Exercise intervention does not reduce the likelihood of VO_2max underestimation in older adults with hypertension

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ABSTRACT

Purpose: The present study aimed to investigate whether training status would influence the capacity of a verification phase (VER) to confirm maximal oxygen uptake (VO_2max) of a previous graded exercise test (GXT) in individuals with hypertension. **Methods:** Twelve older adults with hypertension (8 women) were recruited. Using a within-subject design, participants performed a treadmill GXT to exhaustion followed by a multistage VER both before and after a 12-wk pragmatic combined exercise training program. Individual VO_2max, respiratory exchange ratio (RER), maximal heart rate (HR_{max}), and rating of perceived exertion (RPE) were measured during both GXT and VER tests. Mean values were compared between bouts using paired sample t-tests, and VO_{2max} was also compared between GXT and VER individually. **Results:** Testing was well tolerated by all participants. Absolute and relative VO_2max values were higher in VER than in GXT at baseline, but only absolute VO_2max differed between bouts post-intervention (all $p<0.05$). Individual VO_2max comparisons revealed that 75% of the participants (9/12) achieved a VO_{2max} value that was ≥3% during VER both before (range: from +4.9% to +21%) and after the intervention (range: from +3.4% to +18.8%), whereas 91.7% (11/12) of the tests would have been validated as a maximal effort if the classic criteria were employed (i.e., VO_2 plateau or at least two secondary criteria). **Conclusion:** A 12-wk combined training intervention could not improve the capacity of older adults with hypertension to achieve VO_2max during a GXT, as assessed by VER.

Keywords: Exercise testing; Verification phase; Oxygen consumption; Blood pressure

Highlights:

1. A training intervention did not improve the participants' capacity to achieve their VO_2max during GXT.
2. That is, irrespective of training status, VO_2max was underestimated in a large proportion of these individuals during GXT both at baseline and after the intervention.
3. As such, our results raise questions about the validity of VO_2max measured in the population investigated and support the use of a verification phase to confirm VO_2max attainment during GXT.

1. INTRODUCTION

An adequate cardiorespiratory fitness is regarded as an essential component of a healthy lifestyle, and physical exercise is arguably the most widely recommended approach for maintaining or improving maximal oxygen uptake ($\dot{V}O_2max$) [1]. Those presenting higher $\dot{V}O_2max$ levels are at a lower risk for developing several cardiometabolic risk factors, such as hypertension [2] and hyperglycemia [3], as well as cardiovascular diseases [4] and mortality [4–6]. It is not surprising, therefore, that $\dot{V}O_2max$ is a common primary outcome in clinical trials aiming to investigate the effects of different exercise training regimens in both healthy and clinical populations.

Historically, $\dot{V}O2max$ attainment during graded exercise testing (GXT) has been confirmed based on the presence of a plateau in oxygen uptake ($\dot{V}O_2$) or, when a plateau is not discernible, on secondary criteria such as heart rate (HR) and respiratory exchange ratio (RER) thresholds [7,8]. Reliance on secondary criteria, however, has received criticism [9,10], and even though the plateau is currently considered the gold standard for $\dot{V}O_2max$ determination, its occurrence may vary considerably [11,12]. As such, there has been an ongoing debate as to the most appropriate alternative to confirm whether $\dot{V}O_2max$ was, indeed, attained [13–15].

One such alternative, termed the $\dot{V}O_2max$ verification phase (VER), incorporates an additional exercise bout after GXT [13,16], and allows one to determine if a true $\dot{V}O_2max$ was reached during GXT based on the difference in $\dot{V}O_2$ at the end of the two bouts. This approach allows a direct comparison between GXT and VER $\dot{V}O_2$, the actual outcome of interest, which is not possible through other criteria based solely on a single GXT. Most of the previous studies were performed on healthy young adults and showed that VER helps confirm whether $\dot{V}O_2max$ was attained during

GXT in these individuals [17]. We and others, however, have recently demonstrated that $\dot{V}O_2max$ may be underestimated in sedentary older participants and clinical populations ([18–20]. Together, these data suggest that lower exercise tolerance and/or fitness level may influence someone's capacity to reach $\dot{V}O_2max$ during GXT [21] and raises the question of whether training status would improve the ability to reach $\dot{V}O_2max$ in sedentary older individuals. In the present investigation, hypertensive patients were used as a model for individuals/conditions typically related to lower exercise tolerance and fitness level.

