Nonpharmacologic Treatment of Resistant Hypertensives By Device-Guided Slow Breathing Exercises

Reuven Viskoper, Irena Shapira, Rita Priluck, Rina Mindlin, Larissa Chornia, Anny Laszt, Dror Dicker, Benjamin Gavish, and Ariela Alter

Background: Recent studies have demonstrated the antihypertensive effect of slow breathing exercises, guided interactively by a device, in patients with uncontrolled blood pressure (BP) without changing medication. This study examined the response to the same treatment protocol in resistant hypertensives.

Methods: Seventeen resistant hypertensives exercised device-guided slow breathing for 8 weeks, 15 min daily, and self-monitored BP. Data stored in the devices were collected on a PC-based system. Clinical outcomes were office and home BP changes from baseline to end values.

Results: Significant reductions in both office BP (−12.9/−6.9 mm Hg, $P < .001$ and home BP (−6.4/−2.6 mm Hg, $P < .01$/$P < .05$) without side effects with 82% responders and good compliance.

Conclusions: Resistant hypertensives can benefit from and are compliant with self-treatment by device-guided slow breathing. Am J Hypertens 2003;16: 000–000 © 2003 American Journal of Hypertension, Ltd.

Key Words: Lifestyle modification, nonpharmacologic therapy, respiratory pacing, refractory hypertension, home blood pressure.

Hypertension is a primary risk factor for heart disease and stroke. Only 30% of the treated patients achieve goal blood pressure (BP).

Resistant hypertension, usually defined as failure to achieve goal BP despite the use of a rational triple-drug regimen in optimal doses, is not infrequent, is associated with increased cardiovascular risk, and results in high cost to the healthcare system,[1–3] where contributing factors are partial adherence to treatment[1] and "white coat" effect,[4] which may be falsely interpreted as resistance to treatment.[5] Often office BP measurements result in hypertension misdiagnosis or mistreatment.[4] The efficacy of a 8-week, 15-min daily use of a device-guided slow breathing exercise in reducing high BP has been recently demonstrated in hypertensives, mostly treated with antihypertensive drugs.[6–10] The objectives of the present study were to evaluate 1) the safety and efficacy of using the same intervention for treating resistant hypertensives in the community setting, and 2) compliance and self-monitored home BP using devices with automatic data storage combined with a PC-based data collection system on the Web that assures objective and quantitative monitoring of both.[11] Home BP is particularly valuable, being free of placebo- and white coat effects.[12]

Methods

Study Design

This three-clinic trial with "before and after" design included two baseline visits (eligibility and enrolment) 1 week apart, followed by an 8-week, 15 min/day of self treatment by device-guided slow breathing exercises and self-BP monitoring with follow-up visits after 4 and 8 weeks (follow-up and termination); pharmacologic treatment was unchanged during the study. The study protocol was approved by an Institutional Review Committee for the Helsinki guidelines.

Study Population

Patients were recruited from two family clinics and one hospital outpatient clinic. Inclusion criteria were age 40 to 80 years, with resistance to drug therapy (ie, having office systolic BP in the range 140 to 160 mm Hg or diastolic BP in the range 90 to 100 mm Hg in spite of taking three or

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From the WHO Collaborative Center for Prevention of CVD (RV, IS, RP, RM, LC, AL, DD), the Barzilai Medical Center Ashkelon, affiliated to the University of the Negev and InterCure, Ltd. (BG, AA), Lod, Israel.

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Address correspondence and reprint requests to Dr. Reuven Viskoper, Director Department of Medicine B, the Barzilai Medical Center, Ashkelon, Israel; e-mail: reuvenv@barzi.health.gov.il

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more antihypertensive drugs at maximal dosage and without changing of medication 3 weeks before the study). Obese, diabetics, patients with severe chronic conditions, concomitant drug therapy causing hypertension, or secondary forms of hypertension were excluded. All participants were required to sign a consent form before their participation in the study.

