Characteristics associated with responsiveness to isometric handgrip training in medicated hypertensives: Secondary data anaylysis

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This is a non-final version of an article published in final form in Farah, Breno Q.a,b; Forjaz, Claudia L.M.c; O'Driscoll, Jamie M.d,e; Millar, Philip J.f; Oliveira, Marcelo S.a,g; Fecchio, Rafaelb; Kanegusuku, Helcioh; Sousa, Julio C.S.c; Correia, Marilia A.b; Ritti-Dias, Raphael M.b. Characteristics associated with responsiveness to isometric handgrip training in medicated hypertensive patients: secondary data analysis. Journal of Hypertension ():10.1097/HJH.0000000000003749, April 23, 2024. | DOI: 10.1097/HJH.0000000000003749

CHARACTERISTICS ASSOCIATED WITH RESPONSIVENESS TO ISOMETRIC HANDGRIP TRAINING IN MEDICATED HYPERTENSIVES: SECONDARY DATA ANALYSIS

Short title: Factors influencing responsiveness to IHT.

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Financial Disclosure Statement: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgements: This study was also supported by 'Coordenação de Aperfeiçoamento de Pessoal de Nível Superior' (CAPES), the National Council for Scientific and Technological Development (CNPq), 'Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco' (FACEPE) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Word count: 2073 **Figures:** 2 **Tables:** 3

ABSTRACT

Objective: Isometric handgrip training (IHT) has been shown to reduce blood pressure (BP) in hypertensives. However, factors that predict responsiveness to IHT are largely unknown. The aim of this study was to investigate the patient characteristics associated with the anti-hypertensive response to IHT using a recommended statistical approach for evaluating interindividual responses. **Methods:** Data from four randomized controlled trials were joined, totaling 81 patients undergoing IHT (48.8% women; 60±11 yr) and 90 control patients (45.6% women; 62±12 yr). IHT consisted of 4x2-minute isometric contractions at 30% of maximal voluntary contraction, performed three times/week for 8-12 weeks. BP was measured at baseline and following IHT and control interventions. The interindividual variation was assessed by the standard deviation of the individual responses (SD_{ir}), and linear regression analyses were conducted to explore response predictors. **Results:** IHT significantly decreased both systolic (-5.4; 95%CI: -9.5 to -1.3 mmHg) and diastolic (-2.8; 95%CI: -5.1 to -0.6 mmHg) BPs. The interindividual variation of BP change was moderate for systolic (SD_{ir}=5.2 mmHg, 0.30 standardized units) and low for diastolic (SD_{ir}=1.7 mmHg, 0.15 standardized units). Sex, age, and body mass index were not associated with the anti-hypertensive effect of IHT. However, a higher baseline systolic BP (b=-0.467, p<0.001) and absence of dihydropyridine calcium channel blockers use (b=0.340, p=0.001) were associated with greater BP reductions. **Conclusion**: IHT reduced BP in medicated hypertensive patients regardless of age, sex, and BMI. Patients with a higher baseline systolic BP and those not prescribed dihydropyridine calcium channel blockers were more responsive to IHT.

Keywords: isometric exercise, resistance training, blood pressure, hypertension.

INTRODUCTION

Position papers from the World Hypertension League and European Society of Hypertension [1], American Heart Association [2], Australia Association for Exercise and Sports Science [3], and Hypertension Canada Committee [4] describe isometric handgrip training (IHT) as a potentially viable exercise intervention for hypertension treatment in association with medications and other exercise therapies such as aerobic and dynamic resistance training.

A recent meta-analysis demonstrated that IHT reduces systolic and diastolic blood pressures (BP) by -7.1 (-9.5 to -4.7) and -3.5 (-5.2 to -1.7) mmHg, respectively, after 8 to 12 weeks of training [5]. However, the interindividual variability to the BP-lowering effect of IHT varies a lot among hypertensive patients [6, 7], suggesting that factors related to the patients' baseline characteristics may affect this response. Along this line, some evidence suggests that patients with a lower baseline BP respond less favorably to IHT compared to those with a higher baseline BP [8, 9]. On the other hand, the use of specific classes of anti-hypertensive medications and the body mass index are not associated to the BP decrease after training [8]. Finally, the role of other potential characteristics, such as age and sex remain controversial [7-10].

