IMPORTANCE  Biofeedback with device-guided lowering of breathing frequency could be an alternate nonpharmacologic treatment option for hypertension. Evidence from trials with high methodologic quality is lacking.

OBJECTIVE  To evaluate the effects of device-guided lowering of breathing frequency on blood pressure in patients with type 2 diabetes mellitus and hypertension.

DESIGN  Single-center, double-blind, sham-controlled trial.

SETTING  A large nonacademic teaching hospital in the Netherlands.

PARTICIPANTS  Patients with type 2 diabetes mellitus and hypertension.

INTERVENTION  Fifteen-minute sessions with either the device that guides breathing through musical tones to a lower breathing frequency (aiming at <10 breaths/min) or a sham device (music without aiming at lowering of breathing frequency) for an 8-week study period.

MAIN OUTCOMES AND MEASURES  Systolic and diastolic blood pressure measured in the physician’s office.

RESULTS  Forty-eight patients were randomized; 21 patients (88%) in the intervention group and 24 patients (100%) in the control group completed the study. There were no significant changes in systolic and diastolic blood pressure, with a difference in systolic blood pressure of 2.35 mm Hg (95% CI, –6.50 to 11.20) in favor of the control group and a difference in diastolic blood pressure of 2.25 mm Hg (95% CI, –2.16 to 6.67) in favor of the intervention group. Three patients in the intervention group experienced adverse events.

CONCLUSIONS AND RELEVANCE  This high methodologic quality study shows no significant effect of device-guided lowering of breathing frequency on office-measured blood pressure in patients with type 2 diabetes. On the basis of this study, together with results from all but one previous trial, device-guided lowering of breathing frequency does not appear to be a viable nonpharmacologic option for hypertension treatment.
Type 2 diabetes mellitus (T2DM) and hypertension commonly occur together. Management of hypertension through pharmacologic as well as nonpharmacologic interventions is effective in preventing cardiovascular events.

An example of a nonpharmacologic intervention is a breathing-focused biofeedback device approved by the Food and Drug Administration and available without prescription (RESPeRATE; InterCure Ltd). Through use of biofeedback 15 minutes each day, the objective for the device is to lower blood pressure (BP) by guiding breathing frequency with musical tones to less than 10 breaths/min. The mechanisms proposed are an adaptation of the pulmonary stretch receptors and baroreceptor reflex, which lead to vascular and cardiac relaxation. Slow breathing also could lead to stimulation of the parasympathetic system or reduced sympathetic activation.

A recent systematic review and meta-analysis of 8 randomized clinical trials showed a potential small benefit of device-guided breathing on systolic BP after short-term follow-up. However, the methodologic quality of the included studies was variable. An editorial and systematic review emphasized that an independent double-blind study design with a proper control group would be necessary to determine whether device-guided breathing has any effect on BP. Therefore, we reevaluated the effects of the RESPeRATE device on office-measured BP in patients with T2DM and hypertension in an investigator-initiated, double-blind, sham-controlled trial.

Methods

Study Design
The present study was a single-center, randomized (1:1), double-blind, sham-controlled trial conducted in patients with T2DM and hypertension (Figure) and aimed to investigate the effects on hypertension of biofeedback by lowering breathing frequency with musical tones (with the RESPeRATE device). The device was to be used 15 min/d during an 8-week intervention period.

Study Sample
Patients were recruited from the internal medicine outpatient clinic of the Isala Clinics in Zwolle, the Netherlands. Eligibility criteria were age 18 years or older, a diagnosis of T2DM, hypertension treated with 1 or more antihypertensive drugs, systolic BP between 130 and 170 mm Hg at the previous and last visits (the same day as baseline measurement) to the internist, and unchanged hypertension treatment during the preceding 3 months. The systolic BP before randomization had to be between 140 and 160 mm Hg. Exclusion criteria were orthostatic hypotension (because it theoretically could mitigate the effects of the device), heart failure (New York Heart Association class III or IV), severe lung disease, hospitalization in the past 3 months, deafness, blindness, and insufficient cognitive abilities or knowledge of the Dutch language. Orthostatic hypotension was defined as a fall in BP of at least 20 mm Hg systolic or 10 mm Hg diastolic pressure either 1 or 3 minutes after changing from a supine to upright position.

Study Groups and Procedures
The RESPeRATE device consists of a control box, a sensor that attaches around the user’s chest, and a set of headphones. Users listened to a melody through the headphones, which guides them to slow their breathing rate, preferably to less than 10 breaths/min. The control group used a visually identical device guiding users to a breathing frequency of approximately 14 breaths/min.

