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RESEARCH ARTICLE

A multi-trial, retrospective analysis of the antihypertensive effects of high-resistance, low-volume inspiratory muscle strength training

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Abstract

Above-normal blood pressure (BP) is a primary risk factor for cardiovascular diseases. In a retrospective analysis of five pilot trials, we assessed the BP-lowering effects of high-resistance inspiratory muscle strength training (IMST) in adults aged 18–82 years and the impact of IMST on maximal inspiratory pressure (PI_{MAX}), a gauge of inspiratory muscle strength and independent disease risk factor. Participants were randomized to high-resistance IMST (75% PI_{MAX}) or low-resistance sham (15% PI_{MAX}) training (30 breaths/day, 5–7 days/wk, 6 wk). IMST (n = 67) reduced systolic BP (SBP) by 9 ± 6 mmHg ($P < 0.01$) and diastolic BP (DBP) by 4 ± 4 mmHg ($P < 0.01$). IMST-related reductions in SBP and DBP emerged by *week 2* of training (−4 ± 8 mmHg and −3 ± 6 mmHg; $P \leq 0.01$, respectively) and continued across the 6-wk intervention. SBP and DBP were unchanged with sham training (n = 61, all $P > 0.05$). Select subject characteristics slightly modified the impact of IMST on BP. Greater reductions in SBP were associated with older age (β = −0.07 ± 0.03; P = 0.04) and greater reductions in DBP associated with medication-naïve BP (β = −3 ± 1; P = 0.02) and higher initial DBP (β = −0.12 ± 0.05; P = 0.04). PI_{MAX} increased with high-resistance IMST and low-resistance sham training, with a greater increase from high-resistance IMST (+20 ± 17 vs. +6 ± 14 cmH_2O; $P < 0.01$). Gains in PI_{MAX} had a modest inverse relation with age (β = −0.20 ± 0.09; P = 0.03) and baseline PI_{MAX} (β = −0.15 ± 0.07; P = 0.04) but not to reductions in SBP or DBP. These compiled findings from multiple independent trials provide the strongest evidence to date that high-resistance IMST evokes clinically significant reductions in SBP and DBP, and increases in PI_{MAX}, in adult men and women.

NEW & NOTEWORTHY In young-to-older adult men and women, 6 wk of high-resistance inspiratory muscle strength training lowers casual systolic and diastolic blood pressure by 9 mmHg and 4 mmHg, respectively, with initial reductions observed by *week 2* of training. Given blood pressure outcomes with the intervention were only slightly altered by subject baseline characteristics (i.e., age, blood pressure medication, and health status), inspiratory muscle strength training is effective in lowering blood pressure in a broad range of adults.

blood pressure; maximal inspiratory pressure; time-efficient

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in developed and developing countries. Above-normal blood pressure (BP), defined as having a systolic BP (SBP) ≥ 120 mmHg and/or a diastolic BP (DBP) ≥ 80 mmHg, is the primary modifiable risk factor for CVD (1). Above-normal BP is a highly prevalent health condition that affects more than 50% of adults in the United States (2). The incidence of above-normal BP increases with age, such that 90% of adults who live to 80 years of age will develop unhealthy BP levels, even if they have normal BP at midlife (3). The number of older adults is projected to rapidly rise, predicting a dramatic increase in BP-driven CVD burden (4). Thus, addressing the burden of above-normal BP is an important public health goal.

Interventions that can lower BP to recommended levels (i.e., SBP < 120 mmHg, DBP < 80 mmHg) reduce the risk for both CVD and all-cause mortality by ~25% (5), and therefore, have a large impact on public health. Lifestyle interventions, such as moderate-intensity aerobic exercise, weight loss, or eating a healthy diet (including restricting sodium intake), are first-line strategies to control BP (6). However, adherence to these interventions among adults in the United States is low, with <40% of adults meeting recommendations for each individual intervention (7–9). Among the most commonly cited barriers to adherence are time availability (10–12), cost, facility access, and transportation issues (12–15).

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Originally conceived as a form of physical training intended to improve diaphragm strength and function in ventilator-dependent individuals (16, 17), inspiratory muscle strength training (IMST) entailed repeated inspiratory efforts against a resistance as tolerated for weeks to months. Over the years, a range of IMST protocols, most involving 30 min of training per day, 2–3 times per week (18–21), have been implemented in nonventilator-dependent patient populations (22, 23), healthy adults (24, 25), and athletes (26–28). The reported benefits of IMST in these populations include improved inspiratory muscle strength and athletic performance, as well as reduced perception of effort and dyspnea (22–28).

In its most recent iteration, high-resistance low-volume IMST comprises 30 daily inspiratory efforts against a resistance equivalent to 75% of an individual's maximal inspiratory pressure (PI_{MAX}) and requires ~5 min to complete (29, 30). This IMST format, implemented in a number of small pilot trials, has yielded significant reductions in casual BP (31–35), while also decreasing sympathoadrenal activity and systemic vascular resistance (33–35), and improving vascular endothelial function (31). High user adherence (>90% of prescribed training sessions completed) has been reported in all trials to date (31–35). Thus, current evidence suggests that high-resistance IMST has potential for public health translation (36).

Despite favorable health and adherence outcomes, the small sample sizes arising from individual pilot trials performed to date both limit confidence in prior results and preclude analysis of subject characteristics that may impact effectiveness of the intervention for lowering BP. Accordingly, to address these specific research gaps, we pooled data from five randomized, controlled trials performed in our laboratories at the University of Arizona and the University of Colorado Boulder that used near-identical protocols but with unique participant populations (i.e., normotensive young adults, middle-aged and older adults with above-normal BP, and adults with obstructive sleep apnea and above normal BP). The principal purposes of this investigation were to quantify the BP-lowering effects of IMST in a larger cohort of participants, evaluate the time course of BP reductions, and identify subject characteristics that may predict the magnitude of the BP reduction in response to the intervention. We also evaluated BP outcomes as a function of gains in respiratory muscle strength (PI_{MAX}). We hypothesized that *1*) IMST would reduce SBP and DBP compared with sham training; *2*) reductions in BP would be apparent within the first week of training; and *3*) higher initial BP levels would be associated with larger BP reductions with IMST, but other clinical factors would not appreciably predict the efficacy of IMST.

METHODS

The Institutional Review Boards at The University of Arizona and the University of Colorado Boulder approved all experimental procedures. Written informed consent was obtained for all participants. Individual participant data from five studies conducted over a 7-year period (2015 through 2021) were included in the analysis. Subjects in the trials comprised young adults (32, 34), patients with obstructive sleep apnea (33, 35), and otherwise healthy adults with above-normal SBP (31). Based on all participants having initial BP levels $\leq$ 160/100 mmHg and the presence of other CVD risk factors (e.g., obesity) in some participants, a majority of the participants had low-to-moderate CVD risk (37).

Experimental Measurements

Casual (resting) SBP and DBP were measured in accordance with clinical guidelines (6, 37, 38) using either a manual sphygmomanometer and stethoscope (31–34) or automated oscillometric sphygmomanometer (35) placed over the brachial artery. Subjects were seated quietly for at least 5 min before BP measurements with their feet flat on the floor and arm supported at heart level. Measurements were taken in triplicate and averaged, with >1 min between measurements. BP measurements were made at baseline, weekly during the intervention, and at the end of the intervention.

PI_{MAX} was measured at baseline, weekly during the interventions, and at end of the intervention to determine each individual's appropriate training level and document changes in inspiratory muscle function. Subjects generated a maximal inspiration against near-infinite resistance. Per American Thoracic Society/European Respiratory Society guidelines, the average of three trials was used to define an individual's PI_{MAX} (39). Four of the studies included in this data set measured PI_{MAX} using a customized pressure transducer (Omega-dyne, Inc.) (31–34) and one study measured PI_{MAX} using a POWERbreathe K3 device in TEST mode (35).