Although these previous studies highlighted that some factors may affect the BP response to IHT, they had small sample sizes and an important statistical limitation as they have explored the possible predictors based on the comparison of the mean response obtained in different groups (e.g. males vs. females or normotensives vs. hypertensives). So, these studies did not analyze whether there is a real interindividual variation on the BP response to IHT before searching for the predictors. For this specific purpose, it has been recommended a two-step statistical approach [11, 12] with the calculation of the standard deviation of the individual responses (SD_{ir}) to estimate the interindividual response variability in the intervention versus the control group prior to the exploration of the potential predictors of the responsiveness.

The identification of the patients' characteristics associated with responsiveness to IHT is clinically important to identify individuals mostly like to benefit from IHT. Currently, to the best of our knowledge, no study has employed the recommended statistical procedure to analyze the interindividual response to IHT and its predictors. Therefore, the aim of the present study was to investigate the association between hypertensive patient characteristics (sex, age, body mass index, baseline BP and type of medication used) and the BP response to IHT, using an appropriate statistical approach and pooling data from four randomized controlled trials [13-16].

METHODS

Participants

The present study is a secondary analysis of data obtained from four previously published randomized controlled trials from our group [13-16]. The studies recruited patients with hypertension [13-15] and patients with peripheral artery disease [16], who were not involved in physical training programs. For the present study, only data from the patients who were receiving anti-hypertensive drugs with type or dosage maintained throughout the study period were analyzed. All study procedures were approved by the Institutional Review Boards of each institution in compliance with the Brazilian National Research Ethics System Guidelines. Written informed consent was obtained from each patient before enrollment.

Interventions

The patients allocated to the IHT groups trained three times per week for a total of 8 weeks [16], 10 weeks [15] or 12 weeks [13, 14]. In all studies, the training sessions consisted of four sets of 2-minute isometric handgrip contraction at 30% of the maximal voluntary contraction performed with a handgrip dynamometer (Zhongshan Camry Electronic Co., Ltd., Zhongshan Guangdong, China [13]; Zona Plus, Zona Health, Boise, Idaho, USA [14-16]). Rest intervals of 1-minute [13-15] and 4-minutes [16] were used between the sets. One study [16] employed unilateral training, while the other studies used bilateral training, alternating hands [13-15]. In three studies [13, 14, 16], the patients assigned to the control groups were advised to maintain their dietary habits and received usual care recommendations to increase their physical activity, while in the fourth study [15], the patients in the control group performed 30 min stretching sessions.

Blood pressure

Three studies [13, 14, 16] measured BP using the Omron HEM 742 device (Omron Healthcare, Kyoto, Japan). The assessments were performed after 10 minutes of supine rest with three consecutive measurements taken with one-minute interval between them. The measurements were taken on the right arm, using an appropriately sized cuff for the arm circumference. In the fourth study [15], a trained evaluator used a calibrated aneroid sphygmomanometer (Mikatos, Missouri, Sao Paulo, Brazil) to make the measurements on the dominant arm using an appropriately sized cuff. Measurements were taken three times in a seated position. Systolic and diastolic BPs were respectively defined as phases I and V of the Korotkoff sounds. In all studies, the BP value used in the analyses were the average of the last two measurements [17].

Clinical data

Sex, age, smoking, comorbid conditions, and clinical information were obtained through a face-to-face interview. Body mass index was calculated as body weight divided by height squared in meters. Physical activity level was obtained through the International Physical Activity Questionnaire [13-15] or through a 3-dimensional accelerometry monitor (A300; Polar Electro) [16]. Obesity (body mass index ≥30 kg/m^2), diabetes (doctor-diagnosed or use of glucose-lowering drugs) and dyslipidemia (doctor-diagnosed or use of lipid-lowering drugs).

Statistical analyses

The data were analyzed using the Statistical Package for the Social Sciences (SPSS Version 17.0 for Windows). Normality and homogeneity of variances were verified by means of the Shapiro-Wilk and the Levene tests, respectively. Continuous variables were summarized as mean, standard-deviation (SD), 95% confidence intervals (95%CI) (parametric data) or median (interquartile range) (non-parametric data), whereas categorical variables were summarized as frequency. Differences between the groups at baseline were assessed using unpaired *t*-tests or chi-square tests as appropriate.

