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Device and non-device-guided slow breathing to reduce blood pressure: A systematic review and meta-analysis☆

Ashish Chaddha[a,*], Daniel Modaff[a], Christopher Hooper-Lane[b], David A. Feldstein[a]

[a] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States
[b] Ebling Health Sciences Library, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

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ABSTRACT

Objectives: Interest is increasing in nonpharmacological interventions to treat blood pressure in hypertensive and prehypertensive patients at low cardiac risk. This meta-analysis of randomized controlled trials assesses the impact of device-guided and non-device-guided (pranayama) slow breathing on blood pressure reduction in these patient populations.

Methods: We searched PubMed, EMBASE, CINAHL, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, Web of Science, BIOSIS (Biological Abstracts) Citation Index and Alt HealthWatch for studies meeting these inclusion criteria: randomized controlled trial or first phase of a randomized cross-over study; subjects with hypertension, prehypertension or on antihypertensive medication; intervention consisting of slow breathing at ≤10 breaths/minute for ≥5 min on ≥3 days/week; total intervention duration of ≥4 weeks; follow-up for ≥4 weeks; and a control group. Data were extracted by two authors independently, the Cochrane Risk of Bias Tool assessed bias risk, and data were pooled using the DerSimonian and Laird random effects model. Main outcomes included changes in systolic (SBP) and/or diastolic blood pressure (DBP), heart rate (HR), and/or decreased antihypertensive medication.

Results: Of 103 citations eligible for full-text review, 17 studies were included in the meta-analysis. Overall, slow breathing decreased SBP by -5.62 mmHg [-7.86, -3.38] and DBP by -2.97 mmHg [-4.28, -1.66]. Heterogeneity was high for all analyses.

Conclusions: Slow breathing showed a modest reduction in blood pressure. It may be a reasonable first treatment for low-risk hypertensive and prehypertensive patients who are reluctant to start medication.

1. Introduction

Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in both the United States and worldwide, and hypertension is one of its most important risk factors.[1–3] When blood pressure rises, the risk of CVD increases.[1–3] For example, an increase in systolic blood pressure (SBP) from 115 mmHg to 135 mmHg doubles the risk of CVD and death from stroke.[1–3] According to the Centers for Disease Control and Prevention, the incidence of hypertension and prehypertension in US adults is 29% and 33%, respectively.[4] In 2013, direct health care spending for hypertension totaled $47.4 billion, and 43% of this ($20.4 billion) was related to prescription drug costs.[5]

The current strategy to prevent the adverse health consequences of hypertension is to encourage medication adherence and lifestyle changes. However, compliance with these strategies remains poor.[6] Optimal treatment for certain populations such as hypertensive and prehypertensive patients who are at low cardiac risk (no history of cardiovascular disease and no cardiac risk factors besides hypertension or prehypertension) is unclear because most antihypertensive trials have focused on patients with multiple risk factors.[7] As a result of these issues, there has been increasing interest in non-dietary, nondrug interventions for hypertension.[6] One of these alternative approaches is slow breathing which can be performed unassisted or guided by a device.

Non-device slow breathing, or pranayama, is the controlled breathing that lies at the heart of yoga. Pranayama has been present since 3000 BCE and was used in ancient India to prevent disease and promote long-term survival. Observational studies have shown a blood pressure lowering benefit of pranayama for hypertensive and prehypertensive patients at low cardiac risk.[8,9] RESPeRATE (InterCure

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* Corresponding Author at: William Beaumont Hospital, 1301 West 13 Mile Road, Royal, MI, 48037, United States.
E-mail address: ashish.chaddha@beaumont.org (A. Chaddha).

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Ltd., London, UK) is a Food and Drug Administration-approved device to reduce stress and lower blood pressure by promoting slow, deep breathing. A chest sensor measures respirations and sends the data to a portable device. The device creates a melody that is transmitted via headphones. By synchronizing breathing with the melody, breathing is slowed by long exhalations to less than 10 breaths per minute. Studies indicate RESPeRATE is easy to use and has a high compliance rate.[7] The American Heart Association gives device-guided slow breathing a class IIA (level of evidence B) recommendation for blood pressure lowering efficacy.[6]

To date, two meta-analyses and systematic reviews have assessed slow breathing to treat hypertensive and prehypertensive patients who are at low cardiac risk. Mahtani et al. showed a reduction in blood pressure with short-term use of device-guided slow breathing.[10] However, after removing five of the eight trials because they were industry-sponsored, no overall effect was found. Landman et al. failed to show a blood pressure benefit with device-guided slow breathing, but this meta-analysis only consisted of five randomized controlled trials.[11] Neither of these reviews included randomized controlled trials (RCTs) of non-device-guided slow breathing. This meta-analysis of RCTs evaluates the effect of slow breathing (both device-guided and non-device-guided) on blood pressure in patients with hypertension or prehypertension who are at low cardiac risk.

