

Isometric Exercise and Blood Pressure: 12 Weeks of Training and Detraining in the Elderly

Benjamin D.H. Gordon, PhD, CEP^{1,6}, Emily W. Zacherle, MS^{2,6}, Sarah Whitmire, MS², Larry J. Leamy, PhD³, Jeanette M. Bennett, PhD⁴, Joseph S. Marino, PhD², Adam M. Reitzel, PhD³, Yvette Huet, PhD², Ian L. Swaine, PhD⁵, Daniel S. Baddeley-White, PhD⁵, Reuben Howden, PhD²

ABSTRACT

Background: Elderly people are particularly affected by rising systolic blood pressure (SBP). We hypothesized that resting blood pressure (RBP)-reducing isometric exercise training (IET) can be delivered in a group setting with older adults.

Methods: Participants (63–88 years; N = 19) completed IET at 30% maximum voluntary contraction, 3 days a week for 12 weeks. RBP was measured weekly throughout, plus 6 weeks posttraining. Control participants did not engage in IET (N = 5). Changes in RBP were assessed using a 2-way repeated-measures analysis of variance.

Results: IET induced significant reductions in SBP (−10.5 mmHg; $P < 0.05$), but SBP also declined unexpectedly in the control group (−4.5 mmHg; $P < 0.05$). Diastolic blood pressure declined in the IET group only (−4.7 mmHg; $P < 0.05$). There were no significant differences between groups for SBP or diastolic blood pressure ($P > 0.05$). At 6 weeks posttraining, SBP was still 9.4 mmHg below baseline in the IET group only. A unique finding was that the clinically significant RBP reductions persisted for 6 weeks after IET.

Conclusions: Handgrip IET may be an effective antihypertensive intervention, which persists for several weeks in older adults, even when training ceases. *J Clin Exerc Physiol.* 2023;12(1):3–11.

Keywords: hypertension, isometric exercise training, aging

INTRODUCTION

It is generally accepted that resting blood pressure (RBP) increases with age (1). Data from the Framingham Heart Study across a 30-year period have shown that both systolic blood pressure (SBP) and diastolic blood pressure (DBP) will rise over the lifespan, albeit with a unique pattern for each measure, an inevitable consequence of aging, resulting in hypertension (HTN) in a high proportion of individuals (2). The inverse relationship between exercise and primary

prevention, treatment, and control of HTN is now well established (3). Despite efforts to deliver effective interventions for HTN management, patient adherence rates are low, and a half to two-thirds of diagnosed HTN cases lack effective blood pressure (BP) control (4–6). Moreover, from 2009 to 2014, there was no significant improvement in HTN management (7). HTN control, related to stroke reduction rates, is now a global target of the World Health Organization (8). New HTN management strategies to improve

¹Department of Health and Human Development, University of Pittsburgh, Pittsburgh, PA 15261, USA

²Department of Applied Physiology, Health and Clinical Sciences, UNC Charlotte, Charlotte, NC 28223, USA

³Department of Biological Sciences, UNC Charlotte, Charlotte, NC 28223, USA

⁴Department of Psychological Science, UNC Charlotte, Charlotte, NC 28223, USA

⁵School of Human Sciences, University of Greenwich, London SE10 9LS, UK

⁶Co-first authors with equal contribution

Address for correspondence: Benjamin D.H. Gordon, PhD, Department of Health and Human Development, University of Pittsburgh, 32 Oak Hill Court, Pittsburgh, PA 15261; e-mail: bgordon@pitt.edu; ORCID: 0000-0002-1976-3134.

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adherence rates and prevent complications related to cardiovascular health are needed. Such HTN management strategies must be as immune to health care disparities as possible, especially when considering that lower income is associated with poorer HTN control (9). This problem is especially acute in older populations since HTN prevalence increases to over 50% after 60 years of age, exacerbating the risk of severe cardiovascular outcomes. Prominent features of HTN in the elderly include elevated SBP and wide pulse pressure (10–12). Therefore, an intervention strategy that successfully reduces SBP in aging adults without imposing a significant physiological burden would inherently decrease cardiovascular risk.