Inspiratory Muscle Strength Training Protocol

Detailed descriptions of the interventions have been reported (31–35). In brief, volunteers in all studies were randomized to perform either high-resistance IMST (i.e., training against an inspiratory resistance of 75% PI_{MAX}) or low-resistance sham IMST (i.e., training at 15% PI_{MAX}, believed to have no therapeutic effect). In subsequent studies, we have shown low resistance IMST does contribute to improvements in PI_{MAX} in some individuals and therefore, technically cannot be considered a "sham" intervention. However, for the sake of consistency with our previous work we will continue to refer to low-resistance IMST as sham IMST. All included studies followed a 6-wk intervention wherein participants performed 30 inspiratory efforts/day, performed in a single bout and comprising five sets of six inspiratory efforts, 5–7 days/wk (Table 1). For each inspiratory effort, resistance was controlled but tidal volume and inspiratory duration were not. All participants were instructed to perform as deep of an inspiration as possible on each effort with a target inspiration duration of 1–2 s. There were some between-study differences in the training devices and training load progression (Table 1). In all studies, absolute training intensity was adjusted weekly to account for gains in PI_{MAX}.

Data and Statistical Analysis

Casual SBP, casual DBP, and PI_{MAX} values from baseline, weekly during the intervention, and at the end of the 6-wk intervention were included for analysis. One study (32) reported SBP and DBP after 5 wk of training. In this instance,

Table 1. *Inspiratory muscle strength training trial intervention designs*

Author	Training Device	Device Resistance Type	Training Protocol	High Training Load (% PI_{MAX})	Subject Number (*n*)	Subject Population
Vranish et al. (32)	Hans Rudolph 2600 series two-way nonrebreathing valve with flow limitation cap	Constant	30 breaths/day; 5 days/wk; 6 wk	75%	IMST: 10 Sham: 10	Healthy young adults
Vranish et al. (33)	POWERbreathe K3	Tapered loading	30 breaths/day; 7 days/wk; 6 wk	75%	IMST: 12 Sham: 10	Adults with obstructive sleep apnea
DeLucia et al. (34)	Hans Rudolph 2600 series two-way nonrebreathing valve with flow limitation cap	Constant	30 breaths/day; 5 days/wk; 6 wk	75%	IMST: 12 Sham: 13	Healthy young adults
Ramos-Barrera et al. (35)	POWERbreathe K3	Tapered loading	30 breaths/day; 7 days/wk; 6 wk	75%	IMST: 15 Sham: 10	Adults with obstructive sleep apnea
Craighead et al. (31)	POWERbreathe K3	Tapered loading	30 breaths/day; 6 days/wk; 6 wk	55% *week 1*; 65% *week 2*; 75% *weeks 3–6*	IMST: 18 Sham: 18	Midlife and older adults with SBP ≥120 mmHg

IMST, inspiratory muscle strength training; PI_{MAX}, maximal inspiratory pressure; SBP, systolic blood pressure.

SBP and DBP values were imputed with an intention-to-treat approach, wherein the *week 5* BP values were carried forward and imputed as the *week 6* BP values. A second study (35) reported SBP and DBP for a subset of participants (n = 15) in whom the primary outcomes of muscle sympathetic nerve activity and 24-h BP were obtained; however, the current analysis includes values for SBP, DBP, and PI_{MAX} from (n = 25) participants who completed that trial's 6-wk intervention.

Study-level data for SBP, DBP, and PI_{MAX} were compared using forest plots created with a random-effects model. Standardized mean differences (SMD) with 95% confidence intervals between IMST and sham groups were calculated based on group mean change (end-intervention value – baseline value) as described previously (40). SMD, also known as effect sizes, were defined as very small/no effect (<0.20), small (0.20–0.49), moderate (0.50–0.79), or large (≥0.80) (41). Heterogeneity (I^2), study weight, and prediction intervals were calculated as described previously (40). The I^2 statistic is a measure of relative variance between the studies, with a low variance (<50%) suggesting between-study differences are largely due to random error, while moderate or high variance (>50% and >75%, respectively) suggests a substantial portion of the observed variance is due to real differences between studies that could potentially be explained by covariates (40). Study weight was calculated according to each individual study's contribution to the pooled estimate (i.e., inverse of the variance of the treatment effect, largely impacted by sample size) (42). Prediction intervals indicate that with 95% confidence the true effect (i.e., SMD) of a future study will fall within the specified range (40).

Participant-level data from the five studies were combined and statistical comparisons made using SPSS version 27 and GraphPad Prism version 9.4. A two-way (Training Group × Time) repeated-measures ANOVA was used to determine significant group and time main effects or interaction effects of SBP, DBP, and PI_{MAX} at baseline and at end of the intervention. When a significant effect was observed, Sidak's multiple comparison post hoc test was used to assess within- and/or between-group statistical differences. Unpaired t tests also were used to compare the difference in the change in SBP, DBP, and PI_{MAX} between the IMST and sham groups.

A one-way repeated-measures ANOVA with Dunnett's multiple comparisons test was used to assess the onset for changes in SBP, DBP, and PI_{MAX} compared with baseline in response to the intervention in the high-resistance IMST group only. Simple linear regression of the week-to-week change in BP or PI_{MAX} was used to assess trends over time.

We then assessed the extent to which baseline subject characteristics influence the responsiveness (e.g., magnitude of change in BP) to high-resistance IMST. Simple linear regression was used to examine the independent effects of age and baseline measures of SBP, DBP, PI_{MAX}, and body mass index (BMI) to predict changes in SBP, DBP, and PI_{MAX} during 6 wk of high-resistance IMST. Simple linear regression also was used to evaluate the association between change in PI_{MAX} and SBP and between PI_{MAX} and DBP. Unpaired t tests were used to compare the changes in SBP, DBP, and PI_{MAX} between men and women and between BP-medicated and medication-naive participants. A sensitivity analysis was also performed to assess the impact of BP medication when young adults (aged ≤30 yr) were removed from the analysis to more closely match BP-medicated and medication-naïve participants. Stepwise linear regression including all the aforementioned variables was then used to identify variables that independently influence responsiveness to high-resistance IMST.

Statistical significance was set a priori as α = 0.05 for all comparisons, while P values between 0.05 and 0.10 were noted as trends. Values are presented as means ± standard deviation (SD) unless otherwise specified.

RESULTS

Participants

Data from a total of 128 adults were included for retrospective analysis (Table 2). Sixty-seven subjects (29 women/38 men) had been randomized to receive the high-resistance IMST intervention, whereas 61 (24 women/37 men) were randomized to receive sham training. There were no differences in subject characteristics between groups at baseline (all $P > 0.05$).

Table 2. *Subject characteristics under baseline conditions*

	Sham	IMST	*P* Values
n (M/F)	61 (37/24)	67 (38/29)	
Age, yr	50 ± 25	50 ± 22	0.94
Height, cm	170 ± 9	172 ± 10	0.20
Mass, kg	76.3 ± 16.9	78.7 ± 17.3	0.44
BMI, kg/m^2	26.5 ± 5.5	26.5 ± 4.9	0.93
PI_{MAX}, cmH_2O	82 ± 22	87 ± 28	0.30
SBP, mmHg	124 ± 14	127 ± 15	0.32
DBP, mmHg	75 ± 9	76 ± 10	0.49
Training session (*n*)	35 ± 6	37 ± 6	0.30

Data are means ± SD. BMI, body mass index; DBP, diastolic blood pressure; PI_{MAX}, maximal inspiratory pressure; SBP, systolic blood pressure.

Systolic Blood Pressure

All studies showed a large effect for high-resistance IMST on SBP relative to sham training, with a combined SMD of 1.82 (Fig. 1*A*). Heterogeneity of the SBP response between studies was moderate (I^2 = 71.3%).

When individual participant data from the five studies were collapsed into IMST or sham groups, there was a significant group by time interaction for SBP ($P < 0.01$). Casual SBP was unchanged in the sham group (baseline: 124 ± 15 mmHg, end-intervention: 124 ± 14; $P = 0.98$), but in the high-resistance IMST group, SBP decreased from 127 ± 15 mmHg at baseline to 118 ± 15 mmHg at the end of the intervention ($P < 0.01$), such that end-intervention SBP was significantly lower in the IMST group compared with sham ($P = 0.03$) (Fig. 1*B*). Accordingly, the mean reduction in SBP following IMST (−9 ± 6 mmHg) was greater in magnitude than the mean change with sham training (0 ± 6 mmHg; $P < 0.01$, Fig. 1*C*).