2. Methods

2.1. Search strategy

We searched MEDLINE, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials, and BIOSIS (Biological Abstracts) Citation Index from inception until May 2015. Alt HealthWatch and EMBASE were searched from inception until July 2015. Results were restricted to the English language. We reviewed the reference lists of related systematic reviews and the selected papers were manually searched to identify original articles that may have been missed. Clinicaltrials.gov (September, 2015) was searched to identify unpublished trials.

The search strategy used a combination of themes: 1) hypertension OR prehypertension OR blood pressure; 2) breathing exercises OR slow breathing OR device-guided breathing OR pranayama OR resperate OR yogic breathing OR controlled breathing; Results from these 2 search strings were combined with 'AND'. Exact search terms varied by database. The full electronic search strategy is available online in eFig. 1.

2.2. Study selection

Randomized controlled trials or the first phase of randomized crossover studies that evaluated slow breathing ($\leq$10 breaths per minute) in patients with hypertension (SBP $>$ 140 or DBP $>$ 90 mmHg or taking antihypertensives) or in patients with pre-hypertension (SBP $>$ 120 and $\leq$140 and/or DBP $>$ 80 and $\leq$90) were included. Studies had to be $\geq$4 weeks in length and the intervention needed to consist of slow breathing (device-guided or non-device-guided) for $\geq$5 min on at least 3 days per week. Studies needed to report changes in blood pressure, changes in heart rate or changes in antihypertensive medications. Studies of healthy subjects without baseline hypertension or prehypertension were excluded.

References from the electronic search were imported into a reference management program, Zotero (Roy Rosenzweig Center for History and New Media at George Mason University, Fairfax, VA). One author (A.C.) performed the initial screening of studies based on title alone. References that were not trials or were not related to the area of interest were excluded. Two authors (A.C. and D.M.) then independently performed the study selection using an inclusion and exclusion criteria table. Disagreements were resolved by discussion until consensus was reached. Remaining disagreements were resolved by a third investigator (D.A.F.).

2.3. Data extraction

Two authors (A.C. and D.M.) independently extracted data from the included studies using a data extraction form. Data extracted included study year and design; study population and co-morbidities; intervention parameters (i.e., intensity of intervention, device or no-device); comparison group; and outcomes (i.e., blood pressure at various time intervals, decrease in antihypertensive medications). Study authors were contacted to collect missing data. Discrepancies were settled by consensus and a third investigator (D.A.F.) resolved any remaining disagreements.

2.4. Quality assessment

Studies were assessed for risk of bias using the Cochrane Collaboration's risk of bias tool which assesses seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias issues.[13] Two authors (A.C. and D.M.) independently assessed the studies for risk of bias. Disagreements were resolved by consensus and remaining disagreements were settled by a third author (D.A.F.).

2.5. Data synthesis and analysis

Our primary outcomes were changes in systolic and diastolic blood pressure. Secondary outcomes included changes in heart rate and changes in antihypertensive medication use. Office-based blood pressure results were used when available; home blood pressures were used for studies that did not measure office-based blood pressures. If a standard deviation for the within-group change in blood pressure could not be determined from the study, it was imputed using the standard deviation for pre- and post-intervention blood pressure with a correlation coefficient of 0.895 derived from included studies. Results were pooled using the methods of DerSimonian and Laird random effects model.[14] Heterogeneity was assessed using the chi-squared test and the I^2 index, which refers to the percentage of the variability in effect estimates from heterogeneity compared to chance.[15] A priori anticipated sources of heterogeneity were device vs. non-device intervention, subjects with hypertension vs. pre-hypertension, active vs. usual care comparator, ambulatory blood pressure vs. office blood pressure, and abstract only vs. full text. Post-hoc exploration of heterogeneity was performed for study risk of bias and intervention intensity ($<$ 100, 100–200 and $>$ 200 min/week).