Therefore, the present study aimed to investigate whether a training intervention would improve the capacity of older adults with hypertension to achieve $\dot{V}O_2max$ during a GXT. Our hypothesis was that VER would demonstrate GXT's $\dot{V}O_2max$ to be underestimated at a higher frequency at baseline than after the intervention period.

2. MATERIALS AND METHODS

This investigation is an exploratory analysis based on data from the Hypertension Approaches in the Elderly: A Lifestyle Study (HAEL) trial. This multicenter randomized clinical trial compared the effects of pragmatic combined exercise training versus a health education program on ambulatory blood pressure and cardiorespiratory fitness in older adults with hypertension (ClinicalTrials.gov NCT03264443). The current manuscript focuses on the baseline and post-training $\dot{V}O_2$ data of the GXT and VER tests from the participants recruited at the Pelotas centre from February 2018 to June 2019 and includes all but the first recruitment wave of the study. The cross-sectional comparison between GXT and VER at baseline has been previously published and is available elsewhere [18].

2.1 Participants

Of the 42 individuals included in the HAEL study Pelotas centre during the recruitment period of the present investigation, 2 did not perform GXT, 6 refused to participate in the VER study, data from 4 participants could not be retrieved because of equipment malfunction during VER, and 6 of the randomized participants were lost to follow-up (Suppl. Fig. 1), for a total of 24 participants randomized. From these, 12 participants (≥60 years old) were randomly allocated to the training arm of the trial and were included in the present analysis (Table 1). All participants provided their written informed consent, and the research project was previously approved by the Federal University of Pelotas Institutional Review Board (CAAE no. 62427616.0.2001.5313).

Insert table 1 near here

2.2 Experimental Procedures

Participants initially performed a GXT to determine their $\dot{V}O_2max$ and, after a brief recovery period, performed a VER to assess whether $\dot{V}O_2max$ was attained during GTX. They then completed a 12-week pragmatic combined exercise training program, which included group exercise sessions 3 days per week, each consisting of 20-30 min of moderate-intensity walking/running followed by 15-20 min of resistance exercise performed using bodyweight and elastic bands [22]. Both GXT and VER tests were repeated following the 12-wk intervention period at the same time (±2 hours) as before the intervention. A physician supervised all tests for safety reasons, and participants were familiarized with the equipment and safety procedures before the experimental sessions.

2.3 Protocols

Maximal incremental test. Briefly, participants attended the laboratory, and after a 5-min resting interval, baseline resting blood pressure measurement was taken and presented to the physician. After clearance, participants were submitted to a maximal GXT to exhaustion on a motorized treadmill. Participants warmed-up at 3 $km \cdot h^{-1}$ for 3 min, and the test started with 0.5 $km \cdot h^{-1}$ and 1% grade increments per minute until volitional exhaustion. Both GXT and VER protocols have been explained in detail previously [18].

Verification phase. After a 10-min passive recovery interval, each participant underwent a VER to determine whether the $\dot{V}O_2max$ value obtained during GXT was a true maximum. During VER, a new multistage effort bout was performed, which consisted of 2 min at 50% of the maximal speed and grade reached during GXT, followed by 1 min at 70% of the maximal speed and grade at GXT. Then participants exercised to volitional failure at one stage above the last completed stage in their individual GXT [23].

During both GXT and VER, gas exchange data were obtained using a portable metabolic system (VO2000; MedGraphics®, Ann Arbor, MI), calibrated before each session according to the manufacturer's specifications, and recalibrated between GXT and VER to minimize drift. Participants' HR was measured telemetrically using an HR monitor (Polar FT1; Polar Electro, Kempele, Finland), and the rating of perceived exertion (RPE) was measured at the end of GXT and VER using the Borg scale [24].

