Curr Hypertens Rep (2017) 19: 45
DOI 10.1007/s11906-017-0742-1

Role of Paced Breathing for Treatment of Hypertension

Relu Cernes[1,3] · **Reuven Zimlichman**[2,3]

Published online: 3 May 2017

Abstract
Purpose of Review Hypertension remains to be a major contributor to global morbidity and mortality. Despite a plethora of pharmacological options available, an abundance of patients have uncontrolled blood pressure thus creating the need for additional strategies, including non-pharmacologic approaches. In this review, we discuss the antihypertensive effect of slow and deep respiration by increasing baroreflex sensitivity.
Recent Findings Asking patients to carry out paced breathing sessions unaccompanied by a personal coach or unaided by a device may be unfeasible. Among proposed breathing techniques, RESPeRATE is a US Food and Drug Administration–certified device that assists slow breathing. In this review, we consider the mechanisms through which guided breathing mechanisms may impact on blood pressure control and alternative techniques.
Summary Guided breathing techniques along with lifestyle therapies may be helpful as a first step for patients with mild hypertension and prehypertension who do not suffer from cardiovascular disease, renal disease, or diabetes. Drug therapy must be considered after a couple of months if non-pharmacological therapy was unsuccessful. Device-guided paced breathing (DGB) may be recommended for those who cannot obtain full control of their hypertension with medical therapy alone or cannot tolerate potential side effects of pharmacologic treatment. Also, patients with well-controlled hypertension who may wish to try to reduce medication burden may be candidates for DGB. Patients with white coat or labile hypertension who are interested in biofeedback techniques could also be considered.

Keywords Baroreflex sensitivity · Blood pressure · Device-guided breathing · Paced breathing · Hypertension treatment

This article is part of the Topical Collection on *Device-Based Approaches for Hypertension*

✉ Reuven Zimlichman
zimlich@post.tau.ac.il

[1] Department of Nephrology, Tel Aviv University and Wolfson Medical Center, Holon, Israel

[2] Faculty of Medicine, Tel Aviv University and Wolfson Medical Center, Holon, Israel

[3] The Brunner Institute for Cardiovascular Research, Tel Aviv University and Wolfson Medical Center, Holon, Israel

Introduction

Elevated blood pressure (BP) is a major risk factor for adverse cardiovascular events, including myocardial infarction, stroke, heart failure, and death. Worldwide, high BP affects >40% of adults and is the leading global risk factor for death or disability [1•]. After implementation of good large-scale hypertension programs in Canada, BP control rates have significantly improved from 13.2% in 1992 to 64.6% in 2007, but 20% or more of the patients with hypertension do not achieve the target BP of <140/90 mmHg [1•]. Antihypertensive drug therapy reduces the risk of cardiovascular disease (CVD), but many drugs can cause side effects (e.g., gout, asthma, cough, and pedal edema with diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and dihydropyridine calcium antagonists, respectively) and can be costly [2]. For many patients, maximal medical therapy is insufficient to adequately treat severe hypertension. Lifestyle modification remains an important approach in management. The current recommendations to reduce salt intake from 9–12

to 5–6 g/day have a major effect on blood pressure and a further reduction to 3 g/day will have a greater effect and should become the long-term target for population salt intake [3]. The adherence to Mediterranean diet and the Dietary Approaches to Stop Hypertension diet that consists of fruits, vegetables, more fiber, less fats, and weight reduction appears to reduce mortality in the metabolically healthy obese (MHO) phenotype (0 or 1 metabolic abnormality), but not among metabolically unhealthy obese (MUO) phenotype (two or more metabolic abnormalities, based on high glucose, insulin resistance, blood pressure, triglycerides, C-reactive protein, and low high-density lipoprotein cholesterol in an obese population) [4]. Stopping smoking is the most cost-effective strategy for CVD prevention. Prolonged smoking cessation programs are the most efficient intervention. Other means, such as brupopion, varenicicline, and nicotine replacement therapy are also effective [5•]. Drinking three or more alcoholic beverages per day is associated with elevated CVD risk and must be discouraged. Moderate aerobic exercise (150 min/week) or vigorous aerobic exercise (75 min/week) should be recommended [5•]. An alternative to traditional aerobic exercise is isometric handgrip exercise, which is easily attainable, needs little time, and may provide to introduce exercise behaviors to unwilling individuals [6]. Despite proper adherence to the maximum tolerated doses of an appropriate regimen of three antihypertensive drugs (one of which is a diuretic), along with lifestyle modifications, the prevalence of resistant hypertension (RH) is between 13.7 and 16.3% [7]. In the Spanish Ambulatory Blood Pressure Monitoring Registry, the prevalence of office RH is 12%, but more than one third have normal ambulatory blood pressure (ABPM). ABPM is mandatory in resistant hypertensive patients to define true and white coat RH, as the latter group has a better prognosis. True resistant hypertensives have more risk factors like diabetes and smoking and have more target organ damage, including left ventricular hypertrophy, impaired renal function, and microalbuminuria [8].

Because the conventional antihypertensive therapies are variably successful in achieving the challenging target blood pressure values in hypertensive patients, a number of drugs are considered to be used as novel therapies for hypertension. New drug classes—inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, novel mineralocorticoid receptor antagonist, inhibitors of aminopeptidase A, dopamine β-hydroxylase, intestinal Na^+/H^+ exchanger 3, agonists of components of the angiotensin-converting enzyme 2/angiotensin (1–7)/Mas receptor axis, and vaccines directed toward angiotensin II and its type 1 receptor—are in different phases of development [9•]. This array of medications has now been complemented by a number of new approaches of non-pharmacological strategies. New invasive technologies and interventions, such as renal denervation, baroreflex activation therapy, carotid body ablation, central iliac arteriovenous anastomosis, deep brain stimulation, median nerve stimulation, and vagal nerve stimulation, are being investigated [10•].

