Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis

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Objective To examine the longitudinal effects of isometric handgrip (IHG) exercise training on blood pressure using hierarchical linear modeling.

Methods Data from 43 participants who were medicated for hypertension at the time of training were amalgamated from three previous investigations. In each study, IHG training was completed 3 days/week for 8 weeks at 30% of maximal voluntary contraction and resting blood pressure was assessed at twice-weekly intervals throughout.

Results Hierarchical linear modeling analysis revealed a linear pattern of blood pressure decline over time with estimated reductions of 5.7 and 3 mmHg reductions in systolic and diastolic pressure, respectively. Participants with higher initial systolic pressure showed greater rates of blood pressure decline ($r = -0.67$), inferring that individuals with higher blood pressure stand to achieve greater benefits from this method of training.

Conclusions These results provide further evidence that IHG training lowers resting blood pressure among persons medicated for hypertension. Blood Press Monit 12:307–314 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Hypertension is estimated to affect nearly 30% of the global population [1,2]. It is a major risk factor contributing to cardiovascular and kidney disease and costs the global economy billions of dollars per year [2]. Hypertension is commonly treated with lifestyle modification (e.g. diet, exercise) and use of pharmacological agents. Pharmacological therapies, however, provide adequate control of blood pressure for only about 53% of individuals with hypertension [3]. As such a large proportion of people with hypertension are unable to control their blood pressure with medication, research identifying effective lifestyle modifications that can be used in conjunction with pharmacological treatments is essential [4].

One method of treatment that has shown some promise in lowering blood pressure is isometric handgrip (IHG) training. This form of exercise has repeatedly demonstrated reductions in resting blood pressure in both individuals with normotension and individuals with hypertension of up to 19, 15, and 11 mmHg in systolic, diastolic, and mean arterial pressure, respectively [5–8]. Following these results, researchers have sought to determine mechanisms responsible for the attenuations in resting blood pressure. To date, these investigations have examined muscle sympathetic nerve activity, sympathovagal balance, and antioxidant formation as potential causes for the observed training effect [6–8].

Continued research examining the potential mechanisms responsible for the attenuations in blood pressure is important to understand how and why the effect occurs. A more thorough examination and description of the basic effect, however, may still be required for several reasons. One reason for further examination of the IHG blood pressure reduction effect is that the effect does not appear to be uniform across or within studies. For example, some individuals have shown dramatic reductions in blood pressure whereas others have shown subtle increases. A second reason is that studies carried out thus far have utilized small convenience samples of participants. Small sample sizes compromise the power of an investigation (i.e. increased risk of Type I error) and reduce one's ability to generalize findings. Studies involving a greater number of participants would allow sufficient power to detect meaningful effects and generate greater confidence in the extrapolation of results beyond the small study samples themselves.

Studies on IHG training to date are also limited in at least one key aspect. Specifically, all of these studies have been designed to analyze their data as pre–post comparisons. This approach is problematic because variations in blood pressure can occur in the presence of many transient stimuli and single pre–post comparisons may not accurately account for the volatility and episodic nature of arterial pressure. The steps undertaken to diagnose hypertension provide an illustration of the problem at hand. According to Chobanian et al. [2], diagnosis of hypertension should not be made unless two or more measurements have been taken over a minimum of two visits. Therefore, to align with this diagnostic criterion, posttest measurements of blood pressure in IHG training studies should be taken on at least two occasions.

One way to overcome the limitations of a pre–post design is to examine changes in blood pressure as they occur over time (i.e. throughout the training period). Such an approach is possible with regular monitoring (i.e. tracking) of blood pressure and the application of multilevel linear regression modeling techniques. Multilevel modeling also allows for greater insights into individual changes in blood pressure as they may occur over time within persons, rather than treating study participants' scores as homogeneous and examining changes in mean scores from pretreatment to posttreatment. Specifically, multilevel modeling allows for estimation of a regression model indicating change over time for each individual in the study and examination of characteristics of the individuals (e.g. age, sex) that may have an impact on those effects.

The purpose of this study was to examine the effects of 8 weeks of IHG training on resting blood pressure through the use of multilevel modeling analyses. On the basis of previous research showing general reductions in blood pressure after IHG training, it was hypothesized that systolic blood pressure (SBP) and diastolic blood pressure (DBP) scores would show a decreasing linear trend over the course of training. It was also hypothesized that there would be interindividual differences in training effects as reflected by significant variations in the slopes representing trajectories of blood pressure change within persons over time.

