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. *J Am Coll Cardiol* 58(13):1353-62. doi: 10.1016/j.jacc.2011.06.025

Gibala MJ, Little JP, Macdonald MJ and Hawley JA (2012) Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol* 590(Pt 5):1077-84. doi: 10.1113/jphysiol.2011.224725

Gibbs CL and Gibson WR (1972) Energy production of rat soleus muscle. *Am J Physiol* 223(4):864-71.

1 Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S,  
2 Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ,  
3  
4 Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D,  
5  
6 Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME,  
7  
8 Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND,  
9  
10 Woo D, Turner MB, American Heart Association Statistics C and Stroke Statistics S (2013)  
11  
12 Heart disease and stroke statistics--2013 update: a report from the American Heart  
13  
14 Association. *Circulation* 127(1):e6-e245. doi: 10.1161/CIR.0b013e31828124ad  
15  
16  
17  
18  
19

20 Guimaraes GV, Ciolac EG, Carvalho VO, D'Avila VM, Bortolotto LA and Bocchi EA (2010)  
21  
22 Effects of continuous vs. interval exercise training on blood pressure and arterial stiffness in  
23  
24 treated hypertension. *Hypertens Res* 33(6):627-632.  
25  
26  
27

28 Hansen AH, Nielsen JJ, Saltin B and Hellsten Y (2010) Exercise training normalizes skeletal  
29  
30 muscle vascular endothelial growth factor levels in patients with essential hypertension. *J*  
31  
32 *Hypertens* 28(6):1176-85. doi: 10.1097/HJH.0b013e3283379120  
33  
34  
35  
36

37 Hering D, Kucharska W, Kara T, Somers VK, Parati G and Narkiewicz K (2013) Effects of  
38  
39 acute and long-term slow breathing exercise on muscle sympathetic nerve activity in  
40  
41 untreated male patients with hypertension. *J Hypertens* 31(4):739-46. doi:  
42  
43 10.1097/HJH.0b013e32835eb2cf  
44  
45  
46

47 Hoff J, Tjonna AE, Steinshamn S, Hoydal M, Richardson RS and Helgerud J (2007) Maximal  
48  
49 strength training of the legs in COPD: a therapy for mechanical inefficiency. *Med Sci Sports*  
50  
51 *Exerc* 39(2):220-6. doi: 10.1249/01.mss.0000246989.48729.39  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 Hood MS, Little JP, Tarnopolsky MA, Myslik F and Gibala MJ (2011) Low-volume interval  
2 training improves muscle oxidative capacity in sedentary adults. *Med Sci Sports Exerc*  
3  
4 43(10):1849-56. doi: 10.1249/MSS.0b013e3182199834  
5  
6

7  
8 Hunter GR, Newcomer BR, Larson-Meyer DE, Bamman MM and Weinsier RL (2001)  
9  
10 Muscle metabolic economy is inversely related to exercise intensity and type II myofiber  
11  
12 distribution. *Muscle Nerve* 24(5):654-61. doi: 10.1002/mus.1051 [pii]  
13  
14  
15

16  
17 Karlsen T, Helgerud J, Stoylen A, Lauritsen N and Hoff J (2009) Maximal strength training  
18  
19 restores walking mechanical efficiency in heart patients. *Int J Sports Med* 30(5):337-42. doi:  
20  
21 10.1055/s-0028-1105946  
22  
23

24  
25 Lamina S (2010) Effects of continuous and interval training programs in the management of  
26  
27 hypertension: a randomized controlled trial. *J Clinical Hypertens* 12(11):841-9. doi:  
28  
29 10.1111/j.1751-7176.2010.00315.x  
30  
31

32  
33 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova  
34  
35 R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen  
36  
37 SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P,  
38  
39 Viigimaa M, Waeber B, Zannad F and List of authors Task Force M (2013) 2013 ESH/ESC  
40  
41 Guidelines for the management of arterial hypertension: The Task Force for the management  
42  
43 of arterial hypertension of the European Society of Hypertension (ESH) and of the European  
44  
45 Society of Cardiology (ESC). *J Hypertens* 31(7):1281-357. doi:  
46  
47 10.1097/01.hjh.0000431740.32696.cc  
48  
49  
50  
51  
52