Casual SBP declined by 1.5 ± 7.9 mmHg/wk on average during the 6-wk high-resistance IMST intervention, such that casual SBP was lower than baseline from the end of *week 2* of training each week until end of the intervention (all $P < 0.05$). The week-to-week rate of reduction in SBP did not change across the 6-wk intervention [β = 0.17 ± 0.23 (standard error of the mean; SEM), $P = 0.46$].

Diastolic Blood Pressure

Study-level data for all five trials showed large effects of high-resistance IMST on casual DBP relative to sham training (Fig. 2*A*). In addition, heterogeneity between studies was low (I^2 = 6.8%).

For participant-level data, there was a significant group by time interaction for DBP ($P < 0.01$). Casual DBP was unchanged in the sham group (baseline: 74 ± 9 mmHg, end-intervention: 76 ± 9 mmHg; $P = 0.10$), but in the high-resistance IMST group, DBP decreased from 76 ± 10 mmHg at baseline to 72 ± 10 mmHg at the end of the intervention ($P < 0.01$), such that end-intervention DBP was significantly lower in the IMST group compared with sham ($P = 0.03$) (Fig. 2*B*). The mean reduction in DBP following IMST (−4 ± 4 mmHg) also was significantly greater than the mean change with sham training (1 ± 5 mmHg; $P < 0.01$, Fig. 2*C*).

Casual DBP was reduced by 0.6 ± 5.8 mmHg/wk on average during the high-resistance IMST intervention, such that casual DBP was significantly lower than baseline from the end of *week 1* of training until end of the intervention (all $P <$

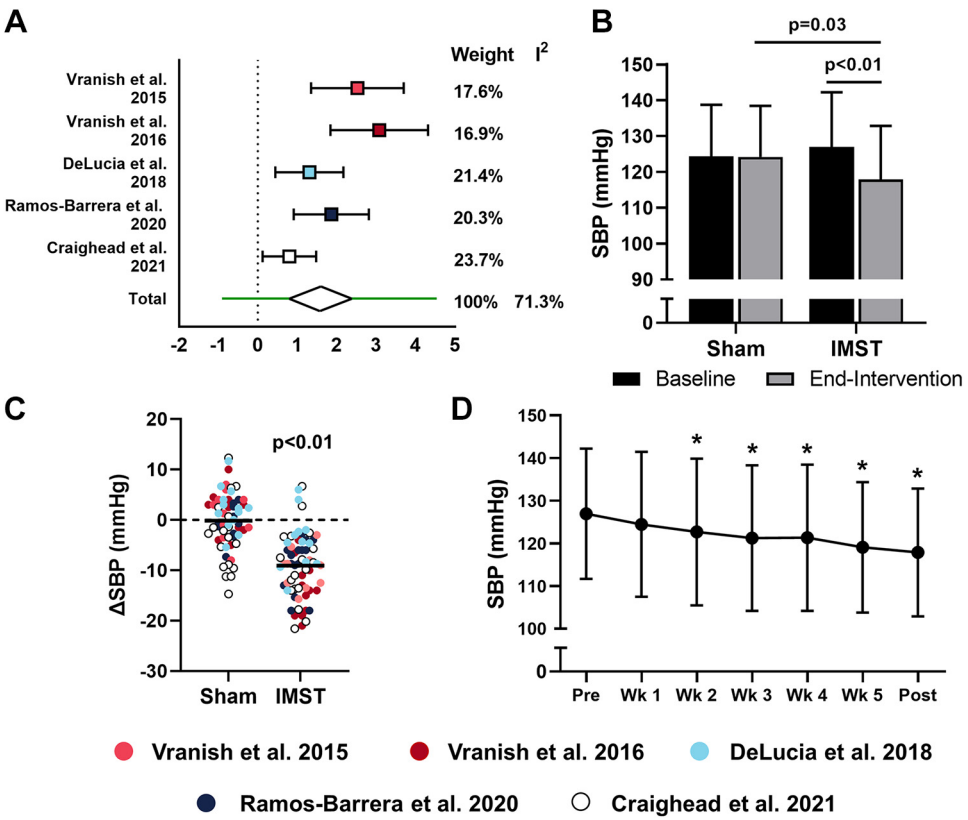

Figure 1. Systolic blood pressure (SBP) data in the sham (*n* = 61; 37 men, 24 women) and inspiratory muscle strength training (IMST; *n* = 67; 38 men, 29 women) groups. *A*: forest plot showing standardized mean difference (SMD) between IMST and sham groups. Boxes and whiskers indicate SMD ± 95% confidence intervals. The diamond indicates the combined SMD ± 95% confidence interval, whereas the green line indicates the 95% prediction interval. Positive values indicate favoring IMST and negative values indicate favoring Sham. *B*: two-way (Training group × Time) repeated-measures ANOVA revealed a group × time interaction ($P < 0.01$), with SBP in the IMST group significantly lower from baseline and end-intervention ($P < 0.01$) and lower than sham at end-intervention ($P = 0.03$). *C*: independent *t* tests revealed a significant between-group difference for the change in SBP over the 6-wk intervention ($P < 0.01$). *D*: one-way repeated-measures ANOVA with Dunnett's multiple comparisons test revealed a significant reduction in SBP compared with baseline after 2 wk of training (all $P < 0.05$). Data (*B* and *D*) are means ± SD. *$P < 0.05$ vs. pre.

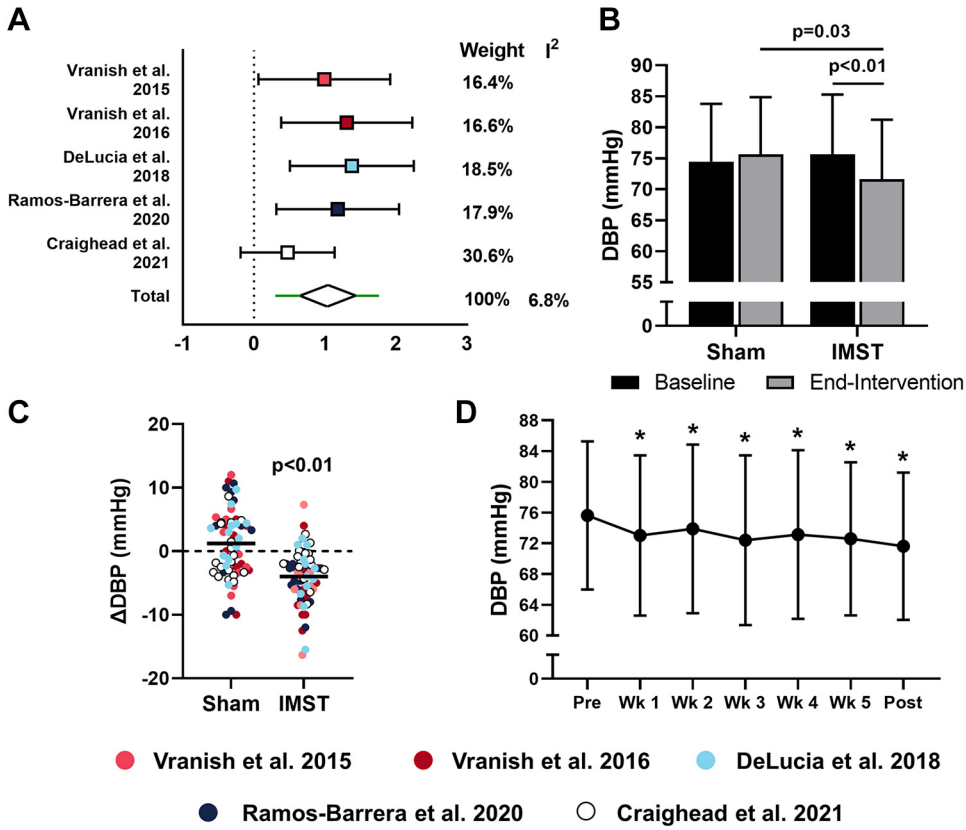

Figure 2. Diastolic blood pressure (DBP) data in the sham (n = 61, 37 men, 24 women) and inspiratory muscle strength training (IMST; n = 67; 38 men, 29 women) groups. *A*: forest plot showing standardized mean difference (SMD) between IMST and sham groups. Boxes and whiskers indicate SMD ± 95% confidence intervals. The diamond indicates the combined SMD ± 95% confidence interval, whereas the green line indicates the 95% prediction interval. Positive values indicate favoring IMST and negative values indicate favoring Sham. *B*: two-way (Training group × Time) repeated-measures ANOVA revealed a group × time interaction ($P < 0.01$), with DBP in the IMST group significantly lower from baseline and end-intervention ($P < 0.01$) and lower than sham at end-intervention ($P = 0.03$). *C*: independent *t* tests revealed a significant between-group difference for the change in DBP over the 6-wk intervention ($P < 0.01$). *D*: one-way repeated-measures ANOVA with Dunnett's multiple comparisons test revealed a significant reduction in DBP compared with baseline after 1 wk of training (all $P < 0.05$). Data (*B* and *D*) are means ± SD. *$P < 0.05$ vs. pre.