Methods

Participants

Data from medicated men (31) and women (12) with hypertension aged 38–77 years (66 ± 1.02) were consolidated for analyses from three methodologically linked studies carried out in the same laboratory over a period of 4 years [7,9,10]. All participants were volunteers recruited from the community who completed identical sets of questionnaires to determine their state of health before participation. Individuals indicating congestive heart failure or physical limitations preventing IHG exercise were excluded from each study. During pretesting and before the onset of the IHG training protocol, each medicated participant with hypertension had a baseline resting seated blood pressure ofZ 130 and Z 80 mmHg for SBP and DBP, respectively. At the time of study (i.e. before recruitment and throughout the training), each participant was undergoing pharmacological treatment for hypertension and taking at least one of the following: angiotensin-converting enzyme inhibitor, b-blocker, calcium channel blocker, or diuretic medication. Participants' medications were monitored 2 weeks before and throughout each study. No alterations to participant medication regimen were reported. The research and scientific ethics board approved each investigation, and informed written consent was obtained from each participant before study participation.

Experimental protocol

All participants completed IHG training 3 d/week for 8 weeks. Twenty-seven participants completed unilateral IHG training whereas 16 completed bilateral training. Training was conducted with the aid of a programmed, digital hand dynamometer (CardioGrip Corp, Boise, Idaho, USA), similar to that seen in Fig. 1. Each training set consisted of a maximum voluntary contraction of the hand flexor muscles, followed by four 2-min sustained submaximal contractions completed at 30% maximal voluntary contraction (MVC). Participants undertaking bilateral training performed a single maximum contraction for each hand, whereas those in the unilateral training condition performed two maximum contractions with their dominant hand only. Participants involved in bilateral training were afforded 1 min of rest between submaximal contractions, whereas participants engaging in unilateral training had 3-min rest breaks between submaximal contractions.

The handgrip device was programmable and used to calculate MVC before each training session. The device itself provided instructive text prompts via liquid crystal display for each step of the training session as well as visual (liquid crystal display pressure gauge) and audible signals for feedback to ensure compliance with the

Fig. 1

Digital isometric handgrip trainer (image used with permission of Zona Health).

training intensity protocol (i.e. maintaining a contraction of 30% MVC). Trained research assistants supervised two of the weekly training sessions at the laboratory, while participants carried out the third session independently at home. All participants and assistants completed training log books recording the date of exercise, their MVC for each training session, and a summary compliance score provided by the handgrip device indicating the percentage of time during which the participant had maintained Z 30% MVC throughout the 2-min contraction. For the latter measure, in all cases, scores in excess of 90% were recorded for each of the 16 training sessions.

Blood pressure measurement

Participants underwent seated blood pressure measurements before each of their twice-weekly supervised training sessions. Blood pressure was taken following 10 min of isolated, seated rest by either a standard sphygmomanometer or an automated acquisition system (Dinamap Pro 100, Critikon Corp, Tampa, Florida, USA). The method of blood pressure measurement was consistent for each participant for the duration of the study protocol. Participants were directed to keep both feet on the floor and their left arm was maintained at approximately heart level during rest. Blood pressure was measured a minimum of three times during each visit, with each measurement separated by 1 min. The average blood pressure was calculated for analysis. Baseline pretest and posttesting supine blood pressure measurements were also completed but not used for analysis in this investigation. All participants were familiarized with the environment and testing procedures through a laboratory orientation and habituation session before the start of each study.

Data analysis

The primary outcomes in this study were changes in resting SBP and DBP as a result of IHG training. Changes in resting blood pressure over time were analyzed using hierarchical linear modeling procedures (HLM, version 6.02, Scientific Software International Inc., Lincolnwood, Illinois, USA) [11]. HLM allows examination of all data points for each participant and provides an indication of the direction and trajectory of change within and between participants. This procedure also has the advantage of allowing interpretation of models showing the effects of training while allowing both the intercepts and slopes to vary across individuals. In this case, a two-level model was utilized for each of SBP and DBP. The level 1 model represented the repeated assessments (i.e. the SBP and DBP scores at 16 assessments over 8 weeks of training) that were nested within the participant at level 2. At the participant level, we also included sex, age, and type of training (i.e. unilateral or bilateral) as predictors of change in blood pressure. All data are expressed as mean ± SE, unless otherwise indicated. Results were considered statistically significant at $P < 0.05$.