Patients visited the clinic twice. The first investigator (G.W.D.L.) performed baseline measurements and determined eligibility for inclusion (not randomization). The use of the device and home BP monitor was explained by a second investigator (I.D.). All patients were informed that the objective was to study the effects of music therapy. All instructions were given both verbally and in writing and were repeated after 1 week by telephone. Patients were asked to perform the exercise 15 minutes each day at approximately the same time of day for 8 weeks. During the second visit, patients were seen by a third investigator (K.J.J.v.H. and P.R.v.D.) blinded to treatment allocation. Data on home BP measurements from the study diary were collected, and questions about knowledge of the working mechanism and the brand name RESPeRATE were asked to test the success of blinding.

Outcome Measures
The primary and secondary outcome measures were change in office-measured systolic and diastolic BP, respectively. Additional outcome measures were changes in home-measured systolic and diastolic BP. Health-related quality of life was originally planned as a secondary outcome, but prior to inclusion the protocol was amended because of logistic reasons.

Measurements
Baseline data consisted of medical history, smoking status, laboratory data, medication use, height, BP, and body
weight. Blood pressure was measured following a standardized protocol, using a validated digital BP monitor (UA-767 Plus 30; A&D Medical). Home BP was measured on the first and last day of the study, after patients remained seated for a minimum of 5 minutes before performing the exercise. Data on the number and duration of treatment sessions were uploaded from the intervention and sham devices to determine adherence.

Randomization and Sample Size Calculation
Block randomization (blocks of 8) was done by a third party using sealed, nontransparent envelopes. Sample size was calculated with G*Power 3.0 software (http://wwwpsycho.uni-duesseldorf.de/abteilungen/aap/gpower3/download-and-register). The SDs of the change in systolic BP in previous studies were 9.4 mm Hg15 and 10.9 mm Hg.14 To detect a 10–mm Hg absolute reduction in systolic BP, with a power of 0.85, a 2-tailed α value of .05, and an SD of 11 mm Hg (assuming a correlation of 0.5 between baseline and end-of-treatment measures), the total sample size would be 44. For possible loss to follow-up, we increased the sample size to 48. A 10–mm Hg margin in systolic BP was predefined as clinically significant.

Statistical Analysis
Data entry was performed in duplicate. Analyses were carried out by a statistician (K.H.G.) blinded to treatment allocation. Mixed-effect models were used to estimate the effect of the intervention on BP after 8 weeks with and without adjustment for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; IQR, interquartile range. SI conversion factor: To convert HbA1c to a proportion of total hemoglobin, multiply by 0.01.

Results
Patients
From September 8, 2009, through June 15, 2012, a total of 292 white individuals were invited to participate (Figure). From the 48 patients randomized, 3 in the intervention group stopped their participation prematurely: 1 died and 2 withdrew consent, leaving 21 intervention patients (88%) available for analysis of office- and home-measured BP. All 24 patients in the control group were available for analysis of office-measured BP; home-measured BP was analyzed for 14 individuals (58%). No protocol violations were made with regard to adjustment of antihypertensive medication. Baseline characteristics are reported in Table 1. The blinding procedure was successful. No participants reported knowing about the therapy in the other treatment group. One patient reported an unsuccessful attempt at unblinding the study through an Internet search.

Intervention
Mean (SD) breathing frequency during the exercise was 5.7 (2.0) breaths/min in the intervention group and 14.3 (0.6) breaths/min in the control group (P < .0001). Treatment with the intervention device did not lead to a significant difference in office-measured systolic BP (2.35 mm Hg; 95% CI, –6.50 to 11.20, in favor of the control group). Furthermore, there was no significant difference in office-measured diastolic BP (1.11 mm Hg; 95% CI, –7.59 to 9.82, in favor of the control group); the difference in office-measured diastolic BP was 3.48 mm Hg (95% CI, 0.42 to 7.38, in favor of the intervention group). Treatment with the intervention device did not
lead to significant differences in home-measured BP compared with the control group (Table 2). Per-protocol analysis in adherent patients (14 in the intervention group [67%] and 18 in the control group [75%]) showed a nonsignificant difference in systolic BP of 2.67 mm Hg (95% CI, −6.97 to 12.32, in favor of the control group), and the difference in diastolic BP was 1.14 mm Hg (95% CI, −6.27 to 4.00, in favor of the intervention group). Two patients (10%) in the intervention group had an average breathing frequency greater than 10 breaths/min. When excluding these patients, the nonsignificant difference in office-measured systolic BP was 2.19 mm Hg (95% CI, −6.49 to 10.87; P = .51, in favor of the control group).

Safety
There were 3 adverse events, all in the intervention group. One patient died of respiratory failure due to underlying heart failure. Another patient reported shortness of breath. The third patient had atypical chest pain with shortness of breath and sought care at the emergency department. Both individuals refused to continue using the device and were unavailable for further BP measurements.