53  
54 Najjar SS, Scuteri A and Lakatta EG (2005) Arterial aging: is it an immutable cardiovascular  
55  
56 risk factor? *Hypertension* 46(3):454-62. doi: 10.1161/01.HYP.0000177474.06749.98  
57  
58  
59

1  
2 Pal S, Radavelli-Bagatini S and Ho S (2013) Potential benefits of exercise on blood pressure  
3 and vascular function. *J Am Soc Hypertens* 7(6):13. doi: 10.1016/j.jash.2013.07.004  
4

5 Patel C (1975) 12-month follow-up of yoga and bio-feedback in the management of  
6 hypertension. *Lancet* 1(7898):62-4.  
7  
8  
9

10 Paterson DH, Govindasamy D, Vidmar M, Cunningham DA and Koval JJ (2004)  
11 Longitudinal study of determinants of dependence in an elderly population. *J Am Geriatr Soc*  
12 52(10):1632-8. doi: 10.1111/j.1532-5415.2004.52454.x  
13  
14  
15  
16  
17  
18  
19 JGS52454 [pii]  
20

21  
22 Perrault H (2006) Efficiency of movement in health and chronic disease. *Clin Invest Med*  
23 29(2):117-21.  
24  
25  
26

27  
28 Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA and Ray CA (2004)  
29 Exercise and Hypertension. *Med Sci Sports Exerc* 36(3):533-553. doi:  
30  
31  
32  
33 10.1249/01.mss.0000115224.88514.3a  
34  
35

36 Pesta D, Hoppel F, Macek C, Messner H, Faulhaber M, Kobel C, Parson W, Burtscher M,  
37  
38 Schocke M and Gnaiger E (2011) Similar qualitative and quantitative changes of  
39 mitochondrial respiration following strength and endurance training in normoxia and hypoxia  
40 in sedentary humans. *Am J Physiol Reg Integr Comp Physiol* 301(4):R1078-87. doi:  
41  
42  
43  
44  
45  
46  
47 10.1152/ajpregu.00285.2011  
48

49  
50 Poole DC, Gaesser GA, Hogan MC, Knight DR and Wagner PD (1992) Pulmonary and leg  
51 VO<sub>2</sub> during submaximal exercise: implications for muscular efficiency. *J Appl Physiol*  
52  
53  
54  
55 72(2):805-10.  
56  
57  
58  
59

1 Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SR, Henry R, Mathieu-Costello O  
2 and Wagner PD (2004) Reduced mechanical efficiency in chronic obstructive pulmonary  
3 disease but normal peak VO<sub>2</sub> with small muscle mass exercise. *Am J Respir Crit Care Med*  
4  
5 169(1):89-96. doi: 10.1164/rccm.200305-627OC  
6  
7

8  
9 Riescher B, Bourdarias JP, Dubourg O and Jondeau G (2004) [Skeletal muscle efficiency in  
10 heart failure]. *Annales de cardiologie et d'angiologie* 53(4):188-92.  
11  
12

13  
14 Rodrigues B, Jorge L, Mostarda CT, Rosa KT, Medeiros A, Malfitano C, de Souza AL, Jr.,  
15 Viegas KA, Lacchini S, Curi R, Brum PC, De Angelis K and Irigoyen MC (2012) Aerobic  
16 exercise training delays cardiac dysfunction and improves autonomic control of circulation in  
17 diabetic rats undergoing myocardial infarction. *J Cardiac Fail* 18(9):734-44. doi:  
18 10.1016/j.cardfail.2012.07.006  
19  
20  
21  
22  
23  
24  
25  
26

27  
28 Santaella DF, Araujo EA, Ortega KC, Tinucci T, Mion D, Jr., Negrao CE and de Moraes  
29 Forjaz CL (2006) Aftereffects of exercise and relaxation on blood pressure. *Clin J Sport Med*  
30 16(4):341-7.  
31  
32  
33  
34  
35  
36

37 Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM and Nair  
38 KS (2003) Impact of aerobic exercise training on age-related changes in insulin sensitivity  
39 and muscle oxidative capacity. *Diabetes* 52(8):1888-96.  
40  
41  
42  
43  
44

45 Sousa N, Mendes R, Abrantes C, Sampaio J and Oliveira J (2013) Long-term effects of  
46 aerobic training versus combined aerobic and resistance training in modifying cardiovascular  
47 disease risk factors in healthy elderly men. *Geriatr Geront Int* 13(4):928-35. doi:  
48 10.1111/ggi.12033  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59