To evaluate the effects of IHT on BP, Generalized Estimating Equations were used, followed by post-hoc pairwise comparisons using the Bonferroni correction for multiple comparisons and adjusting for studies. The individual variation of BP responses were calculated by the SD_{ir}, as previously reported [11]. SD_{ir} represents the true magnitude of the interindividual variation of BP responses adjusted for the random variation derived from biological and measurement sources, with its results being expressed in the actual measurement units (i.e., mmHg). It was calculated by the formula: $SD_{ir} = \sqrt{(SD^2_{handgrip} - SD^2_{control})}$, where $SD_{handgrip}$ and $SD_{control}$ are the SDs of BP responses (i.e., the difference between BP measured post-training and at baseline) observed in the IHT and control groups. To support the interpretation of results, SD_{IR} was also expressed in standardized units, which were calculated by dividing SD_{IR} by the standard deviation of baseline BP and interpreted according to the following cut-off points: <0.30 = low; 0.30 to 0.59 = moderate; and > 0.60 = high variation [12].

When moderate or high variations were identified, further analyses were conducted to explore potential predictors of blood pressure responsiveness to IHT. The patients who reduced their blood pressure by ≥ 4 mmHg were considered responders [18]. Crude and adjusted linear regression analyses were performed to determine whether sex, age, type of medication, body mass index, and baseline BP were predictors for changes in BP (Δ = post-training – baseline) after IHT. In the crude analysis, each variable was assessed in an individual regression analysis. Only variables with a $p<0.05$ in the crude analysis were included in the adjusted analysis. A residual analysis was performed, homoscedasticity and normal distribution was analyzed by graphical analysis. The significance level for all analyses was set at $P<0.05$ (two-tailed).

RESULTS

Data from the four studies resulted in a total of 81 patients in the IHT group and 90 patients in the control group. Baseline characteristics were similar between the groups (**Table 1)**.

IHT decreased systolic and diastolic BPs, while no change was observed in the control group (systolic BP - IHT = 133 ± 18 vs. 126 ± 17 mmHg and control = 137 ± 23 vs. 136 ± 21 mmHg, $P_{interaction}$ = 0.009; diastolic BP - IHT = 77 ± 11 vs. 74 ± 12 mmHg and control = 77 ± 11 vs. 77 ± 12 mmHg; $P_{interaction}$ = 0.012) (**Figure 1**). The interindividual variation in BP responses to IHT was moderate for systolic BP and low for diastolic BP (**Table 2).** Therefore, it was only possible to analyze true individual responses and associated factors for systolic BP. Considering responsiveness as a decrease of at least 4 mmHg in BP, 59.3% of the patients were classified as responders in the IHT group (**Figure 2**).

Multiple regression analysis revealed that patients with higher baseline systolic BP (b=-0.467, p<0.001) and those not taking calcium channel blockers (b=0.340, p=0.001) were more responsive to reductions in systolic BP with IHT. Sex, age, body mass index, and all other medication classes demonstrated no associations with systolic BP responses to IHT (p>0.05 for all) (**Table 3**).

DISCUSSION

The main findings of this study were: i) IHT reduced systolic and diastolic BPs in medicated hypertensive patients; ii) there is an evident interindividual variation in the magnitude of change of systolic BP but not of diastolic BP following IHT, iii) baseline BP and taking calcium channel blockers were associated with changes in systolic BP after IHT.

Consistent with the literature [5-8, 10, 19-21], we demonstrated a decrease in systolic and diastolic BPs with IHT of -5.4 (95%CI: -9.5 to -1.3) mmHg and -2.8 (95%CI: -5.1 to -0.6) mmHg respectively. These results are similar to the most recent meta-analysis that included 17 trials with IHT in normotensive and hypertensives participants [5]. The novelty of the current study was the analysis of the individual responses to IHT using the recommended statistical approach [11, 12], in which the different responsiveness to an intervention can only be identified when the variability of the interindividual responses to this intervention is larger than the variability obtained in a control group. Using this approach, our data revealed a moderate variability in the responses of systolic BP to IHT, but not of diastolic BP. Therefore, the analyses of responsiveness to IHT and factors highlighting responders to this type of training should only be performed with systolic BP.

In the present sample, almost 6 out of every 10 medicated patients (59.3%) demonstrated a clinically relevant reduction (i.e., greater than 4 mmHg) in systolic BP after IHT [18]. These results were higher than those observed after resistance training (51.8%) [22] and continuous aerobic training (33.3%) [23] in similar populations. Interestingly, factors that are frequently reported as associated with responsiveness to other exercise training modalities, such as sex, age, and body mass index [24, 25] were not predictors of BP responsiveness to IHT in the present study. This indicates that IHT can be used to help controlling BP in different populations, such as male, female, young, middle-aged, elderly, obese, overweight, and normal weigh patients.