Another approach is paced breathing. Slow and deep breathing ("paced breathing") has been linked with meditation for centuries. Paced breathing plays an important role in behavioral methods of treating hypertension. Paced breathing has a direct physiological effect on blood pressure. However, it may be unworkable, demanding patients to perform paced breathing sessions without assistance. Apart from the prolonged training, practicing, skill, and motivation needed, effortlessly performed paced breathing involves individualized breathing patterns that typically require personal coaching [11••, 12].

Paced Respiration: Mechanism of Action

Respiratory sinus arrhythmia is the heart pattern that occurs when heart rate increases during inhalation and decreases during exhalation [13]. At six breaths per minute, through a baroreflex, heart rate and blood pressure oscillates in a 180° phase relationship, i.e., completely out of phase, such that blood pressure began falling as soon as heart rate began rising, and blood pressure began rising as soon as heart rate began falling. During slower respiration, each breath stimulates the baroreflex [14, 15]. The increase in baroreflex sensitivity (BRS) depends on the slow breathing rate and not on the regularization obtained by controlling the breathing because controlled breathing at a fixed and faster frequency (15/min) did not produce such an effect [16]. The baroreflex is a reflex mediated by blood pressure sensors in the aorta and carotid artery that help modulate blood pressure fluctuations. Baroreceptors in the walls of these arteries detect stretching of the arteries as blood pressure increases.

The process is believed to be initiated by activated pulmonary mechanoreceptors, which respond to the increased tidal volume that accompanies slow breathing, and which act in concert with cardiac mechanoreceptors to inhibit sympathetic outflow in the skeletal muscle blood vessels, leading to widespread vasodilatation, thus causing a decrease in peripheral resistance and thus decreasing the BP [17, 18••]. When slow breathing is practiced twice daily at home over about a 3-month period, BRS is increased and can help hypertensive patients lower their blood pressure [12, 19].

Several mechanisms contribute to decrease BRS in hypertension, including endothelial dysfunction, reduced vascular compliance of the carotid sinuses and the aortic arch, and an impaired central mediation of the reflex. Patients with essential hypertension, even at an early stage, present with a decrease in BRS, an abnormal increase in sympathetic activity,

and a reduction in parasympathetic activity of the autonomic nervous system [20].

A simulated slow and deep respiration suppressed muscle sympathetic nerve activity (MSNA) about three times greater than a rapid and shallow respiration. Well-trained patients could achieve slowing respiration of 6 times/min, which resulted in a significant reduction in MSNA, whereas poorly trained patients could not slow their breathing with no appreciable changes in MSNA [18••, 21–23•]. Asking patients to perform paced breathing sessions on their own, without a coach, is a very difficult task. Subjects who do not keep breathing effortless may become hypocapnic or hypercapnic by taking breaths that are excessively deep (even during slow breathing) or too shallow, respectively, and may experience dizziness, palpitations, and even breathlessness [16, 19–21]. Device-guided paced breathing (DGB) may offer an easy, efficient and non-invasive option for treating hypertension on a daily basis at home. The benefit of one such US Food and Drug Administration–approved device, named RESPeRATE, has been confirmed in multiple clinical trials (Fig. 1). The device consists of a control box containing a microprocessor, a belt-type respiration sensor, and headphones, which provide feedback to the patient. During a session of device-guided breathing, the device analyzes the breathing rate and pattern and creates a personalized melody composed of two distinct tones—one tone for inhalation and one for exhalation. As the patient synchronizes breathing with the tones, the device gradually prolongs the exhalation tone (primarily) and slows the breathing rate to <10 breaths/min ("slow breathing"). A record of the patient's use of the device is stored in the microprocessor for quantification of total time of device use and adherence to the regimen. [24]. Last RESPeRATE clinical studies are detailed. Also, other paced breathing methods and devices are presented subsequently.

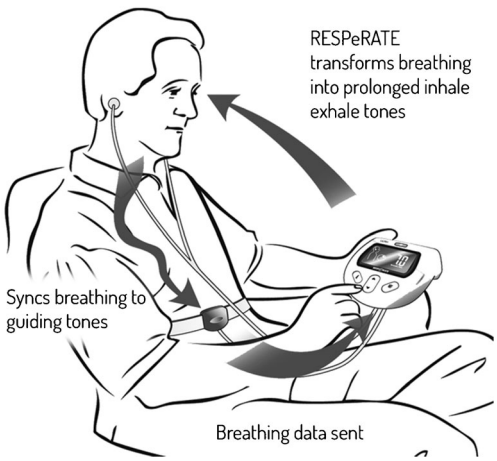

Fig. 1 RESPeRATE—the device

RESPeRATE Clinical Trials and Meta-Analyses

Two randomized studies evaluated the effect of DGB in individuals with diabetes mellitus and hypertension.

One trial was performed in Netherlands. Forty-eight patients with non–insulin-dependent diabetic and hypertension were randomized to RESPeRATE, 15 min daily for 8 weeks versus a sham device. There were no significant changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), with a difference in SBP of 2.35 mmHg (95% CI, −6.50 to 11.20) in favor of the control group and a difference in DBP of 2.25 mmHg (95% CI, −2.16 to 6.67) in favor of the intervention group. The limitation of this study is that more than 78% of eligible patients refused to participate [25•]. The patients in the intervention group had more severe diabetes, and their HBA1C was statistically higher; such patients usually have poorer response [26]. One patient died of congestive heart failure, another patient suffered from ischemic heart disease, and another one suffered from dyspnea. No additional medical information was supplied about these patients. [25•].

The second trial was performed in Austria. A total of 32 patients with diabetes and hypertension were randomized to RESPeRATE, 12 min daily for 8 weeks versus control. Significant reductions were demonstrated in 24-h SBP (126.1 ± 3.0 vs. 123.2 ± 2.7 mmHg; $P = 0.01$). Also, DGB showed a stronger treatment effect in terms of an increase in heart rate (HR) variability, predominantly in the low frequency band ($P < 0.03$ vs. usual care) [27•].

