Efficacy of Device-Guided Breathing for Hypertension in Blinded, Randomized, Active-Controlled Trials
A Meta-analysis of Individual Patient Data

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IMPORTANCE Device-guided breathing (DGB) is recommended by the American Heart Association for its blood pressure–lowering effects. Most previous studies that showed beneficial effects on blood pressure had low methodological quality and only investigated short-term blood pressure effects.

OBJECTIVE To assess the efficacy of DGB on blood pressure in a meta-analysis of individual patient data from blinded, randomized controlled trials with an active control group.

DATA SOURCES MEDLINE, EMBASE, clinicaltrials.gov, and the Cochrane Library.

STUDY SELECTION Included were randomized studies of at least 4 weeks' duration, with a single- or double-blind design and an active control group. Bias was assessed with the Cochrane risk of bias tool, and analyses were performed with linear mixed models.

DATA EXTRACTION AND SYNTHESIS Articles were searched in MEDLINE (using PubMed), EMBASE, and the Cochrane Library.

MAIN OUTCOMES AND MEASURES Office blood pressure.

RESULTS From the 15 selected abstracts, 5 studies were suitable for inclusion. Individual patient data from 2 of 5 studies were not provided. The effect of DGB on office systolic blood pressure compared with music therapy or a sham device was 2.2 mm Hg (95% CI, −2.7 to 7.0) in favor of the control group; DGB did not significantly lower office diastolic blood pressure (0.2 mm Hg [95% CI, −2.8 to 3.1] in favor of DGB).

CONCLUSIONS AND RELEVANCE All trials included in the analysis had a short follow-up period; therefore, no recommendations could be made regarding hypertension treatment. Treatment with DGB did not significantly lower office blood pressure compared with a sham procedure or music therapy.

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Treatment of hypertension often requires a combination of lifestyle interventions and blood pressure-lowering agents. Nonpharmacological treatment options are reduction of sodium consumption, weight loss, exercise, smoking cessation, avoidance of excessive alcohol consumption, and adherence-enhancing strategies. There is growing interest in other nonpharmacological interventions for hypertension. One is slowing of the breathing frequency through device-guided breathing (DGB) exercises. Device-guided breathing is a form of biofeedback that uses musical tones to decrease breathing frequency. Exercises should be performed 5 to 7 days per week for 10 to 15 minutes daily. Effects of DGB on pulmonary stretch receptors, the (para)sympathetic nervous system, and the baroreceptor could theoretically lower blood pressure.

One commercial device, called the RESPeRATE (InterCure Ltd), is currently available. It is claimed that more than 250,000 of these devices have been sold to individual purchasers worldwide, most of whom reside in the United States. This device is reimbursed by the National Health Service and is recommended to a wide range of populations by the American Heart Association for its blood pressure-lowering effects (class IIA evidence, level of recommendation B). This recommendation was based on results of a previous meta-analysis, which showed a small short-term effect on blood pressure, mainly in studies comparing DGB with active control groups and studies with methodological concerns.

The question of whether DGB is more effective than an inactive control group is less interesting when there is an indication for treatment. Device-guided breathing focuses specifically on 1 potential effective element that most relaxation exercises or techniques share: slow breathing. Next to slow breathing, DGB could also affect blood pressure through relaxing or listening to music. Studies that compare DGB with other active interventions or control groups can help provide insight into the physiologic mechanism responsible for effects on blood pressure.

We primarily aimed to investigate the effects of DGB on office blood pressure using individual patient data from randomized clinical trials, which compared DGB with active control groups and had a treatment duration of at least 4 weeks with a single- or double-blind design. When individual patient data could not be retrieved, a secondary analysis was preplanned that aimed to perform a meta-analysis that also included results from published studies with the same inclusion criteria.

Methods

Protocol
The eligibility criteria, outcomes, and main and sensitivity analyses were prespecified and published on PROSPERO (2013: CRD42013005509). The methods and results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (www.prisma-statement.org).

A study was considered eligible if it was randomized; had a single- or double-blind design, an active control group (music therapy, relaxation exercises or techniques, or a sham device), and a duration of intervention of at least 4 weeks; included patients with hypertension; primarily investigated effects on blood pressure; and reported office systolic blood pressure.