As previously established with other modalities of exercise training in hypertension [26], there was a negative relationship between baseline systolic BP and BP responsiveness to IHT, indicating a greater decrease in systolic BP in patients with higher baseline BP. Despite this relationship, these results contrast with the consensus from the European Association of Preventive Cardiology (EAPC) and the ESC Council on Hypertension that suggest that IHT have more a pronounced BP-lowering effect on normotensive than hypertensive individuals [27]. The discrepancy may be associated to the fact that many studies used in these consensuses involved normotensive or unmedicated hypertensive patients, while in the current study, all patients were taking medications, which strengthens the effectiveness of IHT as an adjuvant therapy to medication for hypertension treatment.

A novel observation of the present study was that the use of calcium channel blockers was associated with lower BP responsiveness to IHT. All patients in the IHT group that were using calcium channel blockers (25% of patients) were taking the dihydropyridine subclass that is commonly recommended for hypertension treatment [28-30]. Dihydropyridine calcium channel blockers act by impeding the influx of calcium into the vascular smooth muscle cells during the membrane depolarization, preventing vasoconstriction [31]. Previous studies have shown that the decrease in BP following IHT may be attributed, at least in part, to an enhanced vascular vasodilation [32, 33]. Therefore, it is possible that the vascular effects of calcium channel blockers may limit the potential effects of IHT on vascular function. Future prospective studies are necessary to test this hypothesis in the future.

IHT has emerged as a potential tool to improve BP in the hypertensive population [1-4]. The magnitude of systolic BP reduction obtained with IHT in the present study [-5.4] (95%CI: -9.5 to -1.3) mmHg] is similar to aerobic training [-7.7 (95%CI: -9.6 to -5.8) mmHg], dynamic resistance training [-6.3 (95%CI: -9.5 to -3.1) mmHg], [-11.1 (95%CI: -18.0 to -4.3) mmHg] [5] and anti-hypertensive medication [-9.0 (95%CI: -10.3 to -7.6) mmHg [28]. Therefore, a benefit of IHT is to be implemented as an adjunct therapy to medication and other types of exercise training to assist the patients in controlling their BP levels, which is very important since many hypertensives were not well-controlled besides taking medications [34]. In addition, IHT may be very useful for patients with limitations to do other types of exercise, such as fragile elderly patients, and to those patients with limited time for exercising once the training protocol for IHT only took 11 min per session. Additionally, the main novelty of the present study was to show that patients with greater baseline systolic BP and those not taking dihydropyridine calcium channel blockers present greater BP reduction with IHT, which may indicate the inclusion of IHT in the treatment scheme for patients with higher BP and the choice of other types of exercise training in those patients using dihydropyridine calcium channel blockers.

A strength of our study is the analysis of the predictors of the BP responsiveness to IHT, considering the interindividual variability of the responses in both the intervention and the control groups [11, 12]. However, several limitations warrant discussion. Generalizations of these findings to other populations must be made with caution. Physiological variables, such as central artery stiffness, macro- and micro-vascular function, heart rate variability and other variables were not included in the study, but their analyses in the future could provide valuable insights into individual responses. Although the IHT protocols were similar among the studies included in this analysis, the intervention period ranged from 8 to 12 weeks. Finally, we were not able to determine whether similar reductions in BP would occur in measurements of ambulatory or central BP.

In conclusion, IHT reduces BP in medicated hypertensives, leading to a reduction in systolic BP regardless of sex, age, physical activity level, dyslipidemia, diabetes, and body mass index. Patients with greater baseline systolic BP present greatest systolic BP decrease following IHT, while patients taking dihydropyridine calcium channel blockers had smaller reductions in systolic BP after IHT. These findings may help to identify patients most likely to benefit from IHT as an adjunct therapy for the management of hypertension.

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TABLES

Table 1. Baseline characteristics of the patients of the isometric handgrip training (IHT) and the control groups.

	IHT (n=81)	**Control (n=90)**	**P**
Sex (% women)	48.1	45.6	0.717
Age (years old)	60 ± 11	61 ± 12	0.305
Weight (kg)	78.5 ± 14.2	77.6 ± 17.3	0.735
Body mass index (kg/m²)	29.1 ± 4.4	28.6 ± 5.4	0.460
Systolic blood pressure (mmHg)	133 ± 18	137 ± 23	0.209
Diastolic blood pressure (mmHg)	77 ± 11	77 ± 11	0.937
Physical activity (min/week) *	123 (210)	123 (179)	0.325
Dyslipidemia (%)	42.9	53.7	0.215
Obesity (%)	40.7	39.3	0.851
Diabetes (%)	12.5	27.1	0.019
Smoking (%)	16.7	19.0	0.820
Calcium channel blocker (%)	25.0	23.8	0.841
Diuretic (%)	52.5	42.9	0.216
β -blocker (%)	26.3	26.2	0.993
ACE inhibitor (%)	22.5	262	0.582
Angiotensin receptor blockers (%)	60.0	58.3	0.828

Values are presented as mean ± standard-deviation, median (interquartile range) or frequency. ACE, angiotensin converting enzyme. *IHT: n=62; Control: n=68.