In a small trial, the RESPeRATE device was tested for feasibility of use in a population of ten overweight and obese children. Significant changes in body mass index and BP at the end of the study were not found. The limitations of the study are that the patients did not maintain a special diet nor practiced physical exercise, and less than half of the patients used RESPeRATE daily [28].

Two recent studies have also evaluated the effectiveness of DGB on blood pressure and MSNA.

Using DGB, short-term and long-term slow breathing (SLOWB) effects on BP, HR, and MSNA in essential hypertension were explored in ten hypertensive individuals at rest, during laboratory stressors, before and after acute SLOWB, and 8 weeks after SLOWB exercise in a randomized study. Acute SLOWB had no influence on BP and HR, but decreased MSNA ($P < 0.01$). BP, HR, and MSNA responses to handgrip were comparable before and after acute SLOWB. Acute SLOWB tended to reduce SBP ($P = 0.09$) and HR ($P = 0.08$), but not MSNA ($P = 0.20$) responses to mental stress. Long-term SLOWB decreased office SBP ($P < 0.001$), DBP ($P < 0.01$), and HR ($P = 0.004$), but not 24-h BP. Resting MSNA was unchanged after long-term SLOWB ($P = 0.68$). Long-term SLOWB did not influence BP, HR, or MSNA responses to handgrip and cold pressor, but reduced SBP ($P = 0.03$) and HR ($P = 0.03$) responses to

mental stress without MSNA changes. These findings may be indicative of beneficial SLOWB effects on stress reduction in essential hypertension [29•].

The second trial determined the influence of increasing tidal volume and slowing respiratory frequency on MSNA in 18 patients. Ten patients underwent a 15-min device-guided slow respiration and the remaining eight had no respiratory modification. The model predicted that a 1-l, step increase of lung volume decreased MSNA dynamically; its nadir (−33 ± 22%) occurred at 2.4 s, and steady state decreased (−15 ± 5%) at 6 s. Actually, in patients with the device-guided slow and deep respiration, respiratory frequency effectively fell from 16.4 ± 3.9 to 6.7 ± 2.8/min ($P < 0.0001$) with a concomitant increase in tidal volume from 499 ± 206 to 1177 ± 497 ml ($P < 0.001$). Under the condition of slow and deep respiration, heart rate remained unchanged but blood pressure tended to decline. Consequently, steady-state MSNA was decreased by 31% ($P < 0.005$). In patients without respiratory modulation, there were no significant changes in respiratory frequency, tidal volume, and steady-state MSNA. Thus, slow and deep respiration suppresses steady-state sympathetic nerve activity in patients with high levels of resting sympathetic tone as in heart failure [30••].

In a letter to the editor, the treatment of a white 52-year-old hypertensive male nurse was presented. The patient was introduced to non-pharmacological treatment by means of device-guided breathing, an alternative he readily accepted. After a period of 8 weeks of treatment, there was a discrete reduction in office BP and in the mean values of 24-h and awake (132/97 mmHg) ABPM. Also, there was a significant decrease in the values of noradrenalin and MSNA [31].

A crossover open trial assessed the clinical effectiveness of SLOWB training in treated patients with CHF as a novel component of cardiorespiratory rehabilitation programs in CHF. The aim of this study is to evaluate the influence of DGB on BP and whether DGB induces orthostatic hypotension (OH) or changes in quality of life (QoL) in CHF patients. Forty patients (two equal groups) completed the study, with the following baseline characteristics: 32 males/eight females, age 63.3 ± 13.4 years, 25 with ischemic CHF, 37 in New York Heart Association class II and three in class III, left ventricular ejection fraction 30.8 ± 6.7%, mean BP 138.7 ± 16.5/83.1 ± 11.5 mmHg, 23 with arterial hypertension, and 4 with a history of stroke. The patients underwent 10–12 weeks of DGB with the RESPeRATE device and 10–12-week follow-up under usual care. Patients were randomly divided into two groups: group I began with DGB, followed by usual care; group II began with usual care, followed by DGB. Patients undergoing DGB were asked to perform each day two separate 15-min sessions of device-guided SBT at a breathing frequency of 6 breaths/min. DGB is safe, does not affect the prevalence of OH in CHF patients, and shows a non-significant tendency to improve QoL [32].

The authors published a systematic review that evaluated DGB and other SLOWB methods on blood pressure [33]. The studies were randomized or open label [34–46•]. The individuals with uncontrolled blood pressure, diabetes mellitus and hypertension, prehypertension, or sleep apnea practiced DGB daily sessions for a period of 8 weeks. Eleven of 16 RESPeRATE studies reported significant reductions in systolic and diastolic blood pressure. Two meta-analyses that assessed RESPeRATE on blood pressure, included in our previous review, are briefly presented. The first one included all the individuals who participated in seven independent studies; 55% were men, with an average age of 57 ± 11 years, body mass index of 28 ± 4 kg/m^2, and initial office BP of 150 ± 13/90 ± 9 mmHg (9%prehypertensive; 25% stage 2) [10•, 34–46•, 39–41]. Antihypertensive drugs were taken by 78% of the subjects. Overall, the average decrease in office BP after >8 weeks of device-guided breathing among those with uncontrolled hypertension at baseline was 14/8 mmHg, compared with control treatment of 9/4 mmHg ($P = 0.008$ and $P = 0.002$, respectively, for SBP and DBP). The difference was independent of gender and medication status. Control of BP (<140/90 mmHg) was seen more commonly in the group that used the device: 26% versus 4% of those with initial stage 2 hypertension (≥160/100 mmHg; $P < 0.005$), and 48% versus 34% for those with initial stage 1 hypertension (140–159/90–99 mmHg; $P < 0.05$). The drop in office BP was directly related to the duration of slow breathing during the 8 weeks of treatment. Those who used the device and achieved slow breathing more than 15 min/day had the greatest lowering of office BP [10•]. The second one included eight trials of the RESPeRATE device, consisting of 494 adult patients. Non-randomized studies were excluded. Use of this device resulted in significantly reduced SBP by 3.67 mmHg (95% CI, −5.99 to −1.39; $P = 0.002$) and decreased DBP by 2.51 mmHg (95% CI, −4.15 to −0.87; $P = 0.003$). Later, five trials in which RESPeRATE improved blood pressure were excluded because they were labeled as sponsored studies without an explanation. Only three studies in which DGB did not improve blood pressure were reanalyzed. The author's conclusion was that there is no overall effect on BP using the device [47]. Based on this meta-analysis' final conclusion, the British Hypertension Society recommended not to prescribe RESPeRATE [48].