1 Tolonen H, Koponen P, Mindell J, Mannisto S and Kuulasmaa K (2013) European Health  
2 Examination Survey--towards a sustainable monitoring system. Eur J Pub Health. doi:  
3  
4 10.1093/eurpub/ckt107  
5  
6

7  
8 Totsikas C, Rohm J, Kantartzis K, Thamer C, Rittig K, Machann J, Schick F, Hansel J, Niess  
9  
10 A, Fritsche A, Haring HU and Stefan N (2011) Cardiorespiratory fitness determines the  
11 reduction in blood pressure and insulin resistance during lifestyle intervention. J Hypertens  
12  
13 29(6):1220-7. doi: 10.1097/HJH.0b013e3283469910  
14  
15  
16

17  
18  
19 Venturelli M, Richardson RS and Ortega J (2012) Skeletal muscle mechanical efficiency  
20  
21 does/does not increase with age. J Appl Physiol. doi: 10.1152/jappphysiol.01438.2012  
22  
23

24  
25 Venturelli M, Schena F and Richardson RS (2012) The role of exercise capacity in the health  
26  
27 and longevity of centenarians. Maturitas 73(2):115-20. doi: 10.1016/j.maturitas.2012.07.009  
28  
29

30  
31 Venturelli M, Schena F, Scarsini R, Muti E and Richardson RS (2013) Limitations to exercise  
32  
33 in female centenarians: evidence that muscular efficiency tempers the impact of failing lungs.  
34  
35 Age 35(3):861-70. doi: 10.1007/s11357-011-9379-1  
36  
37

38  
39 Zhang Y, Haddad A, Su SW, Celler BG, Coutts AJ, Duffield R, Donges CE and Nguyen HT  
40  
41 (2014) An equivalent circuit model for onset and offset exercise response. Biomed Eng online  
42  
43 13(1):145. doi: 10.1186/1475-925X-13-145  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59

Table 1. Participants characteristics

Group	ET	CT	RT	CTRL
Age (yrs)	68±3	67±4	69±6	66±7
Gender (F/M)	5/5	5/5	5/5	5/5
Comorbidity (n.)				
Diabetes	1	2	1	1
Pharmacological treatments (n.)				
Trazodone	3	2	3	4
Thiazolidinedioe	2	3	2	2
Etofylline	1	1	1	1
Captopril	8	8	9	7
Clortalidone	9	7	7	5

ET = endurance training, CT = circuit training, RT = relaxing training, CTRL = controls, F = female, M = male.

Table 2

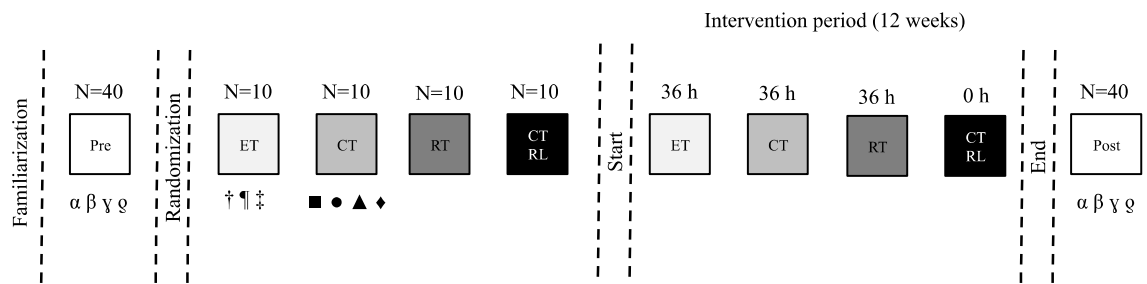
	ET		CT		RT		CTRL	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Stature (m)	1.72±0.05	1.72±0.05	1.75±0.06	1.75±0.06	1.73±0.05	1.73±0.05	1.73±0.06	1.73±0.06
BMI (kg/m <sup>2</sup> )	27±4	27±5	27±3	27±4	26±5	26±4	27±6	27±6
Wcirc. (cm)	95±9	94±7	95±8	94±5	96±9	96±8	98±10	98±11
Hcirc. (cm)	100±9	100±8	102±8	101±9	99±8	99±9	103±11	104±12
Glucose (mg/dl)	108±11	100±6	112±7	86±4 *†	104±13	100±13	101±9	101±7
HDL (mg/dl)	57±9	66±9 *†	55±14	58±22	64±12	59±20	59±9	56±9
LDL (mg/dl)	140±33	126±13*†	143±30	130±28	153±35	151±33	141±39	138±35
Health related quality of life								
SF-36phys (0-100)	33±4	49±4 *	32±4	48±5 *	34±3	36±5	37 ± 11	37 ± 12
SF-36ment (0-100)	29±2	54±3 *	29±3	53±5 *	29±3	50±4 *	28 ± 8	28 ± 9