Demographic and Baseline Characteristics

Between October 2001 and January 2002, a total of 17 resistant hypertensives were enrolled. Subjects were aged 66.5 ± 7.6 years (10 men and 7 women), 11 took 3 drugs (64%) and 6 took 4 to 6 drugs, and they had a body mass index of 28.0 ± 3.3 kg/m^2. Blood pressure and heart rate were 155.4 ± 10.0/88.9 ± 8.5 mm Hg and 76.7 ± 7.2 beats/min in the office setting and 156.4 ± 19.5/88.5 ± 12.6 mm Hg and 67.0 ± 9.2 beats/min at home. The only significant difference between office and home measurements was in heart rate ($P = .002$). Eight of the patients (47%) had isolated systolic hypertension; 16 of the 17 patients displayed a high home BP (systolic ≥135 mm Hg or diastolic ≥85 mm Hg).

There were no significant changes in office BP and heart rate between the first visit and the second visit (+0.6/+0.1 mm Hg and +0.2 beats/min with $P > .7$ for all) and no significant changes or trend in home BP and heart rate during the 10-day baseline.

Treatment

Patients were asked to perform daily a 15-min session of device-guided breathing exercise during each afternoon or evening for 8 weeks. The device (RESPeRATE, InterCure Ltd., Israel) includes a belt-type respiration sensor worn on the clothing around the torso connected to a computerized box that generates musical patterns listened through earphones. The device guides the user interactively to slow breathing with a relatively prolonged expiration by creating the following loop: 1) the monitored breathing pattern is continuously analyzed, 2) its parameters, including inspiration time and expiration time are averaged over the last four breaths and used for synthesizing in real-time musical patterns with differentiated "inspiration" and "expiration" sounds. The duration of the expiration sound is slightly longer than the monitored expiration time. 3) The user synchronizes voluntarily inhaling and exhaling with their guiding musical sounds, which closes the loop. The guiding continues as long as the user can follow conveniently. The inspiration and expiration times are stored automatically once every minute of use together with date and hour and other performance variables. The device shuts off automatically after 15 min of use. Patients were instructed in its use before treatment at visit 2. The device was collected at the end of treatment.

Measurements and Data Collection

Office BP and heart rate were measured as previously described.[7] A single BP measurement was determined as the average of the first two consecutive readings of three or more readings that did not differ by more than 5 mm Hg.

Home BP was measured using an automated digital BP monitor (Omron model HEM-747IC, Japan) with automatic data storage, including date and time, systolic and diastolic BP, and heart rate (up to 350 readings). Patients were trained in operating the BP monitor during visit 2 and then instructed to take a daily measurement of BP at home in the morning, to separate from the treatment session. Patients were requested to take consecutively three BP readings, which result in displayed BP and heart rate, as previously described.[7]

In addition, patients were also asked to bring the BP monitors to the office at each visit for data downloading and to record all readings in a provided diary as backup.

The data stored by both home BP monitor and the treatment device were uploaded to a PC (as a backup) and than transferred to the Web, by a trained nurse from each study site, to a secured database using software tool supplied by the sponsor (available at www.resperate.com/lowerpressure[11]).

Statistical Analysis

The primary efficacy end points of this study were the change in BP measured at home and at office from baseline to end. Baseline of office BP was obtained by averaging BP measurements obtained at the first two office visits, whereas end value was taken at the end of treatment. Home baseline and end values were defined, respectively, as the mean of the average over 10 days starting with the fourth day of treatment (to enable patient's familiarization with the monitor) and the mean of the daily BP values taken during last two days. The calculation of daily averaging from the individual readings was obtained using a procedure published elsewhere (Grossman et al[7]) and were performed automatically by the Web-mediated PC-based data collection system. A case report of home BP variations during the treatment period is shown in Fig. 1A.

Compliance with treatment was evaluated by the ratio between performed and requested number of treatment sessions per week, total number of sessions, and session duration. Compliance with self-BP measurements at home was evaluated by the ratio between the actual number of BP-measuring days and the 56 requested days (8 weeks). All data used for evaluating compliance were obtained from the PC-based system.