A recent review assessed the methodological quality of RESPeRATE studies [49]. From 13 studies briefly presented, 7 studies were excluded because they did not use acceptable control groups. Only six trials were analyzed, three of them published by the review coauthors. The other three studies were harshly criticized. The quality of one study was low; they used an open randomization procedure [38]. The blinding of care providers and the randomization procedure were not clear in another study [41]. The third study did not provide data on compliance and did not mention who performed the outcome

measurements [34]. The same studies were selected by the same authors for evaluation and included in a meta-analysis except one where the control group performed a meditative relaxation exercise [38, 50•]. Music therapy was used as a control in four studies. The fifth study used a sham device that did not lower the breathing frequency. Two of these trials where the authors of this meta-analysis were not authors or coauthors were labeled as "studies with a high risk of bias." In studies with "a high risk of bias," an effect on systolic blood pressure of 4.2 mmHg and diastolic blood pressure of 4.0 mmHg were found, both in favor of DGB. When all four studies that used music therapy as control were assessed, DGB did not significantly lower office systolic or diastolic blood pressure, with mean changes of 1.8 mmHg (95% CI, −2.8 to 6.3; $I^2 = 0.38$) in favor of DGB and 1.6 mmHg (95% CI, −2.3 to 5.4; $I^2 = 0.59$) in favor of DGB, respectively. Eventually, the authors concluded that based on the three studies with acceptable methodological quality and on the results of their meta-analysis, DGB cannot be recommended for treating hypertension [49, 50].

Other Paced Breathing Methods and Devices to Control BP

Yoga

Chandra nadi pranayama is 27 rounds of exclusive left nostril breathing [51]. Bhastrika pranayama is a slow pace breath method (respiratory rate 6/min) where, for 5 min, subjects had to sit comfortably in an easy and steady posture (sukhasana) on a fairly soft seat placed on the floor keeping the head, neck, and trunk erect, eyes closed, and the other muscles reasonably loose. The subject is directed to inhale through both nostrils slowly up to the maximum for about 4 s and then exhale slowly up to the maximum through both nostrils for about 6 s. The breathing must not be abdominal. During the practice, the subject is asked not to think much about the inhalation and exhalation time, but rather was requested to imagine the open blue sky. The pranayama is conducted in a cool, well-ventilated room (18–20 °C) [52]. Both methods are useful in reducing BP [51, 52].

A recent meta-analysis that included seven randomized control studies compared the effects of yoga interventions (≥8 weeks) with usual care or any active control intervention on BP. A total of 452 patients suffering from prehypertension (120–139/80–89 mmHg) or hypertension (≥140/≥90 mmHg) were enrolled. Compared with usual care, very low-quality evidence was found for effects of yoga on systolic [six RCTs, $n = 278$; mean difference (MD) = −9.65 mmHg, 95% confidence interval (CI) = −17.23 to −2.06, $P = 0.01$; heterogeneity: $I^2 = 90\%$, $\chi^2 = 48.21$, $P < 0.01$) and diastolic blood pressure (six RCTs, $n = 278$; MD = −7.22 mmHg, 95% CI = −12.83 to −1.62, $P = 0.01$; heterogeneity—$I^2 = 92\%$, $\chi^2 = 64.84$, $P < 0.01$). More adverse events occurred during yoga than during usual care. Compared with exercise, no evidence was found for effects of yoga on SBP and DBP. Yoga breathing interventions seem to be more effective than those that include physical postures. Yoga was effective as an adjunct intervention to antihypertensive medication but not as an alternative. Yoga seems to be equally effective as conventional exercise or diet [53].

Transcendental Meditation (TM)

TM technique is the principal mind–body modality of the Maharishi Vedic Approach to Health, a comprehensive traditional system of natural health care derived from the ancient Vedic tradition. This technique is a simple, natural, and easy-to-learn procedure that allows the ordinary thinking process to become more quiescent and a unique psychophysiological state of "restful alertness" to be gained. This distinctive state of restful alertness is characterized by decreased respiration rates, sympathetic tone and hypothalamic–pituitary–adrenal axis activity, and high electroencephalography coherence. The program is practiced twice a day for 20 min while sitting comfortably with eyes closed [54]. In a recent review, 406 papers were screened and only four trials that randomized 430 patients more than 3 months' duration were identified. None of the studies measured cardiovascular mortality, all-cause mortality, and fatal events. There were some favorable effects on SBP and DBP. Due to the limited evidence to date, no conclusions as to the effectiveness of TM for the primary prevention of cardiovascular disease were drawn [55].