2.4 Data Analysis

$\dot{V}O_2$ values were time-averaged every 20 s, and the average from the last two 20-s intervals in both GXT and VER was considered as phase-specific $\dot{V}O_2$max [25,26]. The $\dot{V}O_2$max during GXT was confirmed when the difference between VER and GXT $\dot{V}O_2$max was less than 3% [23,27]. In addition, to determine the number of valid tests, GXT results were also confirmed based on the presence of a $\dot{V}O_2$ plateau (≤150 mL·min^{-1}), or when at least two secondary criteria were met (±10 bpm of age-predicted HR [≥220-age], RER > 1.10, or RPE ≥ 18).

2.5 Statistical Analysis

Data are reported as mean ± standard deviation (SD) unless stated otherwise. Comparisons between GXT and VER mean outcomes, both pre- and post-training, were performed using paired sample t-tests. Comparisons between GXT and VER $\dot{V}O_2$max results were also conducted individually, as currently recommended [13,16]. GXT results were valid when VER $\dot{V}O_2$max was less than 3% higher than that observed during GXT [23,27]. The significance level was set at α = 0.05, and all analyses were performed using SPSS software (v. 25.0., IBM, USA).

3. RESULTS

3.1 Baseline measures

Both GXT and VER were well tolerated by all participants, and no adverse event was registered. As shown in Table 2, both absolute and relative $\dot{V}O_2$max results were higher in VER than in GXT (p=0.003). RER was also lower at VER (p=0.002), whereas HRmax and RPE were not different between bouts (p=0.712 and p=0.167). When tests were compared individually, 75% (9/12) achieved $\dot{V}O_2$max values that were ≥3% higher in VER than in GXT (range: 4.9% to 21%), whereas 16.7% (2/12) and 8.3% (1/12) resulted in $\dot{V}O_2max$ values that were within and lower than 3% of those observed at GXT (range from -0.5% to 0.1%, and -7.3%, respectively). Notwithstanding this, when GXT was analysed based on the presence of the classic criteria (i.e., $\dot{V}O_2$ plateau and/or secondary criteria) 91.7% (11/12) of the tests would have been deemed valid.

Insert table 2 near here

3.2 Post-training measures

Both absolute and relative $\dot{V}O_2max$ increased after the intervention (all $p<0.001$). As shown in Table 3, when GXT and VER results were compared post-intervention, absolute $\dot{V}O_2max$ was greater at VER than in GXT ($p=0.045$), whereas relative $\dot{V}O_2max$ was not ($p=0.084$). In addition, RER was lower at VER ($p=0.002$), whereas HRmax and RPE were not different between bouts ($p=0.103$ and $p=0.203$, respectively). When tests were compared individually, 75% (9/12) of those assigned to the training group achieved $\dot{V}O_2max$ values that were ≥3% higher in VER than in GXT (range: 3.4% to 18.8%), whereas 8.3% (1/12) and 16.7% (2/12) resulted in $\dot{V}O_2max$ values that were within and lower than 3% of those observed at GXT (range: 0.2% and -16.5% to -6.9%) respectively. These results are shown in Figure 1, along with a waterfall plot of the individual differences between VER and GXT.

Insert table 3 near here

When classic criteria were applied to post-intervention GXTs, results again diverged from those observed on the individual comparisons between VER and GXT. Specifically, 91.7% (11/12) of participants assigned to the training group would have had their tests considered as valid based on the presence of a plateau in $\dot{V}O_2$ or at least two secondary criteria.

Insert figure 1 near here

4. DISCUSSION

Contrary to our initial hypothesis, the main finding of the present study was that a 12-wk combined training intervention did not improve the capacity of older adults with hypertension to achieve their $\dot{V}O_2$max during a GXT. That is, irrespective of training status, $\dot{V}O_2$max was underestimated in a large proportion of these individuals during GXT, both at baseline and after the intervention compared to the $\dot{V}O_2$max achieved during VER.