Results

Means and standard deviations describing average SBP and DBP for the sample across the 16 measurement points (8 weeks of training) are presented in Table 1. Cursory examinations of these data indicate a linear trend showing progressively lower scores on both measures over time, with substantial between-person variability (SE) at each time point.

Systolic blood pressure

Results of the HLM analyses of SBP are summarized in Table 2. The first step in assessing change in blood pressure over time involved fitting an empty model (Model 1A), that is, the variability in the dependent variable: SBP was modeled to provide an indication of how much of the overall variability in the SBP scores was at the between-person level and the within-person level. Results of that model indicated that 46.49% of the overall variance was at the between-person level and 53.51% was within persons.

The next step involved fitting a simple regression model (Model 1B) accounting for the linear effect of time with the intercept and slope fixed (as in a simple linear regression). As expected, the linear effect of time was significant. As shown in Table 2, the intercept value indicated an average systolic pressure of 139.15 mmHg at the onset of training which decreased, on average, at a rate of −0.32 mmHg per session over the course of 16 measurement occasions.

The third step of the process involved fitting a hierarchical linear model (Model 1C) that kept the slope for time fixed but allowed the intercept of each

Table 1 Longitudinal resting seated blood pressure across 8 weeks (16 twice-weekly sessions) of isometric handgrip training among 43 individuals medicated for hypertension

Measurement	SBP (mmHg)	DBP (mmHg)
1	139.00 ± 2.50	79.48 ± 1.90
2	139.53 ± 2.23	79.88 ± 1.65
3	141.68 ± 2.52	80.13 ± 1.76
4	138.07 ± 1.88	77.76 ± 1.76
5	137.43 ± 2.17	77.47 ± 1.76
6	136.39 ± 2.11	76.90 ± 1.51
7	136.97 ± 2.03	79.56 ± 1.71
8	137.98 ± 1.87	77.57 ± 1.53
9	133.69 ± 2.20	77.09 ± 1.67
10	134.21 ± 1.82	77.07 ± 1.50
11	134.19 ± 1.85	76.13 ± 1.65
12	137.71 ± 2.01	76.34 ± 1.61
13	132.21 ± 2.57	76.75 ± 2.36
14	138.13 ± 1.77	77.05 ± 1.40
15	135.19 ± 1.80	77.08 ± 1.78
16	135.11 ± 1.53	77.03 ± 1.59

All data represented as mean ± SE in mmHg (millimeters of mercury). DBP, diastolic blood pressure; SBP, systolic blood pressure.

participant to vary randomly. Results of that analysis revealed the variance component for the random intercept was significant [$t = 73.01$, $w^2(42) = 545.86$, $P < 0.001$]. This result indicates that the intercepts for SBP were not the same across participants. These results are presented graphically in Fig. 2a, where the lines represent the change trajectories of individual cases with the slopes constrained.