Bi-Level Positive Pressure Device

BiPAP Pro 2 (Philips Respironics, Murrysville, PA) is able to titrate differentially the inspiratory and expiratory pressures high enough to allow the subject to differentiate inspiration from expiration, while maximizing comfort. After 1 min of use, the device algorithm guided participants to reduce their respiratory rate to <10 breaths/min by adjusting selected respiratory parameters. After 15 min of use, the device emitted an audible tone to alert the participants that the session had ended and reverted to spontaneous mode. Participants could then reset the machine to perform another paced breathing session or choose to complete a second session at a later time. One study evaluated if daily device-guided slow breathing may lower BP in patients with hypertension and OSA. Twenty-five subjects with hypertension and OSA were enrolled. Subjects were asked to perform device-guided paced respiration 30 min a day for 8 weeks. The primary outcome was change in office SBP and DBP from baseline to 8 weeks. Twenty-four subjects completed the study. Mean baseline BP was 140.0 ± 10.2 mmHg SBP and 82.7 ± 8.9 mmHg DBP.

Complete device data were available for 17 subjects. Mean device adherence was 81 ± 24% and 51% achieved a mean breath rate ≤10 breaths/min over 8 weeks. Three subjects had changes in their antihypertensive medications during the study. Among the remaining 21 subjects, mean difference in office BP from baseline to 8 weeks was −9.6 ± 11.8 mmHg SBP ($P \leq 0.01$) and −2.52 ± 8.9 mmHg DBP ($P = 0.21$) [46•].

Biofeedback-Assisted Relaxation Training (BFAR)

BFAR involves multiple biofeedback techniques, thermal, electromyographic (EMG), and respiratory sinus arrhythmia, coupled with diaphragmatic breathing, progressive muscle relaxation, and autogenics. Patients performed between four and ten sessions of slow abdominal breathing (6 cycles/min) combined with frontal EMG biofeedback training and daily home practice 7 to 10 days. It has been shown that patients with postmenopausal prehypertension, white coat hypertension, and with stage 1 or 2 hypertension can significantly lower BP [56–58••].

Beat

The *Beat* sensor was designed as a modular patch to be worn on the user's chest and uses standard electrocardiography (ECG) electrodes. It streams a single-lead ECG wirelessly to a mobile phone using Bluetooth Low Energy. The use of small, low-power electronics, a low device profile, and a tapered enclosure allowed for a device that can be unobtrusively worn under clothing. The sensor was designed to operate with a mobile app that guides users through behavioral neurocardiac training (BNT) exercises to train them to a SLOWB technique for stress recovery. The BNT app uses the ECG captured by the sensor to provide heart rate variability biofeedback in the form of a real-time heart rate waveform and reinforce the impact of the training. The outcome of this project was a wearable sensor system to deliver BNT at home. The system has the potential to offer a complementary approach to BP and stress management at home. Future studies should involve participants taking the system home [59•, 60].

Photoplethysmography-Based Devices

An interesting device is the emWave Personal Stress Reliever (PSR), which helps patients acquire the self-regulation skills for reducing emotional stress by displaying their level of heart rhythm coherence in real time as they practice the techniques. The device uses either a fingertip or ear lobe sensor to detect the pulse wave. The device records the HR on a beat-to-beat basis (the interbeat interval). As patients practice the techniques, they can readily see and experience the changes in their heart rhythm patterns, which generally become smoother and more sine wave-like as they feel appreciation and other positive emotions. Sixty-two hypertensive patients were randomized in three groups: group 1 ($n = 30$) was currently taking hypertensive medication as prescribed by their physicians practiced with the emWave PSR device, group 2 ($n = 12$) was not yet taking any medication to control hypertension and was given the same training and emWave practice, and group 3 ($n = 20$) was taking medication as prescribed and was asked to use a method of relaxation that was familiar to them. There was also a significant difference between groups on post-intervention MAP ($F = 4.61$, $P > 0.05$), partial eta squared = 0.139, indicating a strong effect with group 1 (coherence training plus current medication) having significantly lower MAP than group 3 (relaxation plus medication) ($P < 0.05$). Post-intervention MAP was also significantly lower in group 2 (coherence training alone) than group 3 (relaxation plus current medication) ($P < 0.05$) [61]. Four wrist-worn devices (Apple Watch, Fitbit Charge HR, Samsung Gear S, and Mio Alpha) which used also sophisticated photoplethysmography technology also accurately measure heart rate [62].

Conclusions

Although three studies are inconclusive, we believe that the majority of the studies performed in the field indicate that slow deep breathing results in enhancement of BRS which in turn reduces sympathetic tone and lowers BP [16, 20].

One limitation of unassisted SLOWB is the lack of an efficient control on the breathing depth, which largely depends on the breath-sensing method and the patient's sense of strain, making the quantification of respiratory effort rather difficult. In that respect, RESPeRATE provides a beneficial feedback. It can be used at home setting on a daily basis for 15 min every day. It needs patient's adherence to treatment, but does not need a coach. No side effects were reported. Patients with severe lung and heart disease must be excluded.

RESPeRATE along with lifestyle therapies may be helpful as a first step for patients with mild hypertension and prehypertension who do not suffer from cardiovascular disease, renal disease, or diabetes. Drug therapy must be considered after a couple of months if non-pharmacological therapy was unsuccessful [63••, 64•]. DGB may be recommended for those who cannot obtain full control of their hypertension with medical therapy alone or cannot tolerate the adverse effects of the treatment. Also, patients with well-controlled hypertension who try to reduce medications may be suitable candidates. Patients with white coat or labile hypertension who are interested in biofeedback techniques should be considered [63••, 64•]. A Class IIA, Level of Evidence B recommendation for BP-lowering efficacy was bestowed on RESPeRATE by American Heart Association [63••, 65••].