Publication bias was evaluated using funnel plots. Meta-analyses were performed using Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Study selection and characteristics

The initial search included 1984 unique citations. Seventeen articles were included in the systematic review (See Fig. 1 for PRISMA flow diagram). Of these, five were abstracts only. References of included studies were searched and no additional studies for inclusion were identified. Fifteen studies used device-guided breathing[16,17,19–27,29–32] while two used non-device-guided (i.e., pranayama) slow breathing[18,28] (Table 1). The majority of the studies had a maximal breathing rate of 10 while the two non-device-guided studies had a maximal rate of 6. The goal intervention was generally between 10 and 15 min daily. Nine studies did not have an active control group.[19,20,23,24,27,28,31,32] In the remainder, the control condition varied from sham device-guided breathing to music. The follow-up period was eight weeks for all but one study, which had a 65-week follow-up.[30] Six studies were

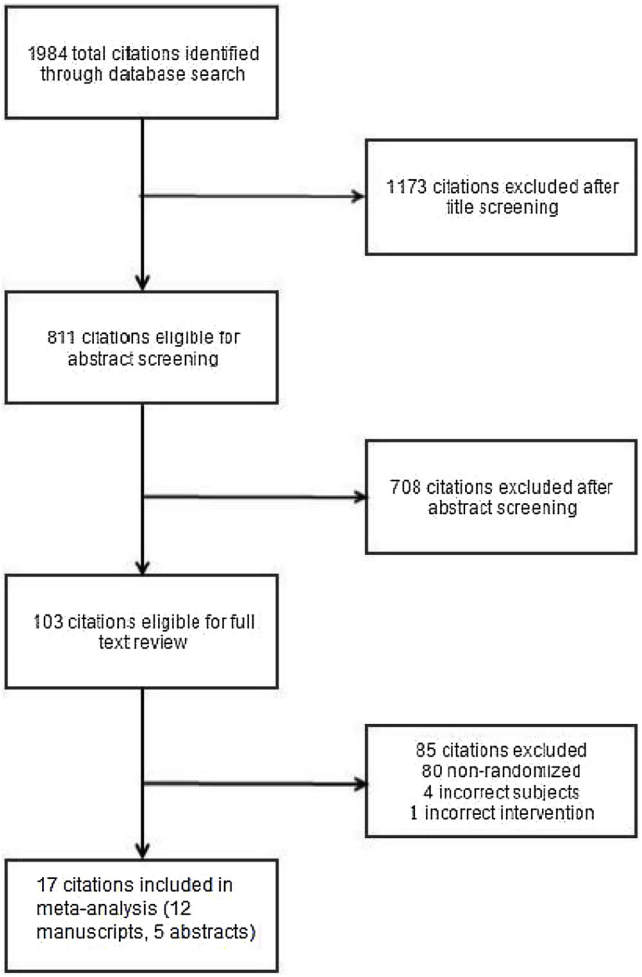

Fig. 1. PRISMA Flow Diagram of Literature Search and Included Studies for Systematic Review and Meta-Analysis.

sponsored by InterCure, Inc., manufacturer of the RESPeRATE slow breathing device.[20,22,27,29,30,32] The overall compliance rate with intervention was high in all trials. No adverse events were reported for any trial.

3.2. Study quality

Most studies had an unclear risk of bias for at least one category.[16–22,24,26–29,31,32] Two studies were at risk of bias for random sequence generation [20,28] and four were at risk for incomplete outcome data (eFig. 2).[20,24,28,32]

3.3. Changes in systolic blood pressure

Systolic blood pressure (SBP) was reported in all 17 studies (1017 subjects). Clinic-based SBP readings were used for 14 studies.[16,17,20–22,24–32]. The overall decrease in SBP was -5.62 mmHg [-7.86, -3.38] ($p < 0.001$) with an I^2 of 84% (Fig. 2). The decrease in SBP for the 15 studies using device-guided slow breathing was -5.28 mmHg [-7.80, -2.76] ($p < 0.001$), which was smaller than the decrease for the two studies using non-device-guided slow breathing −7.69 mmHg [−12.67, -2.72] ($p < 0.00\ 1$). However, device-guided versus non-device-guided breathing had little impact on the large amount of heterogeneity in the analysis with I^2 statistics still 82% and 85% respectively.