Table 2. Quantification of the interindividual variation of blood pressure change after the isometric handgrip training in hypertensives.

	SD_{ir} (mmHg)	SD_{ir} standardised units	Classification
Systolic blood pressure	5.2	0.30	Moderate
Diastolic blood pressure	1.7	0.15	Low

SD_{ir} - standard deviation of the individual responses.

Table 3. Crude and adjusted regression models predicting changes (Δ) in systolic blood pressure after isometric handgrip training in mediated hypertensives (n=81).

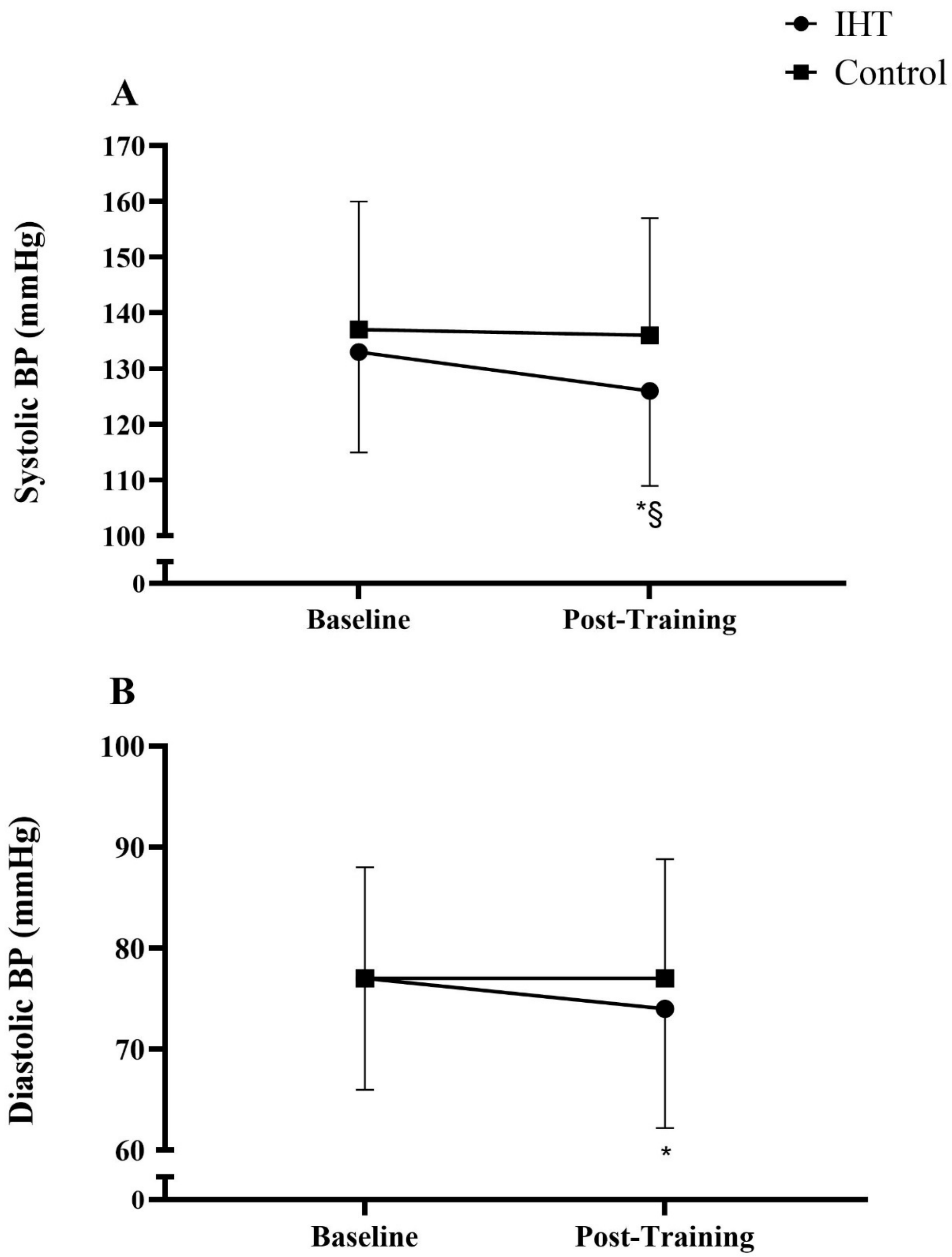
	Δ Systolic Blood Pressure					
	Crude			**Adjusted †**		
	β (EP)	**b**	**P**	**β (EP)**	**b**	**P**
Sex (ref=men)	-2.556 (2.951)	-0.097	0.389	-	-	-
Age (years old)	-0.121 (0.141)	-0.096	0.393	-	-	-
Body mass index (kg/m^2)	-0.082 (0.340)	-0.027	0.809	-	-	-
Baseline systolic blood pressure (mmHg)	-0.335 (0.075)	-0.447	<0.001	-0.353 (0.072)	-0.467	<0.001
Physical activity (min/week)	-0.012 (0.011)	-0.145	0.260			
Dyslipidemia	-1.694 (3.343)	-0.065	0.614			
Diabetes mellitus	-3.201 (4.504)	-0.076	0.504			
Use of calcium channel blocker	9.208 (3.289)	0.302	0.006	10.358 (2.898)	0.340	0.001
Use of diuretic	-2.854 (2.974)	-0.108	0.340	-	-	-
Use of β-blocker	-3.065 (3.377)	-0.102	0.367	-	-	-
Use of ACE inhibitor	-2.630 (3.565)	-0.083	0.463	-	-	-
Use of angiotensin receptor blockers	0.599 (3.049)	0.022	0.845	-	-	-