Compliance with Ethical Standards

Conflict of Interest R.Z. served as a medical consultant to Intercure, the manufacturer of RESPeRATE, from March 21, 2013, until July 11, 2014. R.C. declares no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, Gelfer M, Lamarre-Cliche M, Milot A, Bolli P, DW MK, Tremblay G, Mc Lean D, Tobe SW, Ruzicka M, Burns KD, Vallée M, Ramesh Prasad GV, Lebel M, Feldman RD, Selby P, Pipe A, Schiffrin EL, PA MF, Oh P, Hegele RA, Khara M, Wilson TW, Brian Penner S, Burgess E, Herman RJ, Bacon SL, Rabkin SW, Gilbert RE, Campbell TS, Grover S, Honos G, Lindsay P, Hill MD, Coutts SB, Gubitz G, Campbell NR, Moe GW, Howlett JG, Boulanger JM, Prebtani A, Larochelle P, Leiter LA, Jones C, Ogilvie R, Woo V, Kaczorowski J, Trudeau L, Petrella RJ, Hiremath S, Stone JA, Drouin D, Lavoie KL, Hamet P, Fodor G, Grégoire JC, Fournier A, Lewanczuk R, Dresser GK, Sharma M, Reid D, Benoit G, Feber J, Harris KC, Poirier L, Padwal RS. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2015;31(5):549–68. doi:10.1016/j.cjca. 2015.02.016.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560–72.
3. He FJ, Li J, Mac Gregor GA. Ef fect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomized trials. BMJ. 2013;346:f1325.
4. Park YM, Steck SE, Fung TT, Zhang J, Hazlett LJ, Han K, Merchant AT. Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes. Int J Obes. 2016;40(10):1541–9.
5.• Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Bart Vander Worp H, Van Dis I, Verschuren WM. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;252:207–74. doi:10.1016/j.atherosclerosis. 2016.05.037.
6. Millar PJ, McGowanCL CVA, Araujo CG, Swaine IL. Evidence for the role of isometric exercise training in reducing blood pressure: potential mechanisms and future directions. Sports Med. 2014;44(3):345–56.
7. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. Am J Hypertens. 2015;28(3):355–61.
8. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57(5):898–902. doi:10.1161/HYPERTENSIONAHA.110.168948.
9.• Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res. 2015;116(6):1074–95. doi:10.1161/CIRCRESAHA.116.303603. **This review discusses new drugs and interventional treatments in resistant hypertension**
10.• NgFL SM, Mahfoud F, Pathak A, Lobo MD. Device-based therapy for hypertension. Curr Hypertens Rep. 2016;18(8):61. doi:10.1007/s11906-016-0670-5. **This review studies seven novel invasive devices employed in resistant hypertension treatment**
11.•• Elliott WJ, Izzo JL. Device-guided breathing to lower blood pressure. Case Report and Clinical Overview. 2006;8(3):23. **The first meta-analysis of all clinical trials that evaluates the efficacy of Resperate, demonstrating positive therapeutic effect in hypertensive patients**
12. Gavish B. Device-guided breathing in the home setting: technology, performance and clinical outcomes. Biol Psychol. 2010;84(1):150–6.
13. Lehrer PM, Vaschillo E, Vaschillo B, Lu SE, Eckberg DL, Edelberg R, Shih WJ, Lin Y, Kuusela TA, Tahvanainen KU, Hamer RM. Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. Psychosom Med. 2003;65(5):796–805.
14. Joseph CN, Porta C, Casucci G, Casiraghi N, Maffeis M, Rossi M, et al. Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. Hypertension. 2005;46(4):714–8.
15. Reyes del Paso GA, Cea JI, González-Pinto A, Cabo OM, Caso R, Brazal J, et al. Short-term effects of a brief respiratory training on baroreceptor cardiac reflex function in normotensive and mild hypertensive subjects. Appl Psychophysiol Biofeedback. 2006;31(1):37–49.
16. Schelegle ES, Green JF. An overview of the anatomy and physiology of slowly adapting pulmonary stretch receptors. Respir Physiol. 2001;125(1–2):17–31.
17. Lin G, Xiang Q, Fu X, Wang S, Wang S, Chen S, Shao L, Zhao Y, Wang T. Heart rate variability biofeedback decreases blood pressure in prehypertensive subjects by improving autonomic function and baroreflex. J Altern Complement Med. 2012;18(2):143–52. doi:10.1089/acm.2010.0607.
18.•• Sharma M, Frishman WH, Gandhi K. RESPeRATE: nonpharmacological treatment of hypertension. Cardiol Rev. 2011;19(2):47–51. doi:10.1097/CRD.0b013e3181fc1ae6. **An excellent review that discusses the effects of paced breathing on blood pressure regulation.**
19. Meuret AE, Wilhelm FH, Roth WT. Respiratory biofeedback-assisted therapy in panic disorder. J Clin Psychol. 2004 Feb;60(2):197–207.
20. Giardino ND, Chan L, Borson S. Combined heart rate variability and pulse oximetry biofeedback for chronic obstructive pulmonary disease: preliminary findings. Appl Psychophysiol Biofeedback. 2004;29(2):121–33.
21. Harada D, Asanoi H, Takagawa J, Ishise H, Ueno H, Oda Y, Goso Y, Joho S, Inoue H. Slow and deep respiration suppresses steady-state sympathetic nerve activity in patients with chronic heart failure: from modeling to clinical application. Am J Physiol Heart Circ Physiol. 2014;307(8):H1159–68. doi:10.1152/ajpheart.00109.2014.

22.• RESPERATE to lower blood pressure. http://www.resperate.com/. Accessed 24 Nov 2016. **Information about the device from the manufacturer.**

23.• Landman GW, Drion I, van Hateren KJ, van Dijk PR, Logtenberg SJ, Lambert J, et al. Device-guided breathing as treatment for hypertension in type 2 diabetes mellitus: a randomized, double-blind, sham-controlled trial. JAMA Intern Med. 2013;173(14):1346–50. doi:10.1001/jamainternmed.2013.6883. **This recent study establishes that RESPERATE does not improve BP in hypertensive diabetic patients**

24. Huang AJ, Subak LL. What constitutes an adequate evaluation of device-guided breathing? JAMA Intern Med. 2014;174(4):637. doi:10.1001/jamainternmed.2013.13791.