To the best of our knowledge, our study is among the first to investigate the effect of training status on the capacity of individuals to verify their $\dot{V}O_2$max using a within-subject design. Previously, it has been shown by both our lab and others that untrained clinical populations such as breast cancer survivors [20], chronic heart failure patients [19], and older adults with hypertension [18] tend to underestimate their $\dot{V}O_2$max during GXT (~32-55% of participants). Conversely, in physically active middle-aged and older adults who were tested right after completing an 8-wk exercise trial GXT $\dot{V}O_2$max was found to be confirmed in 16 out of 18 participants [28]. However, no data is available on these individuals before the training intervention. Therefore, compared to the studies mentioned above, it is not possible to assess the extent that the training intervention itself had on the participants' capacity to achieve $\dot{V}$O2max during GXT.

As far as healthy individuals are concerned, the literature has consistently shown that $\dot{V}O_2max$ is typically confirmed during VER in most cases [23,27,29–32]. Recently, a systematic review and meta-analysis concluded that, in apparently healthy participants, the mean highest $\dot{V}O_2$ values were similar between GXT and VER [17]. In line with this finding, although both absolute and relative $\dot{V}O_2max$ were lower during GXT than VER at baseline, relative $\dot{V}O_2max$ was not significantly different between bouts after the training intervention in the participants of the present study. Nevertheless, both these analyses compared $\dot{V}O_2max$ between averaged values across participants, which may conceal a considerable between-trial variability in some participants, even when no difference is observed between the mean values [10,16,23,33,34]. Therefore, the comparison between GXT and VER should be performed, and conclusions should be drawn, on an individual basis.

When comparisons between GXT and VER were performed individually, we observed that 75% of the tests (i.e., 9 out of 12 participants) were underestimated at baseline. Similarly, and in contrast to previous cross-sectional data on physically active older adults [28], no difference was observed in the incidence of underestimation after the intervention. That is, $\dot{V}O_2max$ was found to be underestimated in 9 out of the 12 GXTs performed at the post-intervention time point. Based on these results, it could be suggested that training status is not a determinant factor on the individual's capacity to confirm $\dot{V}O_2max$ when assessed by VER, at least on clinical populations such as older adults with hypertension after 12 weeks of training at moderate intensity.

The absence of a significant difference between GXT and VER relative $\dot{V}O_2max$ results post-intervention, however, led us to take a closer look at what was going on at the individual level. It is well known that there is a high degree of heterogeneity in how individuals respond to exercise (e.g., responders and non-responders) [35]. Accordingly, to allow greater insight into the effects of training status on participants' capacity to confirm $\dot{V}O_2max$ during GXT after the intervention, we performed an additional analysis including only those participants found to respond to it. In other words, we examined only those who increased $\dot{V}O_2max$ after training.

Out of the 12 participants included in the initial analysis, 8 showed an increase in $\dot{V}O_2max$ (15.5 ± 8.2%, range: 4.1% to 28.9%). When the number of tests deemed to be underestimated at baseline was compared to those at post-training, results were close between the two time points. Specifically, 75% (6/8) and 62.5% (5/8) of $\dot{V}O_2max$ values were found to be higher during VER at baseline and after the intervention, respectively. When we compared the magnitude of $\dot{V}O_2max$ underestimation between these time points, however, a considerable reduction was observed, from 14.2 ± 12.1% at baseline to 4.1 ± 10.5% post-intervention, which albeit not significant ($p = 0.083$) had a large effect size ($d = 0.89$).

Taken together, our data suggest that even though training status did not translate into fewer tests being underestimated, the magnitude of $\dot{V}O_2max$ underestimation became lower when compared to baseline. This latter result is, therefore, in line with the body of evidence that shows a relatively greater incidence of GXT test results being confirmed during VER in trained individuals [17,28]. These results also raise the possibility that a more extended training period might induce an even greater reduction in the magnitude of $\dot{V}O_2max$ underestimation during GXT to the point that it may end up reducing the incidence of underestimated tests, as seen in trained young adults [17]. This hypothesis, however, remains to be experimentally tested in future studies.