Isometric exercise training (IET) lowers RBP in prehypertensive and normotensive individuals at various ages (see (13,14) for review and meta-analysis, respectively). Several studies have assessed the effects of bilateral leg IET in young, normotensive subjects (15–18). Moreover, significant reductions in SBP, DBP, and mean arterial pressure (MAP) have been seen in less than 5 weeks of training at 20%–30% maximum voluntary contraction (MVC) (15,17), demonstrating the efficacy of IET over short training periods in young subjects. However, there is a paucity of data regarding the effect of extended IET programs on the elderly and very limited information about the effects of detraining on RBP. After 5 weeks of handgrip IET, reductions in RBP were no longer evident after 4 weeks of detraining (19). It is unclear if posttraining reductions in RBP are more persistent when the training period is longer.

In sedentary, prehypertensive middle-aged men using bilateral leg IET, reductions in MAP, SBP, and heart rate (HR) after 8 weeks of training at 14% MVC were found (20). Other studies used handgrip IET in young and older normotensive subjects and found equivalent reductions in RBP (19,21–24). Moreover, in older pharmacologically controlled HTN patients (51–74 years), SBP, DBP, and MAP were reduced after 10 weeks of IET at 30% MVC, 3 days per week. SBP decreased approximately 8 mmHg, with 83% of those in the training group experiencing a significant reduction in DBP of ≥ 2 mmHg ($P < 0.05$) (25).

Little is known about RBP adaptations to longer IET programs in the elderly or how long RBP adaptations persist during prolonged detraining. We hypothesized that 12 weeks of handgrip IET in an elderly population would reduce RBP, and any RBP reduction would be lost after 6 weeks of detraining.

METHODS

Participants were recruited from the Tyvola Senior Center in Charlotte, North Carolina, and gave written informed consent to participate (Table 1). The University of North Carolina at Charlotte Institutional Review Board approved the study. Inclusion criteria required that participants were ≥ 55 years of age, able to perform maximum handgrip contractions, and had a RBP of less than 160/100 mmHg. All participants were encouraged to continue their normal exercise routine, diet, and medications throughout the study but

TABLE 1. Participant demographics.

	IET	Control
Female (N)	14	2
Male (N)	5	3
Age (y)	73.3 $\pm$ 6.7	73 $\pm$ 8.6
Height (cm)	168.6 $\pm$ 0.1	172.5 $\pm$ 0.1
Mass (kg)	82.4 $\pm$ 18.9	93.6 $\pm$ 10.9
BMI (kg·m ⁻²)	28.9 $\pm$ 6.1	31.6 $\pm$ 4.8
HTN (N)	15	5
Diabetes (N)	4	1
COPD (N)	4	0

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HTN = hypertension; IET = isometric exercise training. Values are mean $\pm$ SD; No significant interactions were found for any variable assessed (all $P > 0.05$)

reported any unavoidable alterations (e.g., changes in medications). Participants consumed only water 2 hours before any testing or exercise.

Procedures

It was our intention to randomize recruited participants to either handgrip IET classes, held at the center, 3 days per week, or control (CON). Initial group allocation (IET and CON) was completed using a random number generator in Excel. However, due to participant enthusiasm for IET, many participants insisted on being placed in the IET group as a condition of their participation, and therefore, true randomization was not possible in the present study.

After an orientation and familiarization session, subjects began IET. Weekly premeasure questionnaires were given to account for caffeine use, fasting, and medication use before each measurement. A Physical Activity Readiness Questionnaire (PAR-Q) was administered every 6 weeks to account for any changes in diet, medications, physical activity, and/or health status.