Data Sources and Searches
An electronic search without language restrictions was performed in MEDLINE (using PubMed), EMBASE, and the Cochrane Library (October 5, 2013; eMethods in the Supplement). Reference lists of selected articles were searched. Completed but unpublished trials were also searched (November 1, 2013) using the website of publicly registered clinical trials (www.clinicaltrials.gov).

Study Selection
Studies selected from MEDLINE, EMBASE, and the Cochrane Library were imported in reference management software (www.endnote.com). After removing duplicate results, 2 of us (N.K. and K.J.J.v.H.) independently performed the study selection. Differences between the reviewers were resolved by consensus or by a third investigator (G.W.D.L.). One investigator (G.W.D.L.) searched the trial register.

Data Collection and Data Items
A data extraction form was designed, and 2 of us (P.R.v.D. and S.J.J.L.) independently abstracted the data; a third investigator (G.W.D.L.) resolved discrepancies. From each study, the following characteristics were extracted: author identification, year of publication, clinical trial number, sample size, type of intervention and control, duration of intervention, participants’ baseline characteristics, and prespecified outcomes of efficacy and safety.

The primary outcome was the change in office systolic blood pressure between the baseline and the end of the study period (end-of-treatment blood pressure) in studies that provided individual patient data. The secondary outcome was the change in office diastolic blood pressure.

A meta-analysis investigating the change in blood pressure using data from published articles was predefined as a secondary analysis. Prespecified subgroup analyses were planned regarding efficacy outcomes in studies with low risk of bias.

Missing Data and Multiple Reports
The primary investigators and InterCure Ltd, the company that manufactures RESPeRATE, were contacted, and individual patient data were requested for trials that had not been performed by our research group. When they did not respond, InterCure Ltd was contacted, and unadjusted data at the end of follow-up (from the date of the actual end of the study) were requested. Data from intention-to-treat trials (all participants randomized) were used when these were available. Unadjusted data were preferred over adjusted data.

Risk-of-Bias Assessment
To assess the risk of bias, the Cochrane Collaboration’s risk-of-bias tool was used. This tool considers the presence of bias...
caused by random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data (because of the high rate of discontinuation, type of analysis, or imputation of missing data), selective reporting, and other forms of bias. Study registration became mandatory in 200412; September 13, 2005, was the last date for trials not registered at inception.13 Studies without registration after this period were considered at high risk of selective reporting. The risk of bias was regarded as high when the presence of bias was high in any domain, low if all key domains (all domains except random sequence generation and allocation concealment) had low bias, and unclear in all other cases. When only the risk of bias in the seventh domain (other bias) was unclear, it was considered to have low risk of bias.11 Two of us (S.J.J.L. and P.R.v.D.) independently assessed the risk of bias; when necessary, consensus was determined through help of a third investigator (G.W.D.L.).

Statistical Analysis
Analyses were carried out by a statistician who was blinded to treatment allocation. Linear mixed-effect models were used to estimate the effect of the intervention on blood pressure with and without adjusting for age, sex, and body mass index. Treatment and confounders were regarded as fixed factors. Patients and their study number were regarded as random-effect factors. Analyses were performed using SPSS, version 20 (IBM Corporation).

Mean differences with standard deviations between the intervention group and all active comparator groups were calculated with an inverse variance random-effects model. If a study did not report standard deviations, these were calculated from the standard error or the 95% CI. Statistical heterogeneity (I²) values of 0.3 to 0.6 and between 0.6 and 0.9 represent moderate and considerable heterogeneity, respectively.11 Potential causes of heterogeneity were explored by excluding articles with and without high overall risk of bias. Sensitivity analyses were planned for every outcome based on its overall risk of bias. All analyses, including data from published articles, were performed with RevMan 5.1 (Nordic Cochrane Centre). A 2-sided significance of P = .05 was used.

Results
In total, 15 abstracts6-14-27 were selected for full-text evaluation, 5 of which were included in the meta-analysis (Figure 1).6,16,20,21,27 All selected studies were retrieved by searching electronic databases. No additional completed trials were retrieved from other sources. In all studies, RESPeRATE was investigated. Music therapy was used as a control in 4 studies,6,16,20,21 and 1 study20 used a sham device that did not lower the breathing frequency. We sent e-mails to the authors of the studies as well as representatives of InterCure Ltd. The company’s representative responded to 1 of several e-mails and ultimately did not provide us with the patient-level data.6,27 Individual patient data could be retrieved from 3 studies.16,20,21

In all studies, the follow-up period was short, and none of the patients in the control groups received formal training that focused on relaxation or guided breathing. Three studies were unsponsored,16,20,21 and 2 were initiated by the manufacturer.6,27

Three adverse events were reported in 1 trial,20 all in the intervention group. Two patients stopped prematurely owing to shortness of breath, and 1 patient died because of respiratory failure. Table 1 and Table 2 summarize the characteristics of the 5 studies.