0.05). There was no evidence that the rate of reduction in DBP changed during the 6-wk intervention (β = 0.15 ± 0.17 SEM, $P = 0.37$).

Maximal Inspiratory Pressure

PI_{MAX} was used to establish the training levels for the high-resistance IMST and sham groups and to document changes in inspiratory muscle strength. Study-level data showed moderate or large effects of high-resistance IMST on PI_{MAX} relative to sham, with the exception of the study by Ramos-Barrera et al. (35) which indicated a greater effect of sham on PI_{MAX} (Fig. 3*A*). Heterogeneity among the studies was high ($I^2 = 80.3\%$).

With participant-level data there was a significant group by time interaction for PI_{MAX} ($P < 0.01$). PI_{MAX} increased in the sham group (baseline: 82 ± 22 cmH_2O, end-intervention: 88 ± 23 cmH_2O; $P = 0.01$) and in the high-resistance IMST group (baseline: 87 ± 28 cmH_2O, end-intervention: 107 ± 28 cmH_2O; $P < 0.01$), such that end-intervention PI_{MAX} was significantly greater in the IMST group compared with sham ($P < 0.01$) (Fig. 3*B*). The average increase in PI_{MAX} following IMST (+20 ± 17 cmH_2O) also was significantly greater relative to sham training (+6 ± 14 cmH_2O; $P < 0.01$, Fig. 3*C*).

PI_{MAX} increased by 3.4 ± 7.8 cmH_2O/wk on average during the high-resistance intervention, such that PI_{MAX} was greater than baseline from training *week 1* until end of the intervention (all $P < 0.05$). The magnitude of the week-to-week increase in PI_{MAX} declined over 6 wk (β = −1.6 ± 0.2 SEM, $P < 0.01$), indicative of diminishing gains as training progressed.

Predictors of Responsiveness

Baseline characteristics from participants in the high-resistance IMST group were examined to identify factors that may predict changes in BP or PI_{MAX}. In addition, the relation between the change in BP and PI_{MAX} was evaluated to determine whether the magnitude of improvement in inspiratory muscle strength bore any correspondence to the magnitude of the BP reduction.

Reductions in casual SBP with high-resistance IMST were not influenced by sex (women: −9 ± 7 mmHg, men: −9 ± 6 mmHg; $P = 0.55$) nor BP-lowering medication (medication-naïve BP: n = 54, mean change −9 ± 6 mmHg, medicated: n = 13, mean change −8 ± 8 mmHg; $P = 0.48$); the impact of BP-lowering medication on SBP was similar when young adult were removed from the analysis (medication-naïve BP: n = 31, mean change −11 ± 6 mmHg, medicated: n = 13, mean change −8 ± 8 mmHg; $P = 0.11$). Reductions in SBP were influenced by older age and higher initial SBP (Table 3). Stepwise linear regression analysis identified only subject age for inclusion in the model (β = −0.07 ± 0.03 SEM, R^2 = 0.07, $P = 0.04$). The decline in SBP was not associated with the change in PI_{MAX} (β = 0.02 ± 0.05 SEM, $R^2 < 0.01$, P = 0.69).

Reductions in casual DBP with high-resistance IMST were slightly greater in men than in women (men: −5 ± 5 mmHg, women: −3 ± 3 mmHg; $P = 0.07$) and greater in participants naïve to BP-lowering medications (medication-naïve BP: −5 ± 4 mmHg; medicated: −2 ± 3 mmHg; $P = 0.04$); the impact of BP-lowering medication on DBP persisted when young adults were removed from the analysis (medication-

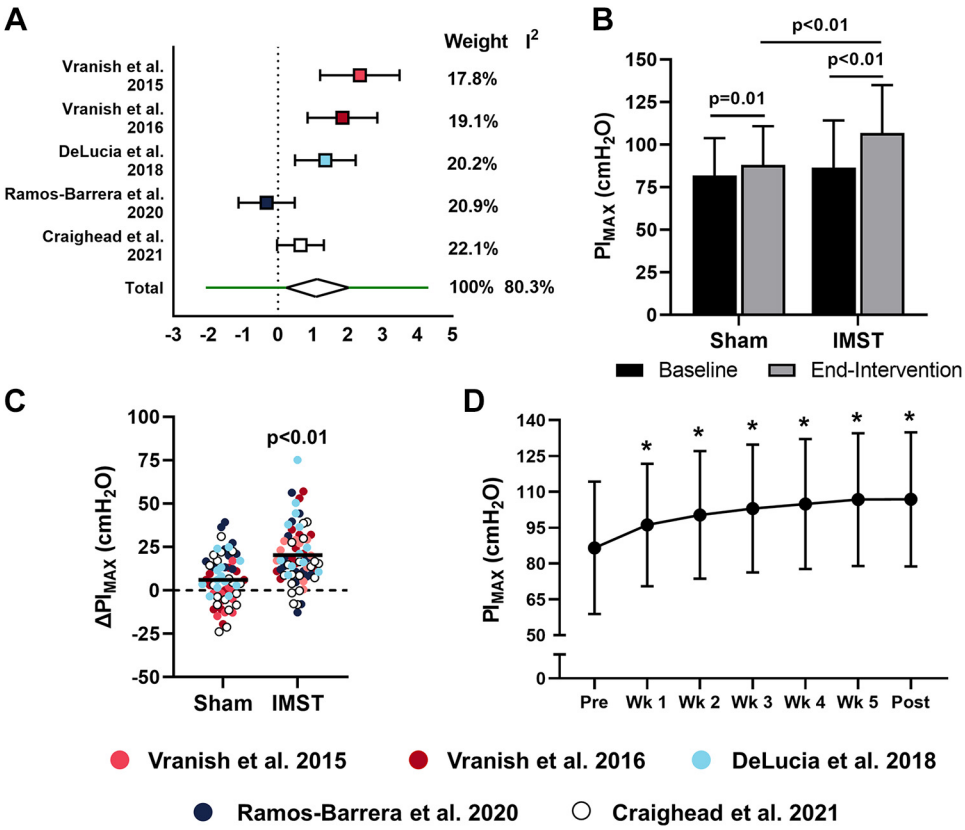

Figure 3. Maximal inspiratory pressure (PI_{MAX}) data in the sham (n = 61; 37 men, 24 women) and inspiratory muscle strength training (IMST; n = 67; 38 men, 29 women) groups. *A*: forest plot showing standardized mean difference (SMD) between IMST and sham groups. Boxes and whiskers indicate SMD ± 95% confidence intervals. The diamond indicates the combined SMD ± 95% confidence interval, whereas the green line indicates the 95% prediction interval. Positive values indicate favoring IMST and negative values indicate favoring Sham. *B*: two-way (Training group × Time) repeated-measures ANOVA revealed a group × time interaction ($P < 0.01$), with PI_{MAX} in the IMST group significantly higher from baseline at end-intervention ($P < 0.01$) and higher than sham at end-intervention ($P < 0.01$). *C*: independent t tests revealed a significant between-group difference for the change in PI_{MAX} over the 6-wk intervention ($P < 0.01$). *D*: one-way repeated-measures ANOVA with Dunnett's multiple comparisons test revealed a significant increase in PI_{MAX} compared with baseline after 1 wk of training (all $P < 0.05$). Data (*B* and *D*) are means ± SD. *$P < 0.05$ vs. pre.

naïve BP: mean change −5 ± 4 mmHg, medicated: mean change −2 ± 3 mmHg; P = 0.01). A higher initial DBP also was associated with a greater reduction in DBP (P = 0.06); no other subject characteristics were associated with the change in DBP (Table 3). Stepwise linear regression identified medication-naïve BP (β = −3.12 ± 1.3 SEM, R^2 = 0.09, P = 0.02) and above-normal baseline DBP (β = −0.12 ± 0.05 SEM, R^2 = 0.08, P = 0.04) as the strongest predictors of IMST-related reductions in DBP. Consistent with SBP, the decline in DBP was not associated with change in PI_{MAX} (β = −0.02 ± 0.05 SEM, R^2 = 0.01, P = 0.45).