Although we evidenced an underestimation of $\dot{V}O_2max$ during GXT in this sample, the reasons or mechanisms behind it are not entirely clear. Clinical populations, such as individuals with hypertension or chronic heart failure patients, for example, are typically characterized by a varying degree of exercise intolerance and, in the latter, cardiac dysfunction. Bowen et al. [19] suggested that in patients with chronic heart failure, a greater $\dot{V}O_2max$ during VER could be related to residual effects of the last bout performed (i.e., GXT), including an accelerated $\dot{V}O_2$ kinetics, increased microvascular O_2 delivery, as well as increased aerobic enzyme activity. Indeed, accelerated $\dot{V}O_2$ kinetics has been constantly suggested as a potential reason for a greater $\dot{V}O_2max$ during VER, but the available data in clinical populations mainly focused on the priming effects of heavy-intensity exercise on a subsequent moderate-intensity exercise [e.g., 36, 37]. It remains to be verified, therefore, if the same holds for subsequent supramaximal exercise in these individuals.

A lack of $\dot{V}O_2max$ attainment during GXT could also be related to poor participant motivation or lack of effort, premature fatigue [17], or simply because individuals were unaccustomed to intense exercise. The fact that a greater $\dot{V}O_2max$ was observed in 75% of the participants both at baseline and post-intervention suggests that lack of motivation or effort is unlikely, at least during VER, as it would be expected that unmotivated participants would likely provide a submaximal effort during both GXT and VER. In addition, we observed an increase not only in GXT duration but also in VER duration after the intervention. Considering that post-intervention VER intensity was prescribed relative to GXT performance, and not at the same absolute intensity as baseline's VER, this is indicative that participants were able to push themselves harder after the intervention.

An additional aspect that might have contributed to the large proportion of $\dot{V}O_2max$ underestimation observed is the VER protocol employed in the current study. As previously discussed by Midgley et al. [10], and recently confirmed by Costa et al., [17], VER protocol typically consists of a square-wave bout with no preceding warm-up period. For those with slower $\dot{V}O_2$ kinetics, such as sedentary, untrained, and/or patient populations, this approach may provide limited time for $\dot{V}O_2max$ to be reached before exhaustion [10]. On the other hand, a multi-stage VER protocol would possibly allow participants to begin exercising at the intended workload (i.e., one stage higher than GXT) on a higher metabolic state while also possibly reducing the anaerobic burden from a square wave transition to (supra)maximal intensity and its adverse effects on exercise tolerance.

Finally, it has been previously suggested [16,28,38] that the application of VER may be especially relevant for the interpretation of studies using repeated measures of $\dot{V}O_2max$ to determine the effectiveness of a training protocol (i.e., a training effect). As typically done in experimental investigations, we compared pre- and post-intervention absolute and relative GXT $\dot{V}O_2max$ results and found that the training intervention effectively improved cardiorespiratory fitness in this study. Notwithstanding this, when baseline and post-training VER $\dot{V}O_2max$ results were compared, no difference ($p = 0.673$) was observed between the two time points, suggesting that, contrary to what was initially observed, $\dot{V}O_2max$ was possibly not modified by the training intervention.

Although our sample comprises just a few participants, the result mentioned above highlights the possible influence that the use of VER might have on the conclusion of experimental studies.

Consequently, post-training assessments may end up overestimating the increase in cardiorespiratory fitness at the end of an intervention. Based on these “flawed” results, both systematic reviews and meta-analyses that incorporate results such as these may lead to misleading conclusions on the effectiveness of training interventions that, ultimately, may directly interfere with clinical practice.

5. LIMITATIONS

As highlighted previously [18], our study is not exempt from limitations. First, the 3% cutoff threshold adopted here to validate a difference between GXT and VER was not based on data from our laboratory. Therefore, it is possible that the GXT test-retest reliability in our laboratory might be slightly different than the one used. In addition, it should be noted that the lack of a non-hypertensive control group is a limitation to make inferences about the influence of hypertension per se on our findings and additional research is necessary to elucidate this. It is also worth mentioning that we were unable to control for potential interactions between the time patients took their medications and the time GXTs were performed. Notwithstanding, all patients performed pre- and post-intervention tests on their medications and at the same time of the day (±2 hours), and testing followed established guidelines for exercise testing in hypertensive and older patients.