3.4. Changes in diastolic blood pressure

Diastolic blood pressure (DBP) was reported in 16 studies (964 subjects). The overall decrease was -2.97 mmHg [−4.28, −1.66] ($p < 0.001$) with an I^2 of 74% (Fig. 3). The decrease in DBP for the 15 studies using device-guided slow breathing was −2.67 mmHg [−3.82, −1.52] ($p < 0.001$).Only a single non-device guided study reported DBP.

3.5. Changes in heart rate

Heart rate was reported in seven studies (343 subjects) which were all device-guided. The overall decrease in heart rate was not significant (−1.23 [−3.82, 1.36] with an I^2 of 76%) (eFig. 3, $p = 0.35$).

3.6. Other results

None of the studies assessed changes in antihypertensive medications. A priori sensitivity analyses of the main outcomes (SBP and DBP) were performed for home vs. office readings, abstract-only vs. full text publication, subjects with hypertension vs. pre-hypertension, and control group receiving usual care vs. active comparator (eFigs. 4–11). There was little impact on the overall result and no statistical differences between subgroups. The I^2 remained > 60% for all analyses.

Post hoc analysis for intervention intensity found a greater reduction in SBP and DBP in the higher intensity groups. SBP decreased -3.01 mmHg [−4.83, −1.18] for interventions < 100 min per week (4 trials; all device guided), -6.44 mmHg [−9.94, −2.93] for interventions of 100–200 minutes per week (8 trials; all device guided), and −14.00 mmHg [−18.85, −9.15] for interventions of > 200 min per week (1 trial; non-device guided) (eFigs. 12–13, $p = 0.00001$). Post hoc analysis of low risk of bias studies revealed a non-significant SBP decrease of −2.14 [−4.76, 0.48] ($p = 0.11$) and DBP decrease of −1.63 [−3.95, 0.69] (eFigs. 14–15, $p = 0.17$). There was also a decrease in heterogeneity with an I^2 of 31%.

3.7. Publication Bias

A funnel plot for SBP revealed evidence of missing studies in the lower left quadrant (eFig. 16). These would have represented smaller studies with greater decreases in blood pressures. However, a large number of included studies were small and industry-sponsored, signifying a risk for publication bias. The funnel plot for SBP is provided in eFig. 17.

4. Discussion

Randomized controlled trials of device-guided slow breathing showed a modest but statistically significant reduction in SBP of −5.28 mmHg and in DBP of −2.67 mmHg. Non-device slow breathing trials showed a slightly larger reduction in SBP of −8.45 mmHg and a significantly greater reduction in DBP of −6.90 mmHg. These findings are potentially important because modest reductions in blood pressure have been shown to improve outcomes in patients with hypertension or prehypertension who are at low cardiac risk.[34,35] Sundstrom et al. reported that an average blood pressure reduction of 3.6/2.4 mmHg was associated with an odds ratio of 0.86 (95% CI, 0.74–1.01) for total cardiovascular events, 0.72 (CI, 0.55 to 0.94) for strokes, 0.91 (CI, 0.74–1.12) for coronary events, 0.80 (CI, 0.57–1.12) for heart failure, 0.75 (CI, 0.57 to 0.98) for cardiovascular deaths, and 0.78 (CI, 0.67 to 0.92) for total deaths.[36] Withdrawal from treatment due to adverse events from antihypertensives was common. Slow breathing showed reductions in blood pressure similar to those for antihypertensives which have demonstrated improved outcomes in low cardiac risk hypertensive and prehypertensive patients.[41] For example, treatment with hydrochlorothiazide lowers blood pressure by -6/-3 mmHg (dose of

Table 1
Description of Included Studies.