Gains in inspiratory muscle strength (i.e., PI_{MAX}) with high-resistance IMST were not influenced by sex (women: +20 ± 16 cmH_2O, men: +20 ± 18 cmH_2O; P = 0.95) but were influenced by BP medication status (medication-naive: +23 ± 17 cmH_2O, medicated: +11 ± 11 cmH_2O; P = 0.03); however, there was no impact of BP-lowering medications on PI_{MAX} when young adults were removed from the analysis (medication-naïve BP: mean change +20 ± 17 cmH_2O, medicated: mean change +11 ± 11 cmH_2O; P = 0.10). Older age and higher baseline PI_{MAX} were negatively associated with training-related improvements in PI_{MAX}; no other variables were associated with change in PI_{MAX} (Table 3). Stepwise linear regression identified age (β = −0.20 ± 0.09 SEM, R^2 = 0.07, P = 0.03) and baseline PI_{MAX} (β = −0.15 ± 0.07 SEM, R^2 = 0.07, P = 0.04) as the strongest predictors of change in PI_{MAX}.

DISCUSSION

We combined data from five randomized, sham-controlled clinical trials to evaluate the efficacy and time course of high-resistance IMST for lowering BP and to identify subject characteristics that may impact the efficacy of the intervention. Whereas individual studies included in the data set represent distinct populations [i.e., normotensive young adults (32, 34), middle-aged, and older adults with obstructive sleep apnea and above-normal BP (33, 35), and generally healthy older adults with above-normal BP (31)], the combined data

Table 3. *Predictors of responsiveness to 6 weeks of high-resistance inspiratory muscle strength training*

	ΔPI$_{MAX}$			ΔCasual SBP			ΔCasual DBP		
Baseline Variable	β	R^2	P Value	β	R^2	P Value	β	R^2	P Value
Age	−0.22 ± 0.09	0.09	0.02*	−0.07 ± 0.03	0.07	0.04*	0.01 ± 0.02	<0.01	0.67
BMI	−0.15 ± 0.43	<0.01	0.73	0.10 ± 0.16	0.01	0.56	−0.03 ± 0.11	<0.01	0.75
PI_{MAX}	−0.17 ± 0.07	0.08	0.02*	0.01 ± 0.03	<0.01	0.66	−0.03 ± 0.02	0.04	0.13
SBP	−0.16 ± 0.14	0.02	0.25	−0.10 ± 0.05	0.06	0.04*	−0.01 ± 0.03	<0.01	0.69
DBP	−0.16 ± 0.22	0.01	0.46	−0.11 ± 0.08	0.03	0.16	−0.10 ± 0.05	0.06	0.06

Results are from simple linear regression. β values are means ± SE. BMI, body mass index; DBP, diastolic blood pressure; PI_{MAX}, maximal inspiratory pressure; SBP, systolic blood pressure. *$P < 0.05$.

set included adults across a broad age range (18–80+ years) with low to moderate CVD risk. Overall, this analysis confirmed our primary hypothesis, as IMST significantly reduced both SBP and DBP relative to sham training. We also hypothesized that significant reductions in BP would be apparent after 1 wk of IMST. Significant reductions in DBP were apparent after 1 wk, and for SBP after 2 wk—both of which highlight a relatively rapid time course for BP reduction with IMST. Finally, our hypothesis that initial BP levels would be the primary clinical factor impacting the effectiveness of IMST was partially confirmed, as initial BP levels and other select clinical factors were only modestly related to changes in BP. Collectively, this large heterogeneous sample supports high-resistance IMST as an effective nonpharmacological therapy to reduce BP in all age groups relatively quickly (1–2 wk).

In the analysis of this large and diverse subject cohort, we found that 6 wk high-resistance IMST lowers average casual SBP by 9 mmHg and casual DBP by 4 mmHg, reductions consistent with a 30% lower risk for CVD (43). This clinically significant reduction in BP is comparable with that observed with pharmacotherapy (44–46) but larger than those seen on average with established lifestyle interventions, such as aerobic exercise (47, 48), dietary sodium restriction (49, 50), and weight loss (51). Importantly, the BP reductions reported here were attained with a weekly training commitment of ~25–35 min, equivalent to 20% of the weekly time required to meet aerobic exercise guidelines (52).

Clinically significant IMST-related reductions in SBP (−4 mmHg) and DBP (−3 mmHg) emerged in the second and first training weeks, respectively. This time course of BP reduction is similar to that observed with dietary sodium restriction (53), but more rapid than the response to aerobic exercise training; the latter has been reported to take ~5 wk of training to lower BP in hypertensive adults (54) and up to ~6 mo in normotensive young adults (55). Importantly, IMST-related declines in SBP and DBP continued throughout the 6-wk intervention, with no evidence of a plateau. We do not expect linear reductions in BP to be sustained indefinitely. Although we do not yet know the precise timepoint at which the response diminishes, one of the individual trials that contributed to the current dataset (31) documented reductions in SBP that persisted (~75%) after abstaining from IMST for 6 wk. On this basis, a reduced training frequency (perhaps 3 days/wk) may be sufficient to preserve the BP reduction over the longer term. The trajectory and potential magnitude of the BP reduction that can be attained with high-resistance IMST currently is the focus of additional ongoing clinical trials with longer treatment durations (56, 57).

Although this retrospective analysis does not provide insight on the mechanisms through which IMST lowers BP, results from the individual trials that comprise this analysis suggest that point to reductions in sympathetic nerve activity (33, 35), improvements in peripheral resistance and vascular endothelial function (31, 34), and changes in circulating factors related to oxidative stress and inflammation (31) as potential mechanisms mediating the BP-lowering effects of IMST.

Six weeks of high-resistance IMST increased PI_{MAX} by 20 cmH_2O on average, with improvements evident after the first training week. However, unlike BP, the magnitude of the weekly gain in PI_{MAX} declined over the course of the intervention and reached a plateau by *week 6*. Similar plateauing has been reported in other muscle groups (e.g., quadriceps) in response to resistance training, wherein the greatest rates of gains in strength occur at the outset of training and diminish over time, despite progressive increases in resistance (58). Sham training also improved PI_{MAX}, although the magnitude of improvement was less than one-third of that observed in the high-resistance IMST groups. In view of these outcomes, and given that age-related declines in PI_{MAX} may increase chronic disease risk (59–67), high-resistance IMST may be an appropriate and accessible training format for use by older adults to improve respiratory muscle strength.

The dissociation of IMST-related changes in PI_{MAX} and BP is a key finding and consistent with previous observations. First, the time course of improvement for BP and PI_{MAX} differed. That is, gains in PI_{MAX} tapered and plateaued by *week 6* whereas SBP and DBP showed steady declines throughout the intervention without evidence of plateau. Second and more notable, whereas both sham training and high-resistance IMST groups made gains in PI_{MAX} there was no relation between gains in PI_{MAX} and reductions in SBP or DBP. Taken together, high-resistance IMST has concomitant effects on PI_{MAX} and BP, however, improvements in BP are not PI_{MAX}-dependent. This suggests it is the repeated generation of large, negative intrathoracic pressure during IMST, and not the concomitant change in inspiratory muscle strength, that leads to reductions in BP.