6. CONCLUSIONS

Contrary to the initial hypothesis, a 12-wk combined training intervention did not improve the capacity of older adults with hypertension to achieve their $\dot{V}O_2max$ during a GXT, suggesting that irrespective of training status, $\dot{V}O_2max$ is likely to be underestimated in individuals with similar conditions taking an incremental test to exhaustion. However, it is worth noting that the magnitude of $\dot{V}O_2max$ underestimation became lower when compared to baseline, and future studies should investigate whether extending the training program (e.g., >20 weeks) could reduce the incidence of underestimated GXT tests. Notwithstanding this, our findings reinforce the use of VER as an additional tool, beyond the traditional criteria, for assessment and validation of incremental tests aiming to determine individual maximal aerobic capacity.

DECLARATIONS

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Conflicts of Interest

All authors declare no competing financial interests related to this publication. All authors declare that the study results are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Availability of data and material

Data from the present study will be made available upon request to the corresponding author.

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Table 1. Participants' characteristics (n = 12).

	Mean ± SD
Age (years)	67.3 ± 5.1
Sex	8 female / 4 male
Race	8 white / 4 black
Height (m)	1.58 ± 0.8
Body mass (kg)	77.9 ± 15.4
Waist circumference (cm)	101.1 ± 10.9
SBP (mmHg)	125.1 ± 10.4
DBP (mmHg)	70 ± 6.4
Antihypertensive medications*	
Diuretics (n)	8
ARB (n)	9
CCB (n)	1
Beta-blockers (n)	3
ACE inhibitors (n)	2

SBP 24-h ambulatory systolic blood pressure; *DBP 24-h ambulatory diastolic blood pressure. ARB angiotensin receptor blockers; CCB calcium channel blockers ACE angiotensinogen converting enzyme.*
*Number of medications per drug class is presented as frequency.

Table 2. Baseline GXT and VER outcomes in older adults with hypertension (mean ± SD).

	GXT	VER	p
$\dot{V}O_{2max}$ (l·min^{-1})	1.72 ± 0.43	1.94 ± 0.45	**0.003**
$\dot{V}O_{2max}$ (ml·kg^{-1}·min^{-1})	22.5 ± 5.6	25.6 ± 6.6	**0.003**
HR_{max} (beats·min^{-1})	148.5 ± 21.3	149.5 ± 18.7	0.712
RER	1.21 ± 0.21	1.00 ± 0.07	**0.002**
RPE	17.5 ± 1.9	16.8 ± 2.1	0.167
Duration (s)	688.8 ± 119.0	288.2 ± 25.4	**<0.001**