Study, Year	Patients (n)	Patient Population	Mean Age (Int/ Cont)	% Men	Int Grp Baseline BP (mmHg)	Cont Grp Baseline BP (mmHg)	Int Condition	Cont Condition	Duration	Outcome	Industry Funding
Altena et al, 2009	30	Hypertensive outpatients, ≥1 antihypertensive	60/59	50	147 (5.8)/ 94 (76.5-97)	151.5 (6.2)/ 87 (82-97)	Device-guided, 10-15 min daily, < 10 breaths/min	Discman with slow music	8 weeks	SBP, DBP, QOL	No
Anderson et al, 2010	40	Hypertensive or prehypertensive	53.4/ 52.9	52.5	142 (13.2)/ 88 (8.8)	140 (11.5)/ 85 (9.9)	Device-guided, 15 min daily, < 10 breaths/min	Meditative relaxation exercise (observe breathing)	4 weeks	SBP, DBP, 24 hr BP, RR, tidal volume	No
Bazzini et al, 2009	84	Hypertensive outpatients		NR	NR	NR	Pranayama, 30 min daily, 4-6 breaths/min	Relax while listening to slow music	30 weeks	24 hr BP, HR	Unsure
Clemow et al, 2015 (Abstract only)	171	Hypertensive, 1 antihypertensive	NR	NR	NR	NR	Device-guided, 15 min/ day, 6-10 breaths/min	No intervention	8 weeks	SBP, DBP	Unsure
Elliott et al, 2004	149	Hypertensive outpatients, on anthypertensive for ≥1 month	59.5/ 58.7	49	150.3 (8.3)/ 84.7 (9.0)	149.8 (9.4)/ 86.8 (8.1)	Device-guided, 15 min/ day, < 10 breaths/min	No intervention	8 weeks	SBP, DBP	Yes
Giannatasio et al, 2002 (Abstract only)	73	Hypertensive outpatients	54 Over-all	58	Overall: 149 (20)/93 (9)		Device-guided, 15 min/ day, 10 breaths/min	NR	8 weeks	SBP, DBP, HR	Unsure
Grossman et al, 2001	33	Hypertensive, 1 antihypertensive for ≥2 months	52/50	69.5	160 (18)/ 96 (7)	155 (11)/ 94 (6)	Device-guided, 10 min daily, 10 breaths/min	Walkman, playing similar music	8 weeks	SBP, DBP, HR	Yes
Howorka et al, 2013	32	Hypertensive outpatients	50/49	47	126.1 (3.0)/ 71 (2.0)	125 (5)/ 72 (2)	Device-guided, 12 min/ day, < 10 breaths/min	No intervention	8 weeks	24 hr BP, 24 hr MAP, 24 hr PP	No
Jones et al, 2010	30	Hypertensive outpatients	53/50	36	136 (12.6)/ 80 (5.5)	131 (9.1)/ 78 (6.5)	Device-guided, 30 min/ day, 6 breaths/min	No intervention	8 weeks	SBP, DBP, HR	No
Landman et al, 2013	48	Hypertensive outpatients, ≥1 antihypertensive	64/65	62.5	151.6 (8.3)/ 82.1 (14.7)	151.2 (10.6)/ 80.7 (8.9)	Device-guided, 15 min/ day, < 10 breaths/min	Visually identical device	8 weeks	SBP, DBP	Yes
Logtenberg et al, 2007	30	Hypertensive outpatients, ≥1 antihypertensive	63/61	44	153.5 (7.5)/ 83.0 (6.7)	150.4 (8.2)/ 87.0 (8.3)	Device-guided, daily min NR, < 10 breaths/ min	Listened to Walkman	8 weeks	SBP, DBP, QOL	No
Meles et al, 2004	79	Treated or untreated hypertensive outpatients	57/49	NR	141 (15.4)/ 88.1 (7.8)	133 (18.3)/ 86 (7.4)	Device-guided, 15 min/ day, breaths/min NR	No intervention	8 weeks	SBP, DBP, HR	Yes
Mourya et al, 2009	40	Hypertensive outpatients	NR	55	146 (2)/ 92 (2)	147 (2)/ 91 (2)	Pranayama, 15 min twice/day, 5-6 breaths/ min	No intervention	12 weeks	SBP, DBP, handgrip test	No
Nord et al, 2010 (Abstract only)	90	Hypertensive outpatients	NR	NR	NR	NR	Device-guided, 15 min/ day, breaths/min NR	Listened to music on CD player	65 weeks	SBP, DBP	Unsure
Schein et al, 2001	65	Hypertensive outpatients	58/57	47	157 (14)/ 97 (8.9)	155 (8.5)/ 93 (7.1)	Device-guided, 10 min/ day, < 10 breaths/min	Listen to music on Walkman	8 weeks	SBP, DBP, MAP, HR	Yes
Schein et al, 2006 (Abstract only)	50	Hypertensive outpatients with NIDDM	63 overall	64	148 (2.1)/ 81 (1.9)	144 (1.7)/ 81 (1.4)	Device-guided, 15 min/ day, breaths/min NR	No intervention	8 weeks	SBP, DBP, anxiety and physical complaints (QSD-R)	Unsure
Schein et al, 2009	71	Hypertensive outpatients with NIDDM	62/63	63	150 (12)/ 81 (10)	147 (10)/ 81 (8)	Device-guided, 15 min/ day, < 10 breaths/min	No intervention	8 weeks	SBP, DBP, HR	Yes