Patient is defined as responder to antihypertensive treatment if the office systolic BP reduction is >10 mm Hg or the office diastolic BP reduction is >5 mm Hg, or if the BP was initially at the high BP range and was converted into the normal or high-normal range (<140/90 mm Hg) by the

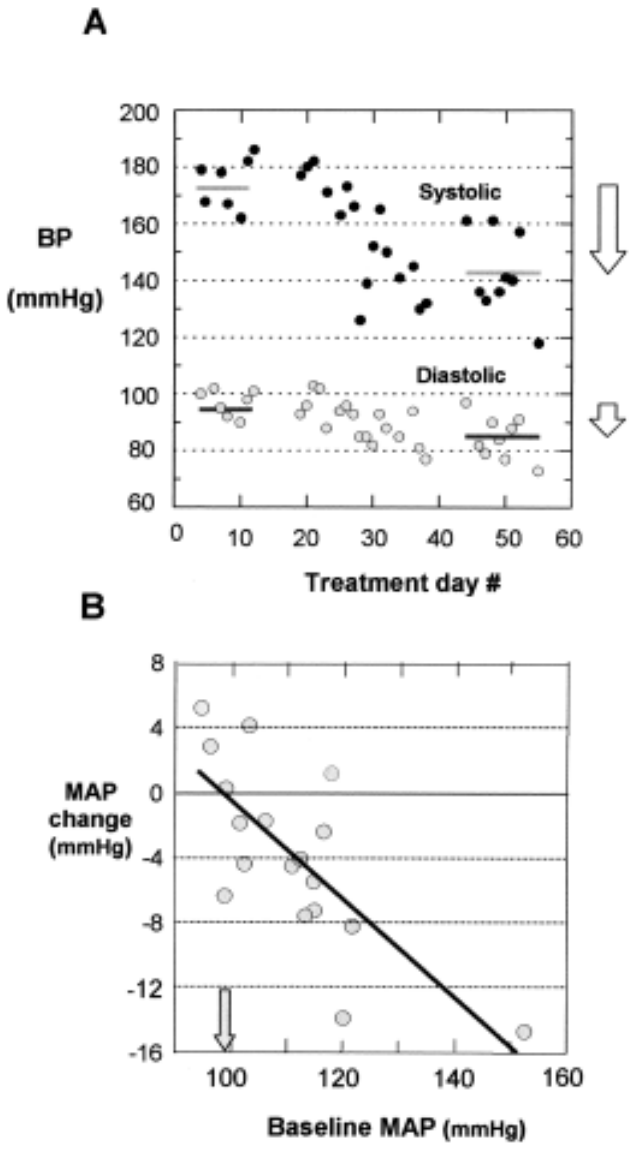

FIG. 1. A) Home blood pressure (BP) data. A case report showing daily variation of home systolic and diastolic BP during the 8-week treatment. Data were obtained from the Web-based data collection system that averages over the individual readings by day. The **gray bars** mark Baseline and End averages that determined the study outcomes. Home BP changes are shown by the **vertical arrows**. **B**) Dependence on baseline MAP level. Data point mark home MAP change in the individual patient, in response to 8 weeks, 15-min daily device-guided slow breathing exercise plotted versus baseline home MAP level. The slope of the regression line (marked) is -0.30 ± 0.07 (mean $\pm$ SE, $P < .001$) with correlation coefficient of $r = 0.73$. The regression model predicts that BP reduction occurs when the baseline level is greater than 98 ± 4 mm Hg (**arrow**).

end of treatment. Continuous variables were compared by paired and unpaired *t* tests or by one-sample *t* test, when compared with a reference value. Linear regression models were used for covariate analysis and for testing correlates, where the significance of the coefficients was evaluated using *t* statistics. All statistical analysis was performed using SYSTAT 7.0 software package (SPSS, Inc.,). $P < .05$ (two tails) was set as the significance level.