RBP and HR Measurements

An automated BP monitor (American Diagnostic Corporation Advia[®]9000, Hauppauge, New York) was used to measure weekly RBP and HR after 15 minutes of seated, quiet rest at the same time of day, in a temperature-controlled room (26). RBP measurements were taken from participants' nondominant arm, with the arm supported and at heart level. Measurements were made twice in one sitting, separated by 5 minutes. An average of the 2 values was used as the subjects' weekly RBP and HR. A third measurement was made if the first and second measurements differed by $\geq 20\%$. For 2 weeks before the start of IET classes, RBP and HR were measured 3 days per week, and the average was used to establish baseline RBP and HR.

MVC Assessment

A Takei digital handgrip dynamometer (T.K.K 5401; Takei Scientific Instruments CO., LTD., Tokyo, Japan) was used to measure participants' MVC once every 6 weeks. Participants performed MVCs seated, with both hands (separately), elbow bent, with arm and hand resting in their lap while holding the dynamometer. All MVCs and handgrip IETs were performed in this position. Participants performed at least 3 (no more than 5) 2-second MVCs, each 120 seconds apart, which did not differ by >20%. Before each exercise session, the IET group measured their own MVC (dominant hand only) using a personal handgrip dynamometer (Camry 200lb Handgrip Dynamometer, City of Industry, California). Participants used this same dynamometer throughout the study. After determining their MVC, a notecard was provided with their 30% MVC workload to reference during exercise sessions.

Exercise Classes

IET group participants exercised 3 days per week (Monday, Wednesday, and Friday). Participants performed 2-minute contractions at 30% MVC, using their dominant hand, completing 4 reps, with 1 minute of rest in between. Research staff provided support and oversaw participants during exercise to ensure (i) they were maintaining the appropriate workload for all contractions and (ii) not experiencing undue discomfort.

Detraining

For the first 6 weeks following training cessation, RBP was monitored weekly (weeks 12–18). On the 12th week following training cessation, a final RBP measurement was recorded in 13 IET group participants and 5 CON participants (week 24).

Statistical Analysis

Our primary expectation was that BP (especially SBP) in the IET group would decline over the first 12 weeks compared with the CON group. To test this, we used a repeated-measures analysis of variance (ANOVA) with group and week as factors. Originally, we used sex as a factor in the model, but it was found to be nonsignificant and was eliminated. The ANOVA yielded *F* tests of both group and week and their interaction. A significant group effect would suggest that the overall mean BP of the IET group differs from the CON group, whereas a significant week effect would imply an overall trend of increase or decrease in the combined IET and CON groups. A significant group $\times$ week interaction would suggest that the trend in BP in the IET group over time differs from the CON group. This test was one-sided because we expected a decline in BP over time with IET only. Therefore, the probabilities produced in the ANOVAs for this interaction were halved.

To determine the direction or significance of the BP trends, we used the MIXED procedure in SAS software (version 9.4, SAS Institute, Cary, North Carolina) for slopes of

best fit for SBP and DBP trends. The signs of these slopes indicated the directional trends in BPs, and individual *t* tests indicated whether the slopes were significantly different from 0. The solution vector also generated *t* tests of the difference between slopes in the 2 groups, although the probabilities associated with these tests were identical to those for the group $\times$ week *F* tests. Beyond slopes, this program produced intercepts (and *t* tests of their significance) of these best-fitting lines as well as *t* tests of their difference in BP between the 2 groups. In all models, we specified a heterogeneous covariance structure that allowed these slopes and intercepts to vary between the 2 groups. This was particularly useful because it adjusted for the large baseline difference of SBP between the 2 groups that was identified earlier.

We used this same approach to test for differences in BP trends between the IET and CON groups in the 6 weeks (weeks 12–18) after training. A significant group $\times$ week interaction in the ANOVA would suggest different trends for BP during this time. One possible trend might be consistent BPs in the CON group and increasing BP in the IET group that would indicate BP levels are not sustainable without continued exercising. A nonsignificant interaction effect with BP in the CON group consistent, on the other hand, would suggest that BPs in the 2 groups are exhibiting parallel trends and that BP in the IET group is sustainable even after training has ceased. All data were analyzed using SAS statistical software.