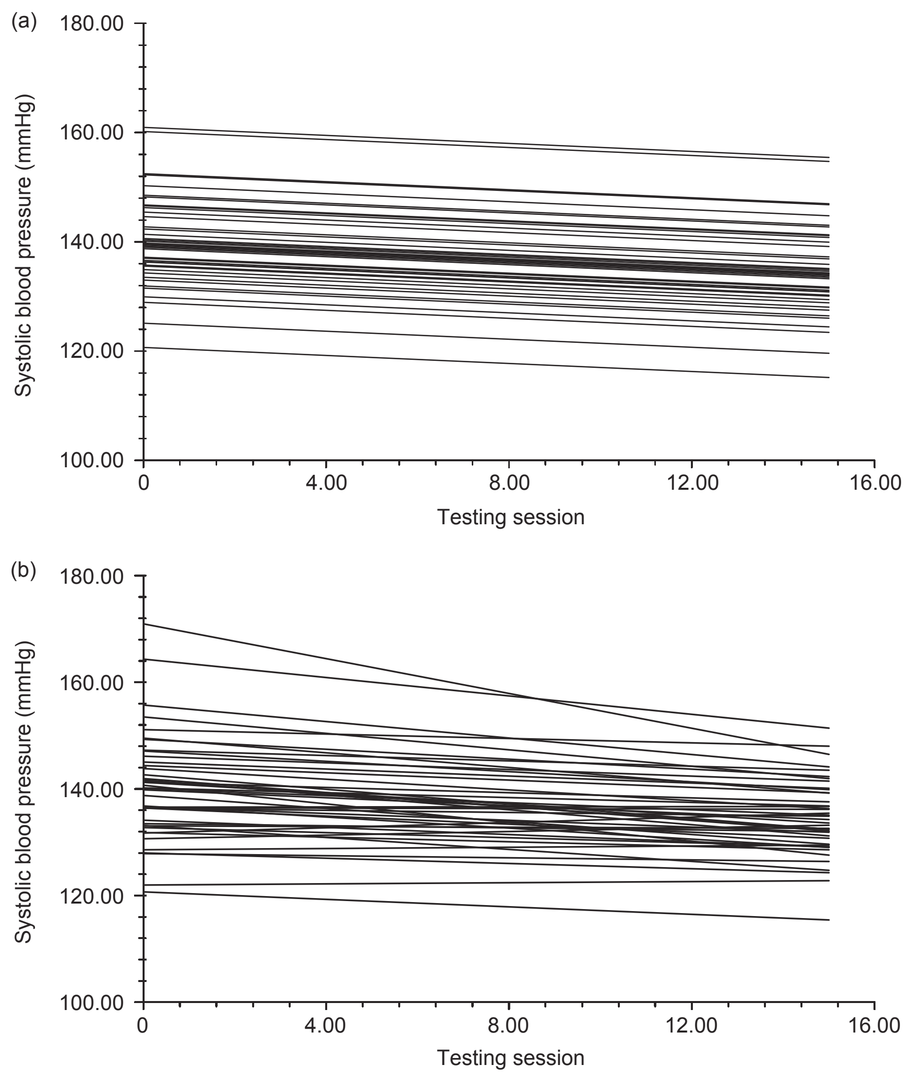
Table 2 Hierarchical linear modeling analysis of change in systolic blood pressure over 8 weeks of isometric handgrip training among 43 individuals medicated for hypertension

	Parameter	Coefficient	SE	t-ratio
Model 1A	Intercept	137.27	1.35	101.67 **
Model 1B	Intercept (fixed)	139.15	0.98	141.94**
	Slope (fixed)	−0.32	0.11	−2.90*
Model 1C	Intercept (random)	139.99	1.75	79.61**
	Slope (fixed)	−0.36	0.11	−3.26*
Model 1D	Intercept (random)	140.11	1.74	80.48**
	Slope (random)	−0.38	0.11	−3.52*

SE, standard error.
*$P < 0.05$.
**$P < 0.01$.

The fourth step involved fitting a model that allowed both the intercept and slope to vary randomly across individuals (Model 1D). Those results revealed that the variance components were significant for both the random intercept [$t = 111.65$, $w^2(42) = 267.32$, $P < 0.001$] and the slope [$t = 0.23$, $w^2(42) = 78.36$, $P < 0.001$], indicating that individuals differed in both their baseline intercepts and their trajectories of change over time. These results are illustrated in Fig. 2b, where the lines represent the change trajectories of individual

Fig. 2



(a) Random intercepts model for systolic blood pressure (Model 1C). (b) Random intercepts and slopes model for systolic blood pressure (Model 1D).

cases with the slopes free to vary. It is evident at the individual case level (represented by single lines) that some participants experienced SBP declines whereas other showed no differences or increases over time.

The final random intercept, random slope model was the most parsimonious, producing an estimated intercept of 140.11 and slope of −0.38, resulting in an estimate in overall change of −5.7 (−0.38*15 intervals) during the 8-week study. Results of the random intercept, random slope model also revealed that the correlation between the intercept and slope was $r = -0.67$, suggesting a strong relationship between the intercept and slope whereby individuals with higher baseline systolic pressure showed greater negative acceleration in slope or more dramatic rates of change.