ET = endurance training, CT = circuit training, RT = relaxing training, CTRL = controls, BMI = body mass index, Wcirc. = waist circumference, Hcirc = hip circumference, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SF-36phys = physical component of health related quality of life, SF-36ment = mental component of health related quality of life,

\* = In-group  $P < 0.05$ ; † = between groups  $P < 0.05$



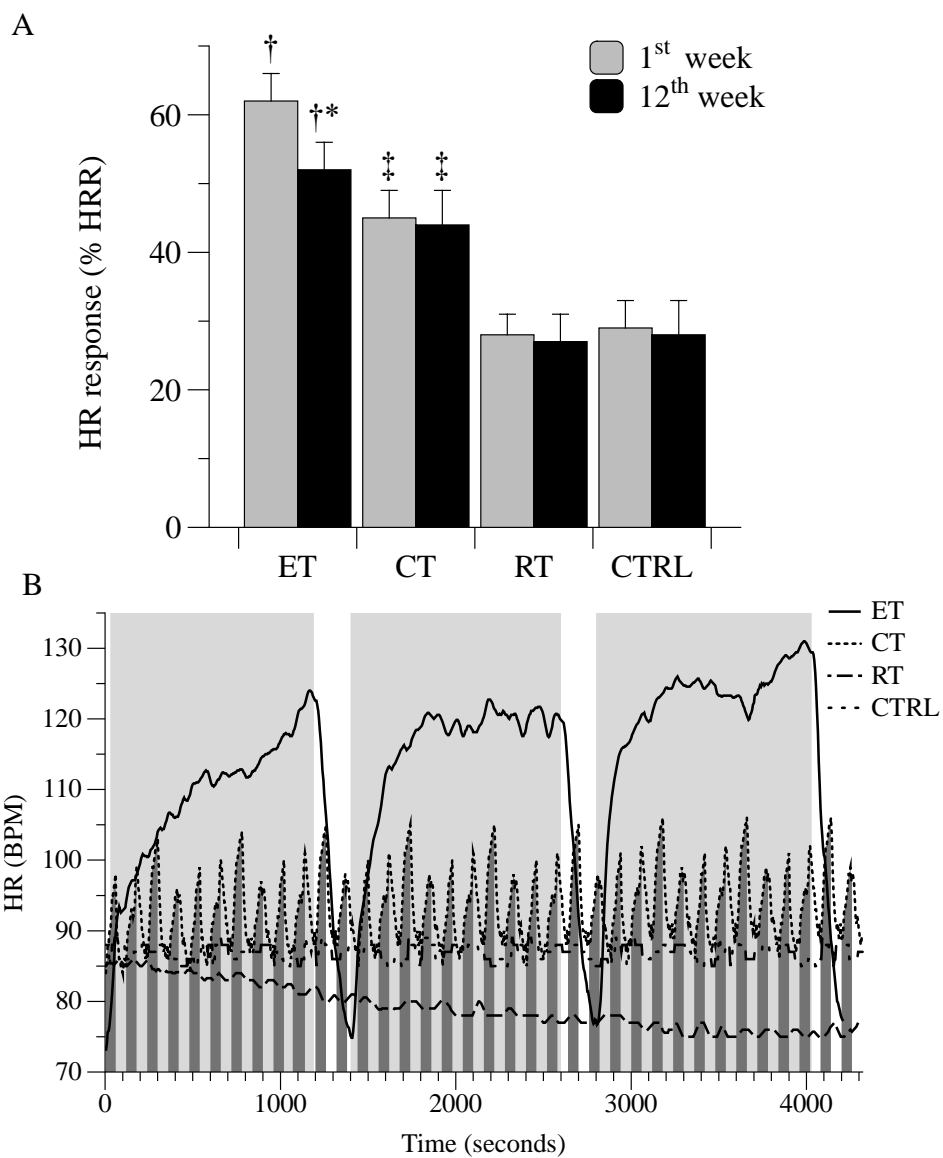
Figure 1 - *Experimental design*: After baseline evaluations (PRE), participants were assigned to four different groups. ET group, endurance exercise training on treadmill, elliptical, and stepper ergometers; CT group, short bouts of dynamic exercises on knee extension (KE), knee flexion (KF), calf rise (CR), and leg press (LP) ergometers; RT group, relaxing training program; CTRL group, no intervention