RESULTS

Participants

Twenty-four participants (IET, *N* = 19; CON, *N* = 5) enrolled in the study. Following the first 6 weeks of detraining (week 18), RBPs were collected from all 24 participants. At week 12 of detraining (week 24), RBPs were recorded in 13 IET and 5 CON participants. No significant differences were found between groups at baseline or across demographic variables (Table 1). Participants were predominantly female, ≥ 65 years old, overweight or Class I obesity, 20% had type 2 diabetes, 16% had chronic obstructive pulmonary disease, and 83% (20 of 24) had HTN. Although some participants found 30% MVC challenging at first, all IET participants were able to maintain the required exercise intensity and completed on average 30 of 36 IET sessions (83%). No single participant completed 100% of the exercise sessions.

Baseline RBP

All participants adhered to premeasure guidelines as evidenced by weekly questionnaires described previously. Despite a ~ 16 mmHg difference in pretraining SBP between IET and CON groups, baseline RBPs were not significantly different ($P > 0.05$; see Figure 1A). Participants were taking a variety of antihypertensive medications. On average, CON group participants reported taking 3.6 ± 1.4 antihypertensive medications compared with 1.6 ± 1.4 antihypertensive medications in the IET group (Table 2). A weak, but significant correlation was found between the number of

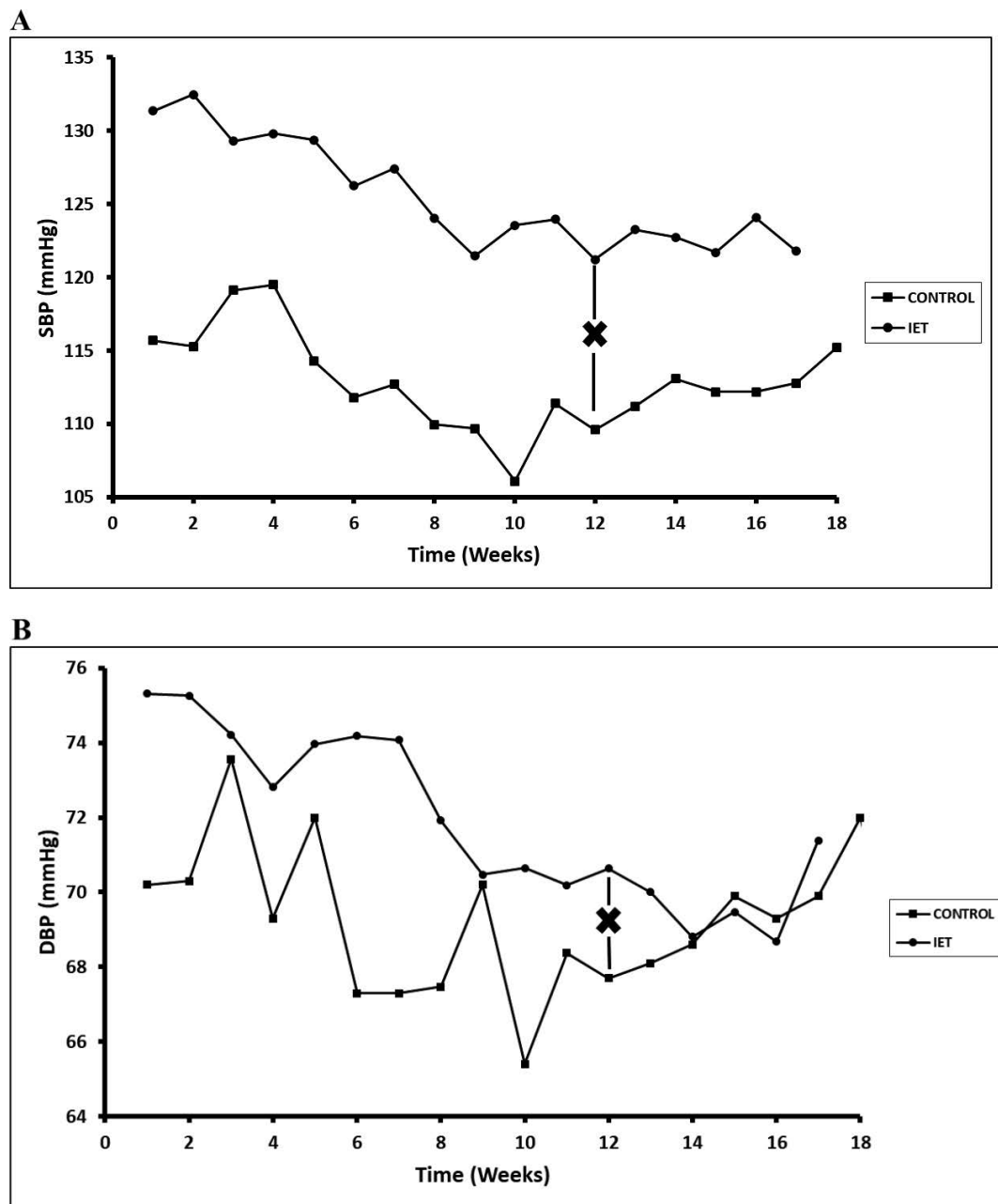


FIGURE 1. Mean $\pm$ SD (A) SBP and (B) DBP responses in the IET and control groups. The end of the training period is indicated by an X.

antihypertensive medications as reported by each participant and pretraining DBP (IET and CON groups combined; $R = -0.44$; $P < 0.05$), but not SBP.