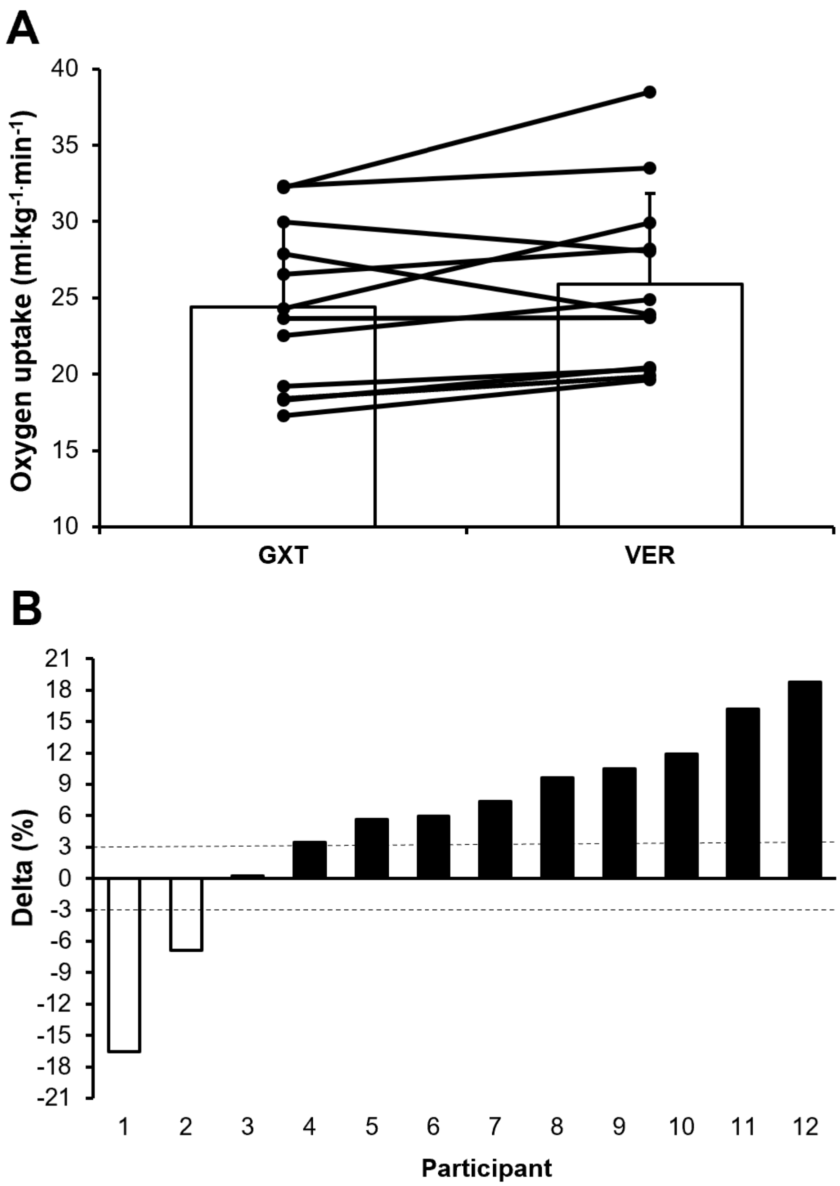
GXT graded exercise test; *VER* verification phase; $\dot{V}O_{2max}$ maximal oxygen uptake; HR_{max} maximal heart rate; *RER* respiratory exchange ratio at the end of the test; *RPE* rating of perceived exertion at the end of the test.

Table 3. Post-intervention GXT and VER outcomes in older adults with hypertension (mean ± SD).

	GXT	VER	p
$\dot{V}O_{2max}$ ($l \cdot min^{-1}$)	1.87 ± 0.44	2.00 ± 0.50	**0.045**
$\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	24.4 ± 5.5	25.9 ± 5.9	0.084
HR_{max} ($beats \cdot min^{-1}$)	149.3 ± 21.9	152.2 ± 19.3	0.103
RER	1.15 ± 0.13	1.03 ± 0.08	**0.002**
RPE	17.0 ± 2.1	17.5 ± 1.9	0.203
Duration (s)	803.8 ± 125.6	311.2 ± 24.0	**<0.001**

GXT graded exercise test; *VER* verification phase; $\dot{V}O_{2max}$ maximal oxygen uptake; HR_{max} maximal heart rate; *RER* respiratory exchange ratio at the end of the test; *RPE* rating of perceived exertion at the end of the test.

Figure 1.



A
Oxygen uptake (ml·kg-1·min-1)
40
35
30
25
20
15
10
GXT
VER
B
Delta (%)
21
18
15
12
9
6
3
0
-3
-6
-9
-12
-15
-18
-21
1
2
3
4
5
6
7
8
9
10
11
12
Participant

Figure captions

Figure 1. (A) Mean (bars) and individual (lines) maximal oxygen uptake ($\dot{V}O_2max$) responses between the GXT and the VER post-intervention. Error bars are SD. (B) Waterfall plot of the individual differences in $\dot{V}O2max$ ($\Delta\dot{V}O_2max$) between VER and GXT after the intervention period. In panel B, values within the dotted lines (gray bars) represent participants with a lower than 3% difference between VER and GXT $\dot{V}O2max$ results, whereas those above (black bars) and below (white bars) correspond to differences greater and lower than 3%, respectively.