25.• Howorka K, Pumprla J, Tamm J, Schabmann A, Klomfar S, Kostineak E, et al. Effects of guided breathing on blood pressure and heart rate variability in hypertensive diabetic patients. Auton Neurosci. 2013;179(1–2):131–7. doi:10.1016/j.autneu. 2013.08.065. **This recent study demonstrates that RESPERATE improves BP in well controlled hypertensive diabetic patients**

26. Wojcicki JM, Geissler JD, Stokes CW, Heyman MB, Tran CT. The use of the RESPeRATE device to lower blood pressure in inner city obese adolescents and children: a pilot feasibility study. High Blood Press Cardiovasc Prev. 2013;20(2):89–92. doi:10.1007/s40292-013-0014-3.

27.• Harada D, Asanoi H, Takagawa J, Ishise H, Ueno H, Oda Y, Goso Y, Joho S, Inoue H. Slow and deep respiration suppresses steady-state sympathetic nerve activity in patients with chronic heart failure: from modeling to clinical application. Am J Physiol Heart Circ Physiol. 2014;15(307(8)):H1159–68. **This recent trial demonstrates that DGB suppresses MSNA in patients with heart failure**

28. de Barros S, da Silva GV, de Gusmão JL, de Araujo TG, Mion D Jr. Reduction of sympathetic nervous activity with device-guided breathing. J Clin Hypertens (Greenwich). 2014;16(8):614–5.

29.• Drozdz T, Bilo G, Debicka-Dabrowska D, Klocek M, Malfatto G, Kielbasa G, Styczkiewicz K, Bednarek A, Czarnecka D, Parati G, Kawecka-Jaszcz K. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. Blood Press. 2016;25(1):4–10. **This recent trial demonstrates that DGB does not affect the prevalence of OH in heart failure**

30.•• Cernes R, Zimlichman R. RESPeRATE: the role of paced breathing in hypertension treatment. J Am Soc Hypertens. 2015;9(1):38–47. doi:10.1016/j.jash. 2014.10.002. **This systematic review of all available clinical trials finds a positive effect of paced breathing and recommends this approach in hypertensive patients**

31. Grossman E, Grossman A, Schein MH, Zimlichman R, Gavish B. Breathing-control lowers blood pressure. J Hum Hypertens. 2001;15(4):263–9.

32. Meles E, Giannattasio C, Failla M, Gentile G, Capra A, Mancia G. Nonpharmacologic treatment of hypertension by respiratory exercise in the home setting. Am J Hypertens. 2004;17(4):370–4.

33. Rosenthal T, Alter A, Peleg E, Gavish B. Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. Am J Hypertens. 2001;14(1):74–6.

34. Bae JH, Kim JH, Choe KH, Hong SP, Kim KS, Kim CH, et al. Blood pressure change following 8-week, 15-minute daily treatment with paced breathing guided by a device: a Korean multicenter study. J Clin Hypertens. 2006;8(5):86.

35. Anderson DE, Mc Neely JD, Windham BG. Regular slow-breathing exercise effects on blood pressure and breathing patterns at rest. Hum Hypertens. 2010;24(12):807–13. doi:10.1038/jhh.2010.18.

36. Elliot WJ, Izzo JL, White WB, Rosing DR, Snyder CS, Alter A, et al. Graded blood pressure reduction in hypertensive outpatients associated with use of a device to assist with slow breathing. J Clin Hypertens (Greenwich). 2004;6(10):553–9.

37. Viskoper R, Shapira I, Priluck R, Mindlin R, Chornia L, Laszt A, et al. Nonpharmacologic treatment of resistant hypertensives by device-guided slow breathing exercises. Am J Hypertens. 2003;16(6):484–7.

38. Schein MH, Gavish B, Herz M, Rosner-Kahana D, Naveh P, Knishkowy B, et al. Treating hypertension with a device that slows and regularizes breathing: a randomized, double-blind controlled study. J Hum Hypertens. 2001;15(4):271–8.

39. Altena MR, Kleefstra N, Logtenberg SJ, Groenier KH, Houweling ST, Bilo HJ. Effect of device-guided breathing exercises on blood pressure in patients with hypertension: a randomized controlled trial. Blood Press. 2009;18(5):273–9. doi:10.3109/08037050903272925.

40. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Bilo HJ. Effect of device-guided breathing exercises on blood pressure in hypertensive patients with type 2 diabetes mellitus: a randomized controlled trial. J Hypertens. 2007;25(1):241–6.

41. Schein MH, Gavish B, Baevsky T, Kaufman M, Levine S, Nessing A, et al. Treating hypertension in type II diabetic patients with device-guided breathing: a randomized controlled trial. J Hum Hypertens. 2009;23(5):325–31.

42. Oneda B, Ortega KC, Gusmão JL, Araújo TG, Mion D. Sympathetic nerve activity is decreased during device-guided slow breathing. Hypertens Res. 2010;33(7):708–12. doi:10.1038/hr.2010.74.

43. Bertisch SM, Schomer A, Kelly EE, Baloa LA, Hueser LE, Pittman SD, et al. Device-guided paced respiration as an adjunctive therapy for hypertension in obstructive sleep apnea: a pilot feasibility study. Appl Psychophysiol Biofeedback. 2011;36(3):173–9. doi:10.1007/s10484-011-9158-x.

44.• Landman GW, van Hateren KJ, van Dijk PR, Logtenberg SJ, Houweling ST, Groenier KH, Bilo HJ, Kleefstra N. Efficacy of device-guided breathing for hypertension in blinded, randomized, active-controlled trials: a meta-analysis of individual patient data. JAMA Intern Med. 2014;174(11):1815–21. doi:10.1001/jamainternmed. 2014.4336. **A recent meta-analysis that criticizes the DGB trials sponsored by manufacturer and appreciates only three studies. DGB as a routine treatment is not recommended**

45. Mahtani KR, Nunan D, Heneghan CJ. Device-guided breathing exercises in the control of human blood pressure: systematic review and meta-analysis. J Hypertens. 2012;30(5):852–60. doi:10.1097/HJH.0b013e3283520077.