Isometric Exercise Training

Figure 1A shows SBP in the IET group declined throughout the first 12-week IET period (10.2 mmHg, Table 3). SBP changed very little after week 12 (mean at week 18 = 121.8). SBP in the CON group showed a similar trend (Figure 1A), although the magnitude was smaller (4.5 mmHg, Table 3). Values for SBP remained higher in the IET than the CON group throughout the 18 weeks such that the 2 curves did not overlap (Figure 1A).

DBP trends showed more fluctuations throughout the study (Figure 1B), but generally declined through week 12 before plateauing. The magnitude of DBP in both groups was smaller than SBP, as expected (see Table 3).

The ANOVA results for SBP during the first 12 weeks (Table 4) were significant for group and week effects, reflecting the parallel decline and separation of SBP in the groups already noted. The group $\times$ week interaction was not significant ($P = 0.38/2 = 0.19$), suggesting that weekly training in the IET group was not successful in reducing SBP compared with CON. The slope of best fit for SBP during the first 12 weeks was -0.96 for the IET group and -0.76 for the CON group, both of which are significantly different from 0 (see Table 5). Note that the t tests for these 2 slopes (Table 5)

TABLE 2. Participant antihypertensive medications by study group and medication class.

Group	Sex	Antihypertensive Medications	
CON	Female = 2	ACE-I	N = 2
	Male = 3	ARB	N = 2
		BB	N = 4
		BT	N = 2
		CCB	N = 2
		Vaso	N = 0
		ANG II B	N = 0
		DIU	N = 2
		None	N = 0
	IET	Female = 14	ACE-I
Male = 5		ARB	N = 7
		BB	N = 5
		BT	N = 2
		CCB	N = 4
		Vaso	N = 0
		ANG II B	N = 0
		DIU	N = 8
		None	N = 7