Results

Efficacy and Safety

Both office and home BP displayed significant reduction in response to the treatment: office BP, $-12.9 \pm 11.4/-6.9 \pm 6.3$ mm Hg ($P < .001$ for both) and home BP, $-6.4 \pm 8.1/-2.6 \pm 5.1$ mm Hg ($P < .01/P < .05$). The reductions were greater for patients whose baseline BP was elevated: -13.1 ± 11.7 mm Hg for office systolic BP >140 mm Hg ($P < .001$, $n = 16$); -10.6 ± 5.1 mm Hg for office diastolic BP >90 mm Hg ($P < .001$, $n = 7$); -7.1 ± 8.1 mm Hg for home systolic BP >135 mm Hg ($P < .01$, $n = 16$) and -4.7 ± 4.4 mm Hg for home diastolic BP >85 mm Hg ($P < .01$, $n = 10$). The systolic and diastolic BP were considered separately as elevated value in one of them is sufficient to define BP as "elevated," masking the possibility that the treatment may affect only one variable. There was no significant change in heart rate during the treatment period either at office (-3.2 ± 8.3 beats/min) or at home (-1.5 ± 4.2 beats/min).

Fig. 1B shows that mean arterial pressure (MAP) reductions at home are significantly correlated with the corresponding baseline MAP, showing that the treatment reduced home BP only in those patients who had MAP ≥98 mm Hg, which corresponds to the higher than normal level (BP <135/85 mm Hg). Changes in office systolic BP were correlated with the difference between office and home baseline systolic BP levels ($P < .05$). Age, gender, and number of antihypertensive medications were found not to have a significant effect on the outcome.

Fourteen of the 17 (82%) patients with initially uncontrolled office BP were found to be responders, whereas 9 patients (53%) terminated the study with office BP at the normal or high normal range (<140/90 mm Hg).

Safety of the treatment has been assessed by the lack of any side effect of treatment observed or reported by any of the patients.

Compliance

The majority of patients applied the treatment and BP measurement as requested. Patients performed 79% of the seven sessions requested per week, and 70% of the total 56 sessions requested. They exercised 97% of the treatment session duration in average and by measuring 74% of measurements requested, showed high compliance to BP measurement.

Discussion

Resistant hypertensives responded favorably to nonpharmacologic treatment by slow breathing exercises guided interactively by a device and have demonstrated good compliance with both treatment and BP monitoring in the home setting.

These findings generalize previous results obtained with the same treatment protocol in uncontrolled hypertensives,[6–10] but not specifically in these hard-to-treat pa-

tients. The good compliance observed, in spite of the fact the present protocol requires much more time and attention than pharmacologic therapy, which these patients are frequently noncompliant with, reflect perhaps a change in patient's attitude toward this treatment modality. The potential contribution of the white coat[4] effect is excluded for the tested population, as mean home and office baselines BP levels were remarkably similar. The increase of home BP reduction for greater baseline value (Fig. 1B), which has been observed in previous studies,[7,9] has clinical implications in the practice, as patients at higher risk appear to benefit more. This result is unlikely to be a statistical artifact (ie, "regression to the mean") due to the repeated baseline measurements involved in home BP monitoring (Fig. 1A), or reflecting a placebo effect, to which home BP measurements are known to be insensitive.[12]

The successful use of PC-based data collection system in the study for both treatment and diagnostic devices used at the home setting is in line with the future view of telemedicine.[13] The patient is proactive in treatment and follow-up, all related variables are objective, reliable, cannot be manipulated and can be reviewed by the physician. This may enhance compliance and responsibility sharing between the patient and the physician.

Results may have a physiologic rationale. Evidence suggests that slow breathing has some modulating effect on the cardiovascular system, which may be beneficial in hypertension, as in increasing baroreflex sensitivity, heart rate variability, venous return, and reducing peripheral resistance,[14,15] These effects are mediated by both mechanical and neural pathways, which may differ from those affected by drugs.

The main limitations of the present study are its small sample size and the lack of control for placebo effect. Consistency of the results, generalizing previous randomized controlled studies, are encouraging.

In summary, the present study has demonstrated that device-guided slow breathing exercises may be a beneficial nonpharmacologic adjunct in treating resistant hypertensives. The lack of side effects, the demonstrated efficacy and compliance show that there is a potential benefit for using this therapy in the clinical practice, especially when pharmacologic therapy has already failed to achieve BP control.

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