Further steps in the analysis process were also undertaken to examine whether fitting a quadratic (curvilinear) function to the level 1 data improved the model fit and to examine demographic and procedural factors at level 2 that may have affected the results. The results of the model including the quadratic function showed there was no significant effect ($P > 0.05$) for the quadratic term. The effects of sex, age, and whether the isometric training was carried out unilaterally or bilaterally, assessed at the between-person level, were found to be non-significant ($P > 0.05$).

Diastolic blood pressure

The steps undertaken in the analysis of the DBP data were identical to those carried out for SBP. The findings at each step in the analysis process were largely consistent with the analysis of SBP (see Table 3). As shown in Table 3, the intercept value indicated an average diastolic pressure of 79.16 mmHg at the beginning of training, which decreased, on average, at a rate of −0.20 mmHg per session over the course of 16 measurement occasions. In the third model, the variance component allowing the intercept to vary randomly was significant [$t = 70.35$, $w^2(42) = 1453.58$, $P < 0.001$], showing differences across individuals. Results of the random intercept, random slope model (Model 2D) revealed that the variance components were significant for both the random intercept [$t = 75.08$, $w^2(42) = 475.58$, $P < 0.001$] and the slope [$t = 0.05$, $w^2(42) = 65.15$, $P < 0.05$], indicating that individuals also differed in both their baseline intercepts and their trajectories of change in DBP over time. The correlation between the intercept and slope wasr = −0.26, revealing a trend toward participants with higher intercepts having a slightly more accelerated change in diastolic pressure over time. Noteworthy differences between the analyses included a greater proportion of total variance in DBP at the within-person level (71.22%). In each step of the model, the coefficients for intercepts and the slopes were also considerably smaller – the latter indicating small changes in diastolic pressure over time. Results of the analyses are summarized in Table 3 and shown graphically in Fig. 3a and b.

Table 3 Hierarchical linear modeling analysis of change in diastolic blood pressure over 8 weeks of isometric handgrip training among 43 individuals medicated for hypertension

Model	Parameter	Coefficient	SE	t-ratio
Model 2A	Intercept	77.70	1.29	60.44
Model 2B	Intercept (fixed)	79.16	0.80	99.16**
	Slope (fixed)	−0.20	0.70	−2.99*
Model 2C	Intercept (random)	79.14	1.38	57.53**
	Slope (fixed)	−0.19	0.06	−3.30*
Model 2D	Intercept (random)	79.17	1.37	57.64**
	Slope (random)	−0.20	0.06	−3.31*

SE, standard error.
*$P < 0.05$.
**$P < 0.01$.