ACE-I = ace inhibitor; ANG II B = angiotensin II blocker; ARB = angiotensin receptor blocker; BB = beta blocker; BT = blood thinner; CCB = calcium channel blocker; CON = control; DIU = diuretic; IET = isometric exercise training; Vaso = vasodilator. The number of participants on specific antihypertensive medications

yielded the same probability ($P = 0.38$) as the interaction test in the ANOVA, again confirming that SBP in the IET group did not decrease when compared with CON. The difference in the intercepts of the best-fit lines for SBP in each group was significant (Table 5), reflecting the large initial difference in SBP between groups already noted. For SBP in the last 6 weeks (week 12–18), all 3 factors in the ANOVA as well as both t tests were nonsignificant (Table 5). This suggests that the decline in SBP achieved in the first 12 weeks was maintained after the training had stopped.

The ANOVA results for DBP during the first 12 weeks (Table 6) show significance only for group effects, reflecting the overall decline of DBP in the combined groups. The nonsignificant group $\times$ week factor ($P = 0.47/2 = 0.24$) again suggests that DBP has not declined compared with that seen in the control group. The 0–12-week slope estimate for DBP in the IET group is -0.47 and highly significant, whereas that for the CON group is less (-0.35) but still significant ($P = 0.02$; Table 7). The 12–18-week results for DBP were like those for SBP; none of the ANOVA effects or the 2 t tests are significant. This again suggests that DBP values in the IET group remain about the same in the last 6 weeks and are like those in the CON group.

TABLE 3. Sample sizes (N), means $\pm$ SD of SBP and DBP at weeks 0, 12, and 18 in the CON and IET groups.

Group	Week	N	SBP Mean $\pm$ SD	DBP Mean $\pm$ SD
CON	0	5	115.7 $\pm$ 9	70.2 $\pm$ 3
	12	5	111.2 $\pm$ 14	68.1 $\pm$ 8
	18	5	112.7 $\pm$ 11	67.2 $\pm$ 3
IET	0	19	131.4 $\pm$ 11	75.3 $\pm$ 9
	12	18	121.2 $\pm$ 10	70.6 $\pm$ 9
	18	17	121.8 $\pm$ 12	71.4 $\pm$ 10

CON = control; DBP = diastolic blood pressure; IET = isometric exercise training; SBP = systolic blood pressure. Values are mean $\pm$ SD

TABLE 4. Statistical analysis results for SBP for weeks 0–12 and 12–18, including repeated-measures ANOVA.

	Source	NDF	DDF	F Value	Pr > F
SBP 0–12	Group	1	22	8.39	0.0084
	Week	1	242	54.16	<0.0001
	Group $\times$ week	1	242	0.79	0.38
SBP 12–18	Group	1	22	2.50	0.13
	Week	1	104	0.34	0.56
	Group $\times$ week	1	104	0.45	0.50

ANOVA = analysis of variance; DDF = denominator degrees of freedom; NDF = numerator degrees of freedom; SBP = systolic blood pressure

DISCUSSION

The effect of IET on RBP has been reported mostly in young, relatively healthy adults, but there is insufficient data (<10 studies) on the efficacy of IET in elderly individuals (27) and even fewer data following a prolonged detraining period. In this study, we demonstrated that administering IET to elderly individuals in a group setting is feasible and is potentially effective in larger cohorts.

Twelve weeks of unilateral handgrip IET in elderly adults resulted in significant reductions in resting SBP, like previous reports (28–31). Not only did mean SBP reduce ~ 10 mmHg after 12 weeks of training, but the reduction was also maintained below week 0 values 6 weeks after cessation of training (Figure 1A) and up to 12 weeks posttraining in 13 IET participants (data not shown), which was a novel finding. Although SBP reductions in the IET group were more than double that found in the control group (10.2 mmHg versus 4.5 mmHg), we observed an unexpected, significant reduction in SBP in the control group as well. However, the reduction in SBP found in the IET group is considered clinically significant and exceeds the expected SBP response to nonselective beta-blocker monotherapy (-8 mmHg; (32)). This might suggest that administering IET to a larger cohort

TABLE 5. Statistical analysis results for SBP for weeks 0–12 and 12–18, including the solutions for the group effects.