Clinical factors had a modest impact on BP outcomes. Both older age and higher initial SBP were associated with larger reductions in casual SBP with IMST. However, as advancing age correlates with increased SBP (68), these two variables were considered potential confounding variables in predicting the efficacy of IMST. Further analysis suggested that age was the primary predictor for SBP reductions with IMST, with older adults experiencing larger reductions in SBP. However, although statistically significant, the impact of advancing age appeared modest (i.e., 15 years of aging associated with a 1.0 mmHg greater reduction in SBP with IMST). On this basis, high-resistance IMST may be considered similarly effective at lowering SBP across a broad age range.

Other factors were found to influence the effectiveness of IMST for lowering casual DBP. Adults naive to antihypertensive medications and with higher initial DBP were more likely to exhibit greater reductions in casual DBP (i.e., 8 mmHg higher baseline DBP corresponding to a 1.0 mmHg reduction in DBP). Conversely, those taking BP-lowering medication exhibited smaller reductions in DBP with IMST (−2 mmHg vs. −5 mmHg for those not on BP medication). Importantly, even a 2 mmHg reduction in DBP in those on BP medication confers a significant reduction in CVD risk (69).

Older age was associated with more modest improvements in PI_{MAX}, whereas lower initial PI_{MAX} values were modestly associated with larger improvements in PI_{MAX}. Taking BP-lowering medications initially appeared to attenuate the increase in PI_{MAX} with IMST; however, a sensitivity analysis in which young adults were excluded from consideration nullified this effect. Including age in the regression model also mitigated the impact of BP-lowering medications on

PI_{MAX}; therefore, age appears to be the factor driving this effect. In general, aging is associated with changes in respiratory function (59–61), whereas those with a lower initial PI_{MAX} may have greater capacity for training-induced improvements in PI_{MAX}. Nevertheless, these associations were quite modest, indicating broad efficacy.

Experimental Considerations

All trials that comprised this data set implemented 6 wk of high-resistance (75% PI_{MAX}), low-volume (30 breaths) IMST, 5–7 days/wk. The similarity in the designs of the included studies is a strength of this analysis and allowed for direct comparisons between trials. This study included men and women across a broad age range, making the findings generally applicable across sex and age groups. However, as most participants were non-Hispanic white adults, additional studies that include participants from other racial and ethnic groups are needed. Finally, as the most common health conditions in our cohort were above-normal SBP and obstructive sleep apnea, the findings cannot be extrapolated to other patient populations, such as those with established CVD, at this time.

Conclusions

Using compiled data from several independent small trials, here we provide the strongest evidence to date that 6 wk of high-resistance IMST consistently induces clinically meaningful reductions in casual SBP and DBP, while improving inspiratory muscle function in adult men and women across a wide age range. In addition, we show that improvements in BP and PI_{MAX} are apparent after only 1–2 wk of the intervention. We also demonstrate that the efficacy of high-resistance IMST is only modestly impacted by select subject characteristics, indicating it is likely to be an effective BP-lowering lifestyle intervention for a broad range of users. Finally, we show that the change in BP is not related to changes in PI_{MAX}, suggesting it is the generation of large, negative intrathoracic pressures during IMST, and not the associated change in inspiratory muscle strength, that drive the vascular conditioning effects (e.g., BP-reduction, improved endothelial function) of the intervention. These results provide support for time-efficient, high-resistance IMST as a promising lifestyle intervention for lowering BP and possibly decreasing the risk for CVD and other BP-related health conditions.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

D.H.C. and D.T. conceived and designed research; D.H.C., K.A.F., J.R.V., and C.M.D. performed experiments; D.H.C., D.T., K.A.F., and J.L.M. analyzed data; D.H.C., D.T., K.A.F., J.L.M., D.R.S., and E.F.B. interpreted results of experiments; D.H.C. and D.T. prepared figures; D.H.C. and D.T. drafted manuscript; D.H.C., D.T., K.A.F., J.L.M., J.R.V., C.M.D., D.R.S., and E.F.B. edited and revised manuscript; D.H.C., D.T., K.A.F., J.L.M., J.R.V., C.M.D., D.R.S., and E.F.B. approved final version of manuscript.

REFERENCES

1. **GBD 2017 Risk Factor Collaborators.** Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392: 1923–1994, 2018. doi:10.1016/S0140-6736(18)32225-6.
2. **Tsao CW**, **Aday AW**, **Almarzooq ZI**, **Alonso A**, **Beaton AZ**, **Bittencourt MS**, **et al.** Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation* 145: e153–e639, 2022 [Erratum in *Circulation* 146: e141, 2022]. doi:10.1161/CIR.0000000000001052.
3. **Oliveros E**, **Patel H**, **Kyung S**, **Fugar S**, **Goldberg A**, **Madan N**, **Williams KA.** Hypertension in older adults: assessment, management, and challenges. *Clin Cardiol* 43: 99–107, 2020. doi:10.1002/clc.23303.
4. **Heidenreich PA**, **Trogdon JG**, **Khavjou OA**, **Butler J**, **Dracup K**, **Ezekowitz MD**, **Finkelstein EA**, **Hong Y**, **Johnston SC**, **Khera A**, **Lloyd-Jones DM**, **Nelson SA**, **Nichol G**, **Orenstein D**, **Wilson PWF**, **Woo YJ**; **American Heart Association Advocacy Coordinating Committee, Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease, Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research.** Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 123: 933–944, 2011. doi:10.1161/CIR.0b013e31820a55f5.
5. **Yusuf S**, **Hawken S**, **Ounpuu S**, **Dans T**, **Avezum A**, **Lanas F**, **McQueen M**, **Budaj A**, **Pais P**, **Varigos J**, **Lisheng L**; **INTERHEART Study Investigators.** Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 364: 937–952, 2004. doi:10.1016/S0140-6736(04)17018-9.
6. **Whelton PK**, **Carey RM**, **Aronow WS**, **Casey DE**, **Collins KJ**, **Dennison Himmelfarb C**, **DePalma SM**, **Gidding S**, **Jamerson KA**, **Jones DW**, **MacLaughlin EJ**, **Muntner P**, **Ovbiagele B**, **Smith SC**, **Spencer CC**, **Stafford RS**, **Taler SJ**, **Thomas RJ**, **Williams KA**, **Williamson JD**, **Wright JT.** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 71: e13–e115, 2018. doi:10.1161/HYP.0000000000000065.
7. **Schoenborn CA**, **Stommel M.** Adherence to the 2008 adult physical activity guidelines and mortality risk. *Am J Prev Med* 40: 514–521, 2011. doi:10.1016/j.amepre.2010.12.029.
8. **Troiano RP**, **Berrigan D**, **Dodd KW**, **Mâsse LC**, **Tilert T**, **McDowell M.** Physical activity in the United States measured by accelerometer.

Med Sci Sports Exerc 40: 181–188, 2008. doi:10.1249/mss.0b013e31815a51b3.