Int = Intervention; Cont = Control; Grp = Group; NR = Not Reported; NIDDM = Non-Insulin-Dependent Diabetes Mellitus; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; QOL = Quality of Life; MAP = Mean Arterial Pressure; HR = Heart Rate; RR = Respiratory Rate; PP = Pulse Pressure; MVC = Maximum Voluntary Contraction; QSD-R = Questionnaire on Stress in Patients with Diabetes.
Baseline blood pressure reported in mean (standard deviation).

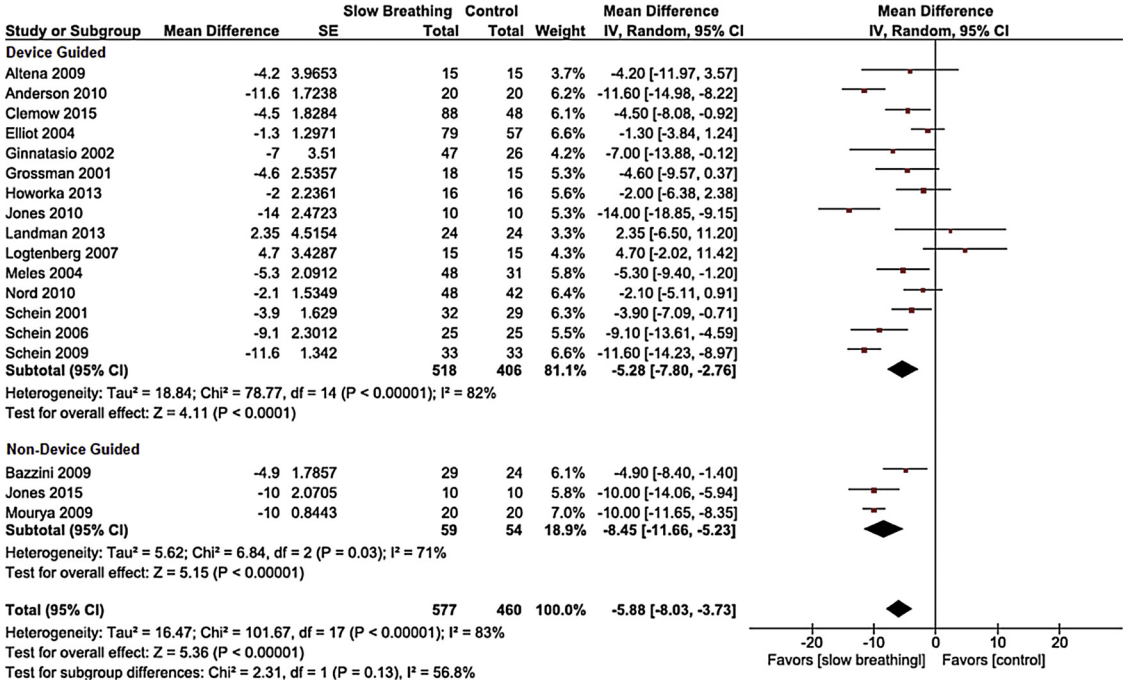

Fig. 2. Forest Plot for change in systolic blood pressure.