	Effect	Group	Estimate	SE	DF	t Value	Pr > t
SBP 0–12	Intercept	Difference	−14.41	4.974	22	−2.90	0.0084
		CON	117.34	4.422	22	26.53	<0.0001
		IET	131.75	2.277	22	57.85	<0.0001
	Slope	Difference	0.207	0.234	242	0.89	0.38
		CON	−0.756	0.190	242	−3.99	<0.0001
		IET	−0.964	0.137	242	−7.06	<0.0001
SBP 12–18	Intercept	Difference	−15.36	9.710	22	−1.58	0.13
		CON	107.79	8.356	22	12.90	<0.0001
		IET	123.15	4.947	22	24.90	<0.0001
	Slope	Difference	0.356	0.532	104	0.67	0.50
		CON	0.332	0.434	104	0.77	0.45
		IET	−0.024	0.308	104	−0.08	0.94

CON = control group; DF = degrees of freedom; IET = isometric exercise training; SBP = systolic blood pressure; SE = standard error

TABLE 6. Statistical analysis results for DBP for weeks 0–12 and 12–18, including repeated-measures ANOVA.

	Source	NDF	DDF	F Value	Pr > F
DBP 0–12	Group	1	22	1.99	0.17
	Week	1	241	23.41	<0.0001
	Group × week	1	241	0.54	0.47
DBP 12–18	Group	1	22	0.15	0.70
	Week	1	104	0.15	0.70
	Group × week	1	104	0.04	0.84

ANOVA = analysis of variance; DBP = diastolic blood pressure; DDF = denominator degrees of freedom; NDF = numerator degrees of freedom

TABLE 7. Statistical analysis results for DBP for weeks 0–12 and 12–18, including the solutions for the group effects.

	Effect	Group	Estimate	SE	DF	t Value	Pr > t
DBP 0–12	Intercept	Difference	−3.89	2.759	22	−1.41	0.17
		CON	71.06	2.044	22	34.77	<0.0001
		IET	74.95	1.854	22	40.43	<0.0001
	Slope	Difference	0.124	0.169	241	0.73	0.47
		CON	−0.347	0.150	241	−2.31	0.02
		IET	−0.471	0.078	241	−6.07	<0.0001
DBP 12–18	Intercept	Difference	0.055	7.875	22	−0.39	0.70
		CON	67.09	7.171	22	9.36	<0.0001
		IET	70.14	3.255	22	21.55	<0.0001
	Slope	Difference	0.099	0.499	104	0.20	0.84
		CON	0.146	0.467	104	0.31	0.75
		IET	0.046	0.175	104	0.27	0.79

CON = control group; DBP = diastolic blood pressure; IET = isometric exercise training; SE = standard error

of elderly participants could yield a reduction in SBP significantly greater than a well-matched control group.

Establishing a relationship between the length of IET and the sustainability of posttraining RBP adaptations has been difficult since detraining periods have not been a feature of IET studies, except for Wiley et al. (19). Moreover, most IET studies have been relatively short (3–8 weeks), except for 2 studies in which 10 weeks of IET were prescribed (25,31). However, post-IET monitoring of RBP was not included in either case. Therefore, this is the first study to incorporate a relatively long IET program, followed by a long post-IET monitoring period. It has been reported that short-term RBP adaptations that are quickly lost after training cessation (15,17,19) may be more due to a physiological change than anatomical (27). Our detraining data, along with previous reports (15,17,19), suggest that the mechanisms responsible for RBP reductions induced by handgrip IET are phasic, like adaptations associated with traditional forms of resistance exercise training (33–35). When comparing these data and data from Wiley et al. (19), we speculate that a relationship exists between the length of training and RBP adaptation sustainability, but further investigation is required to confirm an association.