46.• Mahtani KR, Beinortas T, Bauza K, Nunan D. Device-guided breathing for hypertension: a summary evidence review. Curr Hypertens Rep. 2016;18(4):33. doi:10.1007/s11906-016-0631-z. **A review that presents recent DGB clinical studies sponsored and not sponsored by the manufacturer and summarizes a recent meta-analysis previously published by some authors of this paper. DGB as a routine treatment is not recommended**

47. van Hateren KJ, Landman GW, Logtenberg SJ, Bilo HJ, Kleefstra N. Device-guided breathing exercises for the treatment of hypertension: an overview. World J Cardiol. 2014;6(5):277–82. doi:10.4330/wjc. v6.i5.277.

48. Bhavanani A.B.,Madanmohan, and Sanjay Z. Immediate effect of chandra nadi pranayama (left unilateral forced nostril breathing) on cardiovascular parameters in hypertensive patients. Int J Yoga 2012; 5(2):108–111. doi: 10.4103/0973-6131. 98221.

49. Pramanik T, Sharma HO, Mishra S, Mishra A, Prajapati R, Singh S. Immediate effect of slow pace bhastrika pranayama on blood pressure and heart rate. J Altern Complement Med. 2009;15(3):293–5. doi:10.1089/acm. 2008.0440.

50. Wang SZ, Li S, Xu XY, Lin GP, Shao L, Zhao Y, et al. Effect of slow abdominal breathing combined with biofeedback on blood

pressure and heart rate variability in prehypertension. J Altern Complement Med. 2010;16(10):1039–45. doi:10.1089/acm. 2009. 0577.

51. Nakao M, Nomura S, Shimosawa T, Fujita T, Kuboki T. Blood pressure biofeedback treatment of white-coat hypertension. J Psychosom Res. 2000;48(2):161–9.
52. Yucha CB, Tsai PS, Calderon KS, Tian L. Biofeedback-assisted relaxation training for essential hypertension: who is most likely to benefit? J Cardiovasc Nurs. 2005;20(3):198–205.
53. Hartley L, Mavrodaris A, Flowers N, Ernst E, Barnes VA RK, Treiber FA, Johnson MH. Impact of transcendental meditation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;12:CD010359.
54. Uddin AA, Morita PP, Tallevi K, Armour K, Li J, Nolan RP, Cafazzo JA. Development of a wearable cardiac monitoring system for behavioral neurocardiac training: a usability study. J MIR M health Uhealth. 2016;22(4(2)):e45. doi:10.2196/mhealth.5288.
55. Nolan RP, Floras JS, Harvey PJ, Kamath MV, Picton PE, Chessex C, Hiscock N, Powell J, Catt M, Hendrickx H, Talbot D, Chen MH. Behavioral neurocardiac training in hypertension: a randomized, controlled trial. Hypertension. 2010;55(4):1033–9. doi:10.1161/ HYPERTENSIONAHA.109.146233.
56. Alabdulgader AA. Coherence: a novel nonpharmacological modality for lowering blood pressure in hypertensive patients. Glob Adv Health Med. 2012;1(2):56–64. doi:10.7453/gahmj.2012.1.2.011.
57. Vaschillo E, Lehrer P, Rishe N, Konstantinov M. Heart rate variability biofeedback as a method for assessing baroreflex function: a preliminary study of resonance in the cardiovascular system. Appl Psychophysiol Biofeedback. 2002;27(1):1–27.
58.•• Lehrer PM, Gevirtz R. Heart rate variability biofeedback: how and why does it work? Front Psychol. 2014;2(5):756. doi:10.3389/ fpsyg. 2014.00756. **A review that summarizes the possible mechanisms for the effectiveness of respiratory sinus arrhythmia**
59.• Hering D, Kucharska W, Kara T, Somers VK, Parati G, Narkiewicz K. Effects of acute and long-term slow breathing exercise on muscle sympathetic nerve activity in untreated male patients with hypertension. J Hypertens. 2013;31(4):739–46. doi:10.1097/HJH. 0b013e32835eb2cf. **This recent trial demonstrates that DGB improves MSNA in short term and attenuates cardiovascular response to mental stress**
60. Cramer H, Haller H, Lauche R, Steckhan N, Michalsen A, Dobos G. A systematic review and meta-analysis of yoga for hypertension. Am J Hypertens. 2014;27(9):1146–51. doi:10.1093/ajh/hpu 078.
61. Nidich SI, Rainforth MV, Haaga DA, Hagelin J, Salerno JW, Travis F, et al. A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults. AmJ Hypertens. 2009;22(12):1326–31. doi:10.1038/ajh. 2009.184.
62. Wallen MP, Gomersall SR, Keating SE, Wisløff U, Coombes JS. Accuracy of heart rate watches: implications for weight management. PLoS One. 2016;11(5):e0154420. doi:10.1371/journal.pone. 0154420. **eCollection 2016**
63.•• Brook RD, Jackson EA, Giorgini P, McGowan CL. When and how to recommend 'alternative approaches' in the management of high blood pressure. Am J Med. 2015;128(6):567–70. doi:10.1016/j. amjmed.2014.12.029. **A review that presents who are hypertensive candidates for trials of alternative approaches, such as device-guided breathing and isometric handgrip**
64.• Sica DA. Device-guided breathing and hypertension: a yet to be determined positioning. Am J Med. 2015;1208(6):567–70. **An editorial that recommends device-guided breathing for several types of hypertensive patients**
65.•• Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. Hypertension. 2013;61(6):1360–83. doi:10.1161/HYP.0b013e318293645f. **The American Heart Association confers a Class IIA, Level of Evidence B on device-guided breathing.**