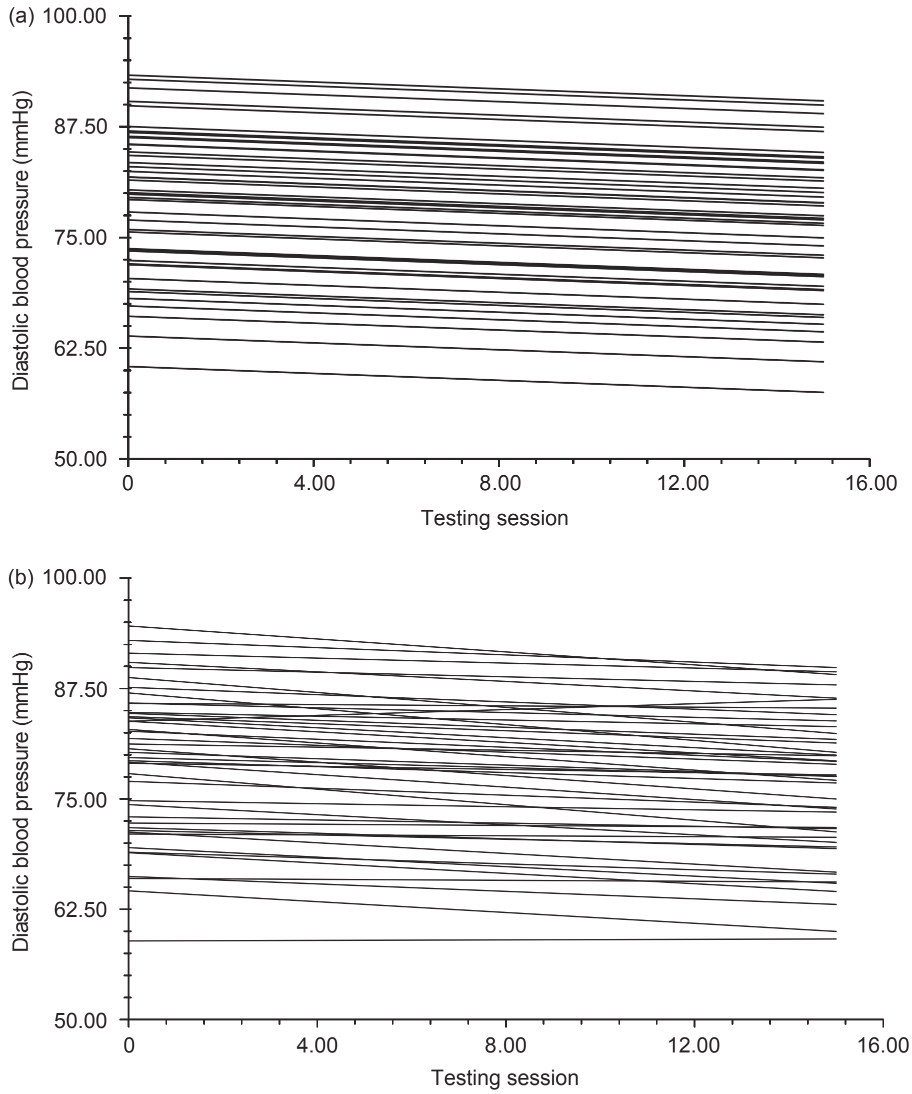
As was evident in the HLM analysis of the SBP data, the final random intercept, random slope model for diastolic pressure was the most parsimonious. The estimated intercept was 79.17 with a slope of −0.20, providing an estimate in overall change of −3.00 (−0.20*15 intervals) during the 8-week study.

Discussion

In a sample of 43 men and women aged 38–77 years, 8 weeks of IHG training resulted in significant reductions in both systolic and diastolic resting blood pressures over time. Consistent with the hypothesis, there was a negative linear trend in resting blood pressure over time that was more pronounced for systolic than DBP. Reductions were most pronounced among participants with higher baseline blood pressure values. Changes in blood pressure were not associated with sex, age, or mode of IHG training (unilateral vs. bilateral).

This study contributes to a growing body of literature showing promising effects of IHG training for people with hypertension through the use of hierarchical linear modeling techniques. HLM provides a novel and improved set of analytic techniques for studying change over time in clinical research designs [12,13]. One way in which the HLM analysis was useful in this study was in establishing that changes in blood pressure that occurred over 8 weeks of training showed a linear trend. This overall pattern of results is based on a greater amount of data collected over time, which may provide a more accurate indication of change over time than simple pre–postcomparisons. Concerns over single pre–post assessments arise when one considers that blood pressure readings may be inflated at the outset of a study owing to nervousness or excitement arising from exposure to a novel laboratory or training setting. It is thus conceivable that resting blood pressure could have undergone a normal reduction (e.g. regression to the mean) shortly after the study began. In addition, people may experience anxiety or concerns over completing the study and

Fig. 3



(a) Random intercepts model for diastolic blood pressure (Model 2C). (b) Random intercepts and slopes model for diastolic blood pressure (Model 2D).

forecast that they will not gain important health benefits from training when attending their final testing session, resulting in increased blood pressure at the time of post-testing. In the former case, observed pre–post effects may be misleadingly pronounced. In the latter, pre–post effects may be misleadingly blunted. Consequently, potential errors in the prestudy and poststudy arterial pressure measurements make it difficult to ascertain training effects and may contribute to false negative and positive results. The interested reader can refer to Table 1 where it is evident that the pre–post (i.e. measurements 1–16) group reductions in systolic and DBP were 3.89 and 2.45 mmHg, respectively, which are slightly smaller than the estimates provided by the regression models for the 8 weeks (estimated D systolic = –5.70 and estimated D diastolic = –3.00). The discrepancy in these results provides evidence that pre–postcomparisons alone may underestimate the attenuations in blood pressure associated with this form of exercise training.