Discussion
To our knowledge, this is the first randomized, double-blind, sham-controlled trial investigating short-term effects of device-guided slowing of breathing in patients with T2DM and hypertension. Our study did not show beneficial effects of device-guided slowing of breathing on office- and home-measured BP. Per-protocol analyses excluding patients not reaching the target breathing frequency and analyses excluding nonadherent patients showed similar results. We observed 3 adverse events in the intervention group; 2 of these could have been related to the use of the RESPeRATE device.

A recent systematic review and meta-analysis including 8 trials investigating the RESPeRATE device showed that all previous studies were subject to methodologic flaws. None of these studies had a sham-controlled, double-blind design. Only 4 studies had a design with a control group qualifying as a “reasonable control group.” Only 3 studies claimed to have a double-blind design but used either a Walkman or no control device. Only 1 of the 8 studies included in the systematic review and meta-analysis reported a significantly lower office-measured systolic BP, and 2 studies reported a significantly lower office-measured diastolic BP. The meta-analysis indicated that there could be a modest beneficial effect of short-term use of the RESPeRATE device, with a decrease in systolic BP of 3.1 mm Hg (95% CI, 1.4–4.7). The study with the largest effect on the results of the meta-analysis also had the highest risk of bias; that study had no adequate control group, was not blinded, and was carried out by the manufacturer. The manufacturer was involved in all but 3 studies. All studies that reported a beneficial effect of the RESPeRATE device were initiated or sponsored by the manufacturer. A sensitivity analysis excluding sponsored studies showed no effect of device-guided breathing on BP. The authors of the aforementioned meta-analysis postulated a possible conflict of interest in their results.

Our study was investigator-initiated and its strength lies in the use of a sham device by the control group and the successful double-blinding procedure. Our trial was limited by a short duration of 8 weeks and was relatively small. We predefined a 10-mm Hg margin as clinically significant, arguing that this margin was acceptable for a device requiring a tremendous amount of effort and persistence. Although we were able to exclude an advantage of 10 mm Hg with 85% power, this 10-mm Hg margin used for the sample-size calculation is subject to debate. Given the relatively wide 95% CI of the difference in systolic BP, we also could not exclude a relevant harmful effect of the RESPeRATE device. Furthermore, only 16% of eligible patients were included. We had to extend the inclusion period by 2 years because of this low participation rate. Most patients refused participation because of the time-consuming nature of the device, indicating that the target population of RESPeRATE will likely be small. Several other recruited patients did not meet our inclusion criteria, which indicates that our study population is representative for a few of the Dutch population of patients with T2DM and hypertension. The generalizability was further limited to a white population.

In conclusion, this study showed no beneficial effects of the RESPeRATE device on BP in patients with T2DM and hypertension. Furthermore, possible harmful effects were seen. By confirming the results of 7 of the 8 previous trials, the promotion of the RESPeRATE device as an effective biofeedback modality for hypertension treatment should be reevaluated, at least for white patients with T2DM.

Table 2. Estimated Changes in Measurements of BP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Change in BP</th>
<th>Difference in BP, Mean (95% CI)*</th>
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<tbody>
<tr>
<td><strong>Office-measured BP, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−6.03</td>
<td>−3.35</td>
</tr>
<tr>
<td>Diastolic</td>
<td>−5.92</td>
<td>−3.67</td>
</tr>
<tr>
<td><strong>Home-measured BP, mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−3.66</td>
<td>−0.64</td>
</tr>
<tr>
<td>Diastolic</td>
<td>−1.38</td>
<td>−1.48</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.

*Ten patients did not perform home BP measurements.

bDifference is control − intervention, unadjusted for baseline values.
**Research Original Investigation**

**ARTICLE INFORMATION**

Accepted for Publication: February 28, 2013.

Author Contributions: Dr Landman had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Landman, van Hateren, Logtenberg, Bilo, and Kleefstra.

Acquisition of data: Landman, Drion, van Hateren, van Dijk, and Lambert.

Analysis and interpretation of data: Landman, Lambert, Groenier, and Bilo.

Drafting of the manuscript: Landman and Drion.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: van Hateren and Groenier.

Obtained funding: Bilo.

Administrative, technical, and material support: Landman, Drion, van Hateren, and Lambert.

Additional Contributions: We thank all the participating hypertension centers.

Conflict of Interest Disclosures: None reported.

Funding/Support: InterCure Ltd provided the RESPeRATE and sham devices.

Role of the Sponsors: The trial was sponsored by the Medical Research Foundation Zwolle.

Additional Contributions: We thank all the participating centers in this trial. Ineke Kloppenberg, as well as Sabine Diepeveen, MD, PhD, Ad Kamper, MD, PhD, and Jan-Evert Heeg, MD, PhD, assisted with the inclusion.

**REFERENCES**