9. **Van Horn L**, **Carson JAS**, **Appel LJ**, **Burke LE**, **Economos C**, **Karmally W**, **Lancaster K**, **Lichtenstein AH**, **Johnson RK**, **Thomas RJ**, **Vos M**, **Wylie-Rosett J**, **Kris-Etherton P**; **American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology, Stroke Council.** Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines: a scientific statement from the American Heart Association. *Circulation* 134: e505–e529, 2016 [Erratum in *Circulation* 134: e534, 2016]. doi:10.1161/CIR.0000000000000462.
10. **Stutts WC.** Physical activity determinants in adults. Perceived benefits, barriers, and self efficacy. *AAOHN J* 50: 499–507, 2002.
11. **El Ansari W**, **Lovell G.** Barriers to exercise in younger and older non-exercising adult women: a cross sectional study in London, United Kingdom. *Int J Environ Res Public Health* 6: 1443–1455, 2009. doi:10.3390/ijerph6041443.
12. **Kelly S**, **Martin S**, **Kuhn I**, **Cowan A**, **Brayne C**, **Lafortune L.** Barriers and facilitators to the uptake and maintenance of healthy behaviours by people at mid-life: a rapid systematic review. *PloS One* 11: e0145074, 2016. doi:10.1371/journal.pone.0145074.
13. **Siddiqi Z**, **Tiro JA**, **Shuval K.** Understanding impediments and enablers to physical activity among African American adults: a systematic review of qualitative studies. *Health Educ Res* 26: 1010–1024, 2011. doi:10.1093/her/cyr068.
14. **Yarwood J**, **Carryer J**, **Gagan MJ.** Women maintaining physical activity at midlife: contextual complexities. *Nurs Prax N Z* 21: 24–37, 2005.
15. **Babakus WS**, **Thompson JL.** Physical activity among South Asian women: a systematic, mixed-methods review. *Int J Behav Nutr Phys Act* 9: 150, 2012. doi:10.1186/1479-5868-9-150.
16. **Elkins M**, **Dentice R.** Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. *J Physiother* 61: 125–134, 2015. doi:10.1016/j.jphys.2015.05.016.
17. **Worraphan S**, **Thammata A**, **Chittawatanarat K**, **Saokaew S**, **Kengkla K**, **Prasannarong M.** Effects of inspiratory muscle training and early mobilization on weaning of mechanical ventilation: a systematic review and network meta-analysis. *Arch Phys Med Rehabil* 101: 2002–2014, 2020. doi:10.1016/j.apmr.2020.07.004.
18. **Rehder-Santos P**, **Abreu RM**, **Signini ÉDF**, **da Silva CD**, **Sakaguchi CA**, **Dato CC**, **Catai AM.** Moderate- and high-intensity inspiratory muscle training equally improves inspiratory muscle strength and endurance-a double-blind randomized controlled trial. *Int J Sports Physiol Perform* 16: 1111–1119, 2021. doi:10.1123/ijspp.2020-0189.
19. **Ferreira JB**, **Plentz RDM**, **Stein C**, **Casali KR**, **Arena R**, **Lago PD.** Inspiratory muscle training reduces blood pressure and sympathetic activity in hypertensive patients: a randomized controlled trial. *Int J Cardiol* 166: 61–67, 2013. doi:10.1016/j.ijcard.2011.09.069.
20. **Saglam M**, **Arikan H**, **Vardar-Yagli N**, **Calik-Kutukcu E**, **Inal-Ince D**, **Savci S**, **Akdogan A**, **Yokusoglu M**, **Kaya EB**, **Tokgozoglu L.** Inspiratory muscle training in pulmonary arterial hypertension. *J Cardiopulm Rehabil Prev* 35: 198–206, 2015. doi:10.1097/HCR.0000000000000117.
21. **Dall'Ago P**, **Chiappa GRS**, **Guths H**, **Stein R**, **Ribeiro JP.** Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol* 47: 757–763, 2006. doi:10.1016/j.jacc.2005.09.052.
22. **Beaumont M**, **Forget P**, **Couturaud F**, **Reychler G.** Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Respir J* 12: 2178–2188, 2018. doi:10.1111/crj.12905.
23. **Smart NA**, **Giallauria F**, **Dieberg G.** Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Int J Cardiol* 167: 1502–1507, 2013. doi:10.1016/j.ijcard.2012.04.029.
24. **Ramsook AH**, **Molgat-Seon Y**, **Schaeffer MR**, **Wilkie SS**, **Camp PG**, **Reid WD**, **Romer LM**, **Guenette JA.** Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. *J Appl Physiol (1985)* 122: 1267–1275, 2017. doi:10.1152/japplphysiol.00046.2017.
25. **Segizbaeva MO**, **Timofeev NN**, **Donina ZA**, **Kur'yanovich EN**, **Aleksandrova NP.** Effects of inspiratory muscle training on resistance to fatigue of respiratory muscles during exhaustive exercise. *Adv Exp Med Biol* 840: 35–43, 2015. doi:10.1007/5584_2014_20.
26. **de Sousa MM**, **Pimentel MDS**, **Sobreira IA**, **Barros R de J**, **Borghi-Silva A**, **Mazzoli-Rocha F.** Inspiratory muscle training improves aerobic capacity in amateur indoor football players. *Int J Sports Med* 42: 456–463, 2021. doi:10.1055/a-1255-3256.
27. **Chang Y-C**, **Chang H-Y**, **Ho C-C**, **Lee P-F**, **Chou Y-C**, **Tsai M-W**, **Chou L-W.** Effects of 4-week inspiratory muscle training on sport performance in college 800-meter track runners. *Medicina (Kaunas)* 57: 72, 2021. doi:10.3390/medicina57010072.
28. **Romer LM**, **McConnell AK**, **Jones DA.** Effects of inspiratory muscle training on time-trial performance in trained cyclists. *J Sports Sci* 20: 547–590, 2002. doi:10.1080/026404102760000053.
29. **Craighead DH**, **Heinbockel TC**, **Hamilton MN**, **Bailey EF**, **MacDonald MJ**, **Gibala MJ**, **Seals DR.** Time-efficient physical training for enhancing cardiovascular function in midlife and older adults: promise and current research gaps. *J Appl Physiol (1985)* 127: 1427–1440, 2019. doi:10.1152/japplphysiol.00381.2019.
30. **Craighead DH**, **Freeberg KA**, **McCarty NP**, **Seals DR.** Time-efficient, high-resistance inspiratory muscle strength training for cardiovascular aging. *Exp Gerontol* 154: 111515, 2021. doi:10.1016/j.exger.2021.111515.
31. **Craighead DH**, **Heinbockel TC**, **Freeberg KA**, **Rossman MJ**, **Jackman RA**, **Jankowski LR**, **Hamilton MN**, **Ziemba BP**, **Reisz JA**, **D'Alessandro A**, **Brewster LM**, **DeSouza CA**, **You Z**, **Chonchol M**, **Bailey EF**, **Seals DR.** Time-efficient inspiratory muscle strength training lowers blood pressure and improves endothelial function, NO bioavailablity and oxidative stress in midlife/older adults with above-normal blood pressure. *J Am Heart Assoc* 10: e020980, 2021. doi:10.1161/JAHA.121.020980.
32. **Vranish JR**, **Bailey EF.** Daily respiratory training with large intrathoracic pressures, but not large lung volumes, lowers blood pressure in normotensive adults. *Respir Physiol Neurobiol* 216: 63–69, 2015. doi:10.1016/j.resp.2015.06.002.
33. **Vranish JR**, **Bailey EF.** Inspiratory muscle training improves sleep and mitigates cardiovascular dysfunction in obstructive sleep apnea. *Sleep* 39: 1179–1185, 2016. doi:10.5665/sleep.5826.
34. **DeLucia CM**, **De Asis RM**, **Bailey EF.** Daily inspiratory muscle training lowers blood pressure and vascular resistance in healthy men and women. *Exp Physiol* 103: 201–211, 2018. doi:10.1113/EP086641.
35. **Ramos-Barrera GE**, **DeLucia CM**, **Bailey EF.** Inspiratory muscle strength training lowers blood pressure and sympathetic activity in older adults with OSA: a randomized controlled pilot trial. *J Appl Physiol (1985)* 129: 449–458, 2020. doi:10.1152/japplphysiol.00024.2020.
36. **Craighead DH**, **Freeberg KA**, **Maurer GS**, **Myers VH**, **Seals DR.** Translational potential of high-resistance inspiratory muscle strength training. *Exerc Sport Sci Rev* 50: 107–117, 2022. doi:10.1249/JES0000000000000293.
37. **Mancia G**, **Fagard R**, **Narkiewicz K**, **Redón J**, **Zanchetti A**, **Böhm M**, **Christiaens T**, **Cifkova R**, **De Backer G**, **Dominiczak A**, **Galderisi M**, **Grobbee DE**, **Jaarsma T**, **Kirchhof P**, **Kjeldsen SE**, **Laurent S**, **Manolis AJ**, **Nilsson PM**, **Ruilope LM**, **Schmieder RE**, **Sirnes PA**, **Sleight P**, **Viigimaa M**, **Waeber B**, **Zannad F**; **Task Force Members.** 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 31: 1281–1357, 2013. doi:10.1097/01.hjh.0000431740.32696.cc.
38. **Pickering TG**, **Hall JE**, **Appel LJ**, **Falkner BE**, **Graves J**, **Hill MN**, **Jones DW**, **Kurtz T**, **Sheps SG**, **Roccella EJ**; **Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research.** Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 45: 142–161, 2005. doi:10.1161/01.HYP.0000150859.47929.8e.
39. **American Thoracic Society/European Respiratory Society.** ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 166: 518–624, 2002. doi:10.1164/rccm.166.4.518.
40. Borenstein M (Editor)**.** *Introduction to Meta-Analysis*. Chichester: Wiley, 2009.