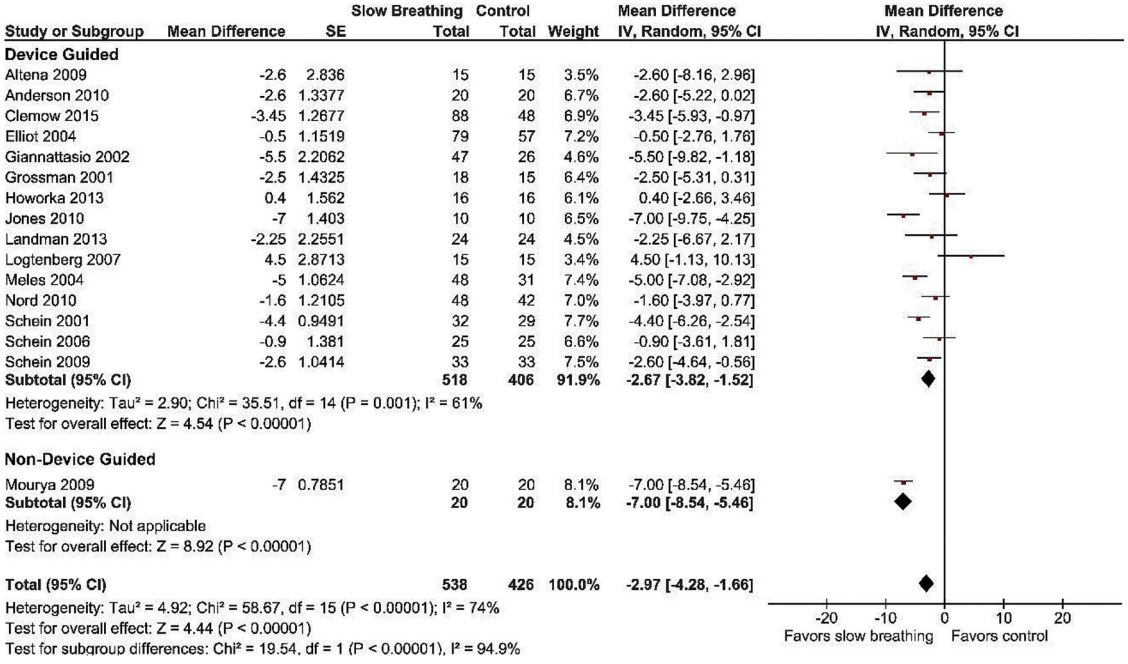

Fig. 3. Forest Plot for change in diastolic blood pressure.

12.5 mg), -8/-3 mmHg (dose of 25 mg), and -11/-5 mmHg (dose of 50 mg).[37] Reductions in blood pressure for beta-blockers, angiotensin inhibitors and angiotensin receptor blocker are similar.[38–40] Slow breathing may be beneficial in treating hypertension in this patient cohort.

Both device and non-device-guided slow breathing are inexpensive interventions, easy to learn, and have minimal side effects. Pranayama may also be beneficial due to its effects on mental health. Mental illness such as depression and anxiety and mental distress such as stress are potent risk factors for cardiovascular disease.[42] Pranayama is a component of yoga, and yoga has been shown to improve mental health and reduce stress.[43] Stress reduction may reduce all-cause mortality by 23% and cardiovascular mortality by 30% [43-44]. Stress reduction may also lower blood pressure by -2-5/-1-2 mmHg [43-44]. Pranayama's mental health benefits may help explain its greater effect on blood pressure reduction compared to device-guided slow breathing.

While the decrease in blood pressure is promising, it has to be tempered by weaknesses in the existing RCTs including large heterogeneity, relatively short follow-up periods, high risk of bias, and post hoc analyses of low risk of bias studies showing an insignificant decrease in blood pressure. The intensity of the intervention could certainly play a role in the level of blood pressure reduction as we saw a trend toward greater reduction with increasing intensity.

Our study has several limitations. First, the heterogeneity pertaining

to trials with device-guided slow breathing is high and we were not able to find an explanation for the large heterogeneity. Next, most of the included trials consist of a short duration of follow-up of 4–8 weeks. As a result, it is unclear if the blood pressure lowering effects of slow breathing are sustainable. These trials were not long enough or powered to assess if slow breathing is associated with improved outcomes which is the true goal of blood pressure reduction. In addition, the quality of the majority of the trials is low or unclear and there was some risk of publication bias. Finally, we did not include non-English studies in our review, however our search did not reveal any foreign language abstracts that would have met inclusion.

Slow breathing may modestly reduce systolic and diastolic blood pressure. While non-device-guided slow breathing may have even a greater effect compared with device guided slow breathing, this is based on a small body of evidence as only two non-device guided studies were included. Slow breathing may be beneficial for treating hypertension in patients with hypertension or prehypertension who are at low cardiac risk, especially for patients who wish to avoid medications initially. However, these results must be interpreted with caution given the limitations of the available data. Larger randomized controlled trials with long-term follow-up are needed to better assess the effect of slow breathing (both device and non-device-guided) on blood pressure and whether these effects are sustained. More study is also needed to assess if slow breathing is associated with improved outcomes in low cardiac risk hypertensive and prehypertensive patients.

Conflicts of interest and source of funding

All authors declare no conflict of interest. This study by medical residents was unfunded.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.03.005.

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