Examination of the linear effect of changes in blood pressure that were observed over time in these data also helps rule out an interpretation that changes in blood pressure are attributable to a regression to the mean, which would be illustrated in a negatively decelerating growth curve. The linear (vs. curvilinear) trend also indicates that IHG training attenuates resting blood pressure over time, but that 8 weeks of training is insufficient to produce maximal training responses. It is currently unknown whether continuation of training would result in further reductions in blood pressure.

Although a linear trend effect could not continue indefinitely with further training, studies of longer duration (>8 weeks) are required to establish the pattern of change in blood pressure that would occur with maintenance of a regimen of IHG training.

The HLM analysis was also illustrative in determining that the trajectories (i.e. slopes) indicating changes in blood pressure were not uniform for all participants. These findings were anticipated and are consistent with the larger body of evidence indicating that physiological adaptations to exercise are variable across individuals [14]. Although none of the person-level variables assessed in this study (i.e. sex, age, type of training) showed any relationship with blood pressure reductions, future research utilizing HLM analysis may shed light on person-level factors that may predict participant characteristics indicating who might stand to benefit the most from IHG training.

The HLM findings did reveal that the intercepts and slopes were highly correlated for SBP and moderately correlated for DBP. In other words, the participants with the greatest response to training possessed the highest blood pressure values at the start of training. This is the first study to accurately detail the enhanced benefits for individuals with higher baseline blood pressure by examining a large sample of participants medicated for hypertension with varying levels of resting blood pressure at the outset of the study. It is possible that individuals with extreme hypertension may experience the greatest benefits from IHG.

Whereas this study advances knowledge empirically, the findings also have important clinical implications for the treatment of people with hypertension. Overall, we determined rates of change indicating −0.38 and −0.20 mmHg reductions per session for SBP and DBP, respectively. These rates correspond to reductions of 5.70 mmHg SBP and 3.00 mmHg DBP over the course of 8 weeks. Reductions in DBP of this order correspond to 15% decreases in risk for stroke and transient ischemic attack and 6% reduction in coronary artery disease risk [15].

According to the results of a recent meta-analysis, dietary modification and aerobic exercise are associated with improvements in SBP of 5.9 mmHg and 3.4 mmHg and DBP reductions of 4.2 mmHg and 2.4 mmHg [16]. These values are in a similar range compared with the 5.70 mmHg SBP and 3.00 mmHg DBP reductions demonstrated in this investigation. The extent to which IHG may be used effectively in concert with other therapies requires investigation. Nevertheless, it would appear that IHG training provides similar reductions to those elicited by exercise and dietary modification strategies that are currently recommended.

Although the results of this study provide novel evidence in support of IHG training effects in hypertension, there are a number of limitations that should be acknowledged. Among these is the fact that our data do not allow for comparisons to participants in a control or sham-training condition. Therefore, placebo effects associated with the training interventions cannot be entirely ruled out. Though no differences were seen between unilateral and bilateral training protocols, between men and women, and across different ages, the sample size for such comparisons was also very small and should be considered another potential limitation.

Despite these caveats, a fact that should not be overlooked is that IHG may offer similar benefits to those offered by aerobic endurance exercise with less time commitment. The protocol utilized in this investigation required only around 35 min of training per week, with half of that time allocated to rest between contractions. Equally important is that the IHG training benefits were evident in participants who were already medicated for hypertension. Whether IHG training produces only additive effects for hypertension treatment beyond medication, interacts with some medications and not others, or has promise as a substitute for pharmacological treatments requires further investigation. Continued research on IHG training will hopefully detail the mechanism(s) responsible for these training adaptations and offer alternative methods of hypertension treatment. In addition to research exploring and determining mechanisms, we acknowledge that a multicentered, randomized-controlled trial is needed to adequately assess the efficacy of IHG training for blood pressure reduction.

In conclusion, our findings provide evidence of a negative linear trend showing reductions in resting blood pressure over the course of 8 weeks of IHG training. The magnitude of blood pressure reduction was positively associated with blood pressure values at the onset of training, with the most severe cases of hypertension exhibiting the greatest responses to training. The results demonstrate IHG training for 8 weeks is associated with a reduction in resting blood pressure similar to that elicited from endurance exercise or dietary modifications. Continued research on IHG training is required to establish whether short-term changes in blood pressure can be sustained with further training and what mechanisms are associated with the effects.

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