Dynamic resistance exercise training promotes significant reductions in SBP with conflicting results on the sustainability of achieved adaptations ranging from 8 to 14 weeks of training (36–38). Eight weeks of resistance exercise training in postmenopausal women (ages 49–62 years) reduced resting SBP by 15 mmHg. However, this adaptation was no longer evident after 8 weeks of detraining (36). Conversely, 12–14 weeks of resistance exercise training in hypertensive older women and men, which led to a marked decrease in SBP ($\Delta 16$ mmHg and $\Delta 18$ mmHg, respectively), resulted in a sustained reduction in SBP 6 weeks after training ended (37,38). These data suggest a correlation between the length of exercise training and the sustainability of RBP adaptations after training cessation, aligning with our speculation.

Millar et al. (27) postulated that older adults may be more responsive to IET, but interindividual responsiveness to IET may be a more important question than age *per se*. In the present study, IET was not universally effective, like previous studies (39–44). Our data support the possibility that older participants undergoing pharmacological HTN management are not equally responsive to IET. According to data compiled from independent investigations and reviews, age and polypharmacy may attenuate participant responses to IET (13,27,29,41,42). Millar et al. (27) suggested an IET response rate (≥ 2 mmHg reductions in RBP) of 50%–83% of medicated HTN adults and 60%–96% of nonmedicated normotensive or hypertensive adults. However, a recent individual meta-analysis of multiple IET studies reported no evidence of an influence of antihypertensive medication on the BP response to IET (14). Therefore, the question of a mechanistic overlap between specific antihypertensive medications and IET-induced BP reductions remains open.

This study was limited in several ways. First, the CON group comprised only 5 participants compared with 19 IET participants. An unbalanced and small sample size in the

present study may not accurately represent the true effects of IET in this population. The participants in the present study self-reported being very stable in terms of their health status and engagement in physical activity, suggesting that a larger control group would not have altered the results. A major recruitment challenge was that many prospective participants were unwilling to be randomized to the CON group and made IET group allocation a condition of their participation. However, this may be important for the success of IET when prescribed as a face-to-face program. Previous reports suggest that older adults (>60 years) prefer exercising in age-matched groups compared with exercising alone (45). Finally, other limitations include a short pretraining baseline RBP period, a wide array of prescribed antihypertensive medications, and while not significantly different, heterogeneity in baseline RBP between subjects within groups. These limitations may have contributed to the limited significance in our findings and should therefore be addressed and accounted for in future IET studies.

Additionally, factors like safety, convenience, and cost effectiveness should be considered when optimizing IET protocols. Elderly adults often present with musculoskeletal disorders such as osteoarthritis and skeletal muscle weakness, leading to functional limitations negatively impacting their participation (46,47). However, the participants in this study were capable of repeatedly performing 2-minute handgrip contractions at 30% MVC without undue discomfort. This type of training also improved handgrip strength, independent of hand dominance, by 10% and 15% (left and right hand, respectively). This is an additional useful adaptation in this age group for improved capacity for activities of daily living and may aid in preventing age-related disability (48,49).

Clinical Implications

The findings of this study suggest that 12 weeks of handgrip IET can lead to significant reductions in RBP that can be sustained for 12 weeks after training cessation in an elderly population, many whom present with HTN. We have demonstrated for the first time the persistence of reduced RBP after an extended IET program in older adults with various comorbidities, which should now be tested in a larger cohort across multiple sites. Given that responses to current IET programs using well-accepted protocols are varied, it is possible that developing individualized training programs is a necessary next step to broadening the scope of IET in the community. At this time, little is known about the dose of IET required to maintain RBP adaptations after a significant reduction in RBP is achieved. A maintenance program comprised of single sessions per week or tapering sessions over several weeks may be sufficient to maintain the benefits that can be achieved in the initial training period, but this remains to be answered.

Compliance With Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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