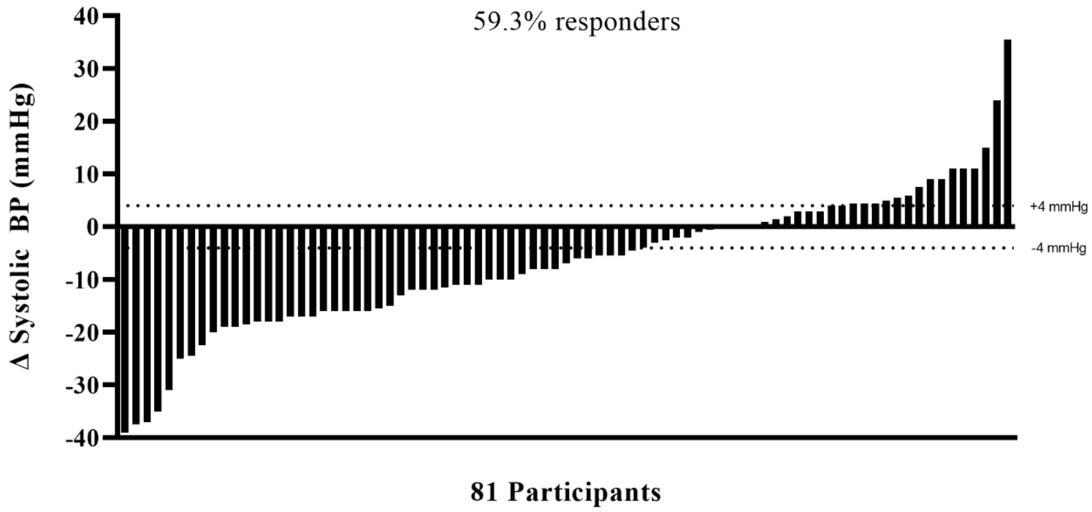
†F = 17.144, $P<0.001$; r = 0.555; $R^2 = 0.308$; R^2 adjusted = 0.290. BP, blood pressure; ACE,angiotensin converting enzyme; β (EP), regression coefficient (error standard); b, standardized coefficients.

FIGURE LEGENDS

Figure 1. Effects of isometric handgrip training on blood pressure (BP) adjusted for the studies. * Significantly different from baseline ($p<0.05$); § Significantly different from the control group at the same time point ($p<0.05$).

Figure 2. Individual changes (Δ) in blood pressure (BP) after isometric handgrip training.


IHT
Control
A
Systolic BP (mmHg)
170
160
150
140
130
120
110
100
0
*§
Baseline
Post-Training
B
Diastolic BP (mmHg)
100
90
80
70
60
0
*
Baseline
Post-Training


59.3% responders
Δ Systolic BP (mmHg)
40
30
20
10
0
-10
-20
-30
-40
+4 mmHg
-4 mmHg
81 Participants