α = Maximal cycling test; β = blood samples; γ = blood pressure; g = Health related quality of life

Maximal tests: † = Treadmill; ¶ = Elliptical; ‡ = Step; ■ = KE; ● = KF; ▲ = CR; ◆ = LP.

Figure 2 – *Heart rate response*: Average heart rate (HR) response, as a percentage of HR reserve (HRR, panel A), in the four groups during interventions at the beginning (1<sup>st</sup> week) and at the end (12<sup>th</sup> week) of treatments. Panel B represents the HR response during an intervention session in representative participants of the four groups. The light and dark grey areas represent the exercise time during ET and CT, respectively. \* = in-group  $P < 0.05$ ; † = between groups  $P < 0.05$ ; ‡ =  $P < 0.05$  vs RT and CTRL.



1  
2 Figure 3 – Cardiovascular variables at rest: Average resting systolic (SBP) and diastolic (DBP) blood pressures  
3 and heart rate (HR) in the four groups before and after interventions. \* = in-group  $P < 0.05$ .  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

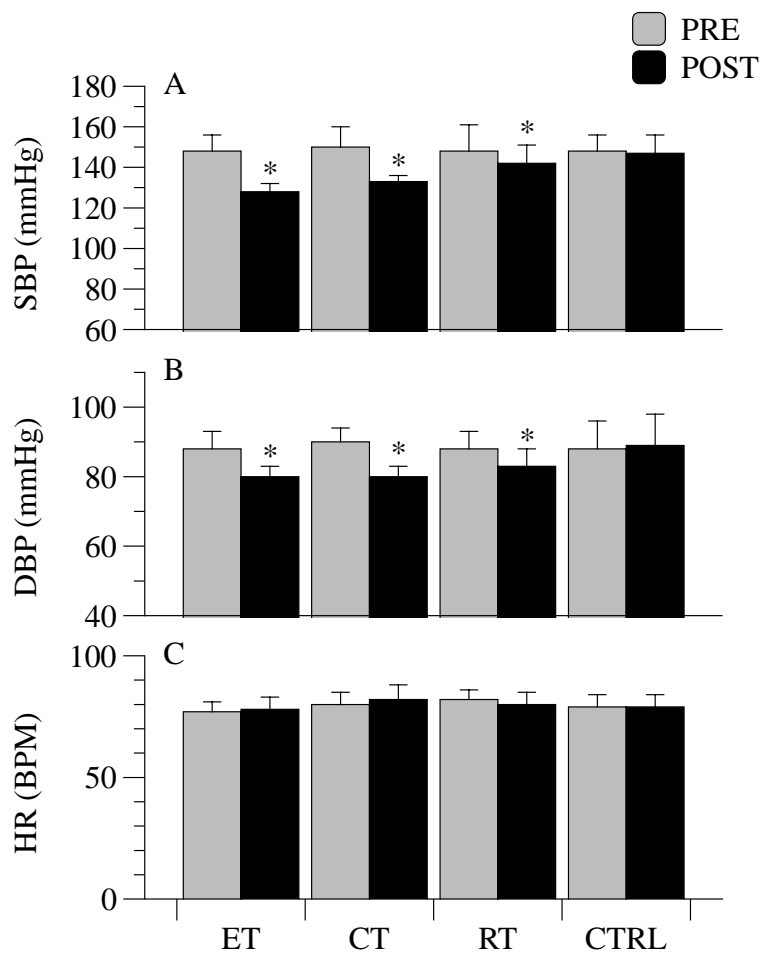
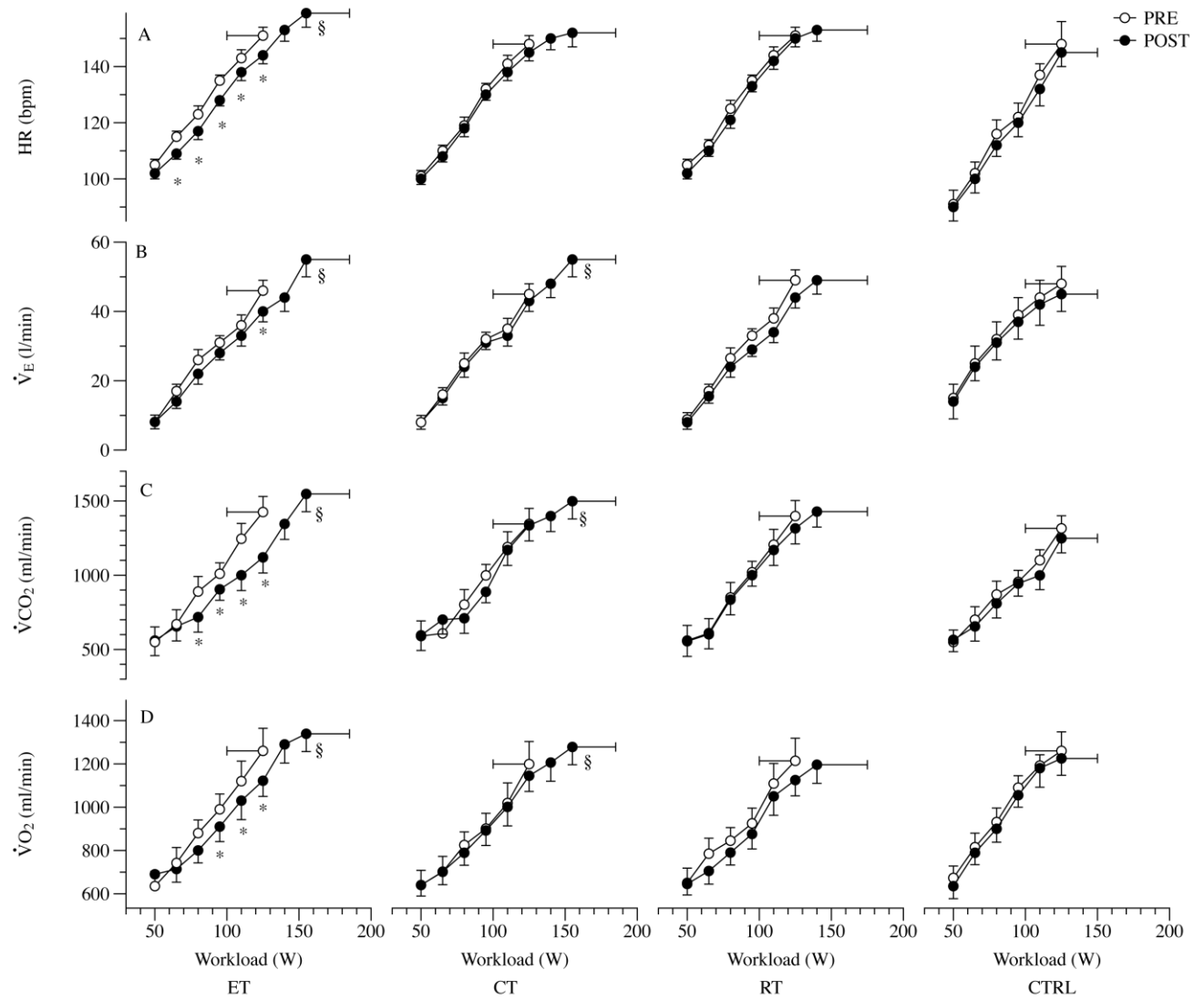


Figure 4 – *Cardiorespiratory response to exercise: average heart rate (HR), expiratory ventilation ( $\dot{V}_E$ ), CO<sub>2</sub> production ( $\dot{V}CO_2$ ), and oxygen uptake ( $\dot{V}O_2$ ) during cycle incremental ramp exercise in the four groups, before and after interventions. \* = in-group  $P < 0.05$ ; § = in-group  $P < 0.05$  at maximal exercise.*



1  
2 Figure 5 – *Exercise efficiency*:  $\Delta$  efficiency ( $\Delta\eta$ ), calculated on the first part of the cycle ramp exercise, in the  
3  
4 four groups, before and after interventions. \* = in-group  $P < 0.05$ .  
5  
6  
7  
8  
9