41. **Hedges LV.** Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Stat* 6: 107–128, 1981. doi:10.3102/10769986006002107. doi:10.2307/1164588.
42. **Chang Y**, **Phillips MR**, **Guymer RH**, **Thabane L**, **Bhandari M**, **Chaudhary V**; **R.E.T.I.N.A. study group.** The 5 min meta-analysis: understanding how to read and interpret a forest plot. *Eye (Lond)* 36: 673–675, 2022. doi:10.1038/s41433-021-01867-6.
43. **Lewington S**, **Clarke R**, **Qizilbash N**, **Peto R**, **Collins R**; **Prospective Studies Collaboration.** Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360: 1903–1913, 2002 [Erratum in *Lancet* 361: 1060, 2003]. doi:10.1016/s0140-6736(02)11911-8.
44. **Musini VM**, **Nazer M**, **Bassett K**, **Wright JM.** Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. *Cochrane Database Syst Rev* CD003824, 2014. doi:10.1002/14651858.CD003824.pub2.
45. **Heran BS**, **Wong MM**, **Heran IK**, **Wright JM.** Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database Syst Rev* 2008: CD003823, 2008. doi:10.1002/14651858.CD003823.pub2.
46. **Heran BS**, **Wong MMY**, **Heran IK**, **Wright JM.** Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev* 2008: CD003822, 2008. doi:10.1002/14651858.CD003822.pub2.
47. **Cornelissen VA**, **Smart NA.** Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2: e004473, 2013. doi:10.1161/JAHA.112.004473.
48. **Whelton SP**, **Chin A**, **Xin X**, **He J.** Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 136: 493–503, 2002. doi:10.7326/0003-4819-136-7-200204020-00006.
49. **Aburto NJ**, **Ziolkovska A**, **Hooper L**, **Elliott P**, **Cappuccio FP**, **Meerpohl JJ.** Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 346: f1326–f1326, 2013. doi:10.1136/bmj.f1326.
50. **He FJ**, **Li J**, **Macgregor GA.** Effect of longer term modest salt reduction on blood pressure: cochrane systematic review and meta-analysis of randomised trials. *BMJ* 346: f1325, 2013. doi:10.1136/bmj.f1325.
51. **Neter JE**, **Stam BE**, **Kok FJ**, **Grobbee DE**, **Geleijnse JM.** Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 42: 878–884, 2003. doi:10.1161/01.HYP.0000094221.86888.AE.
52. **Piercy KL**, **Troiano RP**, **Ballard RM**, **Carlson SA**, **Fulton JE**, **Galuska DA**, **George SM**, **Olson RD.** The physical activity guidelines for Americans. *JAMA* 320: 2020–2028, 2018. doi:10.1001/jama.2018.14854.
53. **Juraschek SP**, **Woodward M**, **Sacks FM**, **Carey VJ**, **Miller ER**, **Appel LJ.** Time course of change in blood pressure from sodium reduction and the DASH diet. *Hypertension* 70: 923–929, 2017. doi:10.1161/HYPERTENSIONAHA.117.10017.
54. **Kiyonaga A**, **Arakawa K**, **Tanaka H**, **Shindo M.** Blood pressure and hormonal responses to aerobic exercise. *Hypertension* 7: 125–131, 1985. doi:10.1161/01.hyp.7.1.125.
55. **Arbab-Zadeh A**, **Perhonen M**, **Howden E**, **Peshock RM**, **Zhang R**, **Adams-Huet B**, **Haykowsky MJ**, **Levine BD.** Cardiac remodeling in response to 1 year of intensive endurance training. *Circulation* 130: 2152–2161, 2014. doi:10.1161/CIRCULATIONAHA.114.010775.
56. **Tavoian D**, **Ramos-Barrera LE**, **Craighead DH**, **Seals DR**, **Bedrick EJ**, **Alpert JS**, **Mashaqi S**, **Bailey EF.** Six months of inspiratory muscle training to lower blood pressure and improve endothelial function in middle-aged and older adults with above-normal blood pressure and obstructive sleep apnea: protocol for the CHART clinical trial. *Front Cardiovasc Med* 8: 760203, 2021. doi:10.3389/fcvm.2021.760203.
57. **Craighead DH**, **Freeberg KA**, **McCarty NP**, **Rossman MJ**, **Moreau KL**, **You Z**, **Choncho M**, **Seals DR.** Inspiratory muscle strength training for lowering blood pressure and improving endothelial function in postmenopausal women: comparison with "standard of care" aerobic exercise. *Front Physiol* 13: 967478, 2022. doi:10.3389/fphys.2022.
58. **American College of Sports Medicine.** American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 41: 687–708, 2009. doi:10.1249/MSS.0b013e3181915670.
59. **Carpenter MA**, **Tockman MS**, **Hutchinson RG**, **Davis CE**, **Heiss G.** Demographic and anthropometric correlates of maximum inspiratory pressure: the atherosclerosis risk in communities study. *Am J Respir Crit Care Med* 159: 415–422, 1999. doi:10.1164/ajrccm.159.2.9708076.
60. **Harik-Khan RI**, **Wise RA**, **Fozard JL.** Determinants of maximal inspiratory pressure. The Baltimore longitudinal study of aging. *Am J Respir Crit Care Med* 158: 1459–1464, 1998. doi:10.1164/ajrccm.158.5.9712006.
61. **Koch B**, **Schäper C**, **Ittermann T**, **Bollmann T**, **Völzke H**, **Felix SB**, **Ewert R**, **Gläser S.** Reference values for respiratory pressures in a general adult population–results of the Study of Health in Pomerania (SHIP). *Clin Physiol Funct Imaging* 30: 460–465, 2010. doi:10.1111/j.1475-097X.2010.00966.x.
62. **Meyer FJ**, **Borst MM**, **Zugck C**, **Kirschke A**, **Schellberg D**, **Kübler W**, **Haass M.** Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation* 103: 2153–2158, 2001. doi:10.1161/01.CIR.103.17.2153.
63. **Ribeiro JP**, **Chiappa GR**, **Neder JA**, **Frankenstein L.** Respiratory muscle function and exercise intolerance in heart failure. *Curr Heart Fail Rep* 6: 95–101, 2009. doi:10.1007/s11897-009-0015-7.
64. **van der Palen J**, **Rea TD**, **Manolio TA**, **Lumley T**, **Newman AB**, **Tracy RP**, **Enright PL**, **Psaty BM.** Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax* 59: 1063–1067, 2004. doi:10.1136/thx.2004.021915.
65. **Ragette R**, **Mellies U**, **Schwake C**, **Voit T**, **Teschler H.** Patterns and predictors of sleep disordered breathing in primary myopathies. *Thorax* 57: 724–728, 2002. doi:10.1136/thorax.57.8.724.
66. **Johnson EM**, **Roberts M**, **Mozaffar T**, **Young P**, **Quartel A**, **Berger KI.** Pulmonary function tests (maximum inspiratory pressure, maximum expiratory pressure, vital capacity, forced vital capacity) predict ventilator use in late-onset Pompe disease. *Neuromuscul Disord* 26: 136–145, 2016. doi:10.1016/j.nmd.2015.11.009.
67. **Polkey MI**, **Lyall RA**, **Yang K**, **Johnson E**, **Leigh PN**, **Moxham J.** Respiratory muscle strength as a predictive biomarker for survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 195: 86–95, 2017. doi:10.1164/rccm.201604-0848OC.
68. **Cheng S**, **Xanthakis V**, **Sullivan LM**, **Vasan RS.** Blood pressure tracking over the adult life course: patterns and correlates in the Framingham heart study. *Hypertension* 60: 1393–1399, 2012. doi:10.1161/HYPERTENSIONAHA.112.201780.
69. **Chobanian AV**, **Bakris GL**, **Black HR**, **Cushman WC**, **Green LA**, **Izzo JL**, **Jones DW**, **Materson BJ**, **Oparil S**, **Wright JT**, **Roccella EJ**; **National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure: the JNC 7 report. *JAMA* 289: 2560–2572, 2003. doi:10.1001/jama.289.19.2560.