Risk of Bias
Overall risk of bias for the primary outcome (eFigure in the Supplement) was high in 2 studies,6,27 unclear in 2 studies, and low in 1 study.20 Two studies,6,27 both initiated by the manufacturer, had a high risk of selective outcome reporting because the primary outcome was analyzed with methods that were not prespecified. Furthermore, both studies only reported multivariate corrected results. One study had a high risk of selection bias because allocation concealment was not reported.6 Two trials had a single-blinded design16,21; the effect of using that design instead of a double-blind method had an unclear influence on the primary outcome. Two trials6,27 claimed to have a double-blind design, although the device was compared with music therapy, and it could not be confirmed whether double-blinding was established.

Effects on Blood Pressure in the Individual Patient Meta-analysis
The effects of DGB on blood pressure for the individual patient meta-analysis are presented in Table 3.
Effects on Blood Pressure
From the Secondary Meta-analysis

The secondary meta-analysis, in which data from 2 studies were added that could not provide individual patient data showed the effects of DGB on office systolic and diastolic blood pressure compared with music therapy or a sham device were 1.1 mm Hg (95% CI, −2.8 to 5.0; $I^2 = 0.27$) in favor of DGB (Table 4 and Figure 2) and 1.9 mm Hg (95% CI, −1.0 to 4.7; $I^2 = 0.46$) in favor of DGB, respectively. We observed moderate heterogeneity in the diastolic office blood pressure analysis, which was caused by 1 study.21

Compared with music therapy,6,16,21,27 DGB did not significantly lower office systolic or diastolic blood pressure, which was 1.8 mm Hg (95% CI, −2.8 to 6.3; $I^2 = 0.38$) in favor of DGB and 1.6 mm Hg (95% CI, −2.3 to 5.4; $I^2 = 0.59$) in favor of DGB. The results were not different after excluding studies

### Table 1. Clinical Characteristics at Baseline of the Patient Populations of Included Studies

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Population/ Setting (Country)</td>
<td>Hypertension/3 urban family practices (Israel)</td>
<td>Hypertension/ T2 diabetes outpatient clinic (the Netherlands)</td>
<td>Hypertension/ T2 diabetes outpatient clinic (the Netherlands)</td>
<td>Hypertension/ T2 diabetes outpatient clinic (the Netherlands)</td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>I 32 18 15 15 24</td>
<td>C 33 15 15 15 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>I 58 (9) 52 (12) 63 (6) 60 (11) 64 (8)</td>
<td>C 57 (8) 50 (4) 61 (8) 59 (12) 65 (8)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female sex, %</td>
<td>I 44 28 80 53 46</td>
<td>C 61 33 33 47 29</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I 157 (14) 160 (18) 154 (8) 147 (5) 152 (8)</td>
<td>C 155 (9) 155 (11) 150 (8) 153 (6) 151 (11)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diastolic</td>
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<td></td>
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</tr>
<tr>
<td>I 97 (9) 95 (7) 83 (7) 88 (11) 82 (15)</td>
<td>C 93 (7) 94 (6) 87 (8) 87 (11) 80 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I 73 77 74 75 75</td>
<td>C 72 81 79 71 75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bpm, beats per minute; C, comparison; I, intervention; T2, type 2.

### Table 2. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Duration of Follow-up, wk</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Primary Outcome</th>
<th>Role of the Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schein 2001 et al,27 2001</td>
<td>8</td>
<td>RESPeRATE 10 min/d</td>
<td>Walkman 10 min/d</td>
<td>Systolic BP, diastolic BP (change)</td>
<td>Study was sponsored by InterCure Ltd, with Dr B. Gavish as Chief Scientist Commercial 3rd party helped with data analysis</td>
</tr>
<tr>
<td>Grossman et al,6 2001</td>
<td>8</td>
<td>RESPeRATE 10 min/d</td>
<td>Walkman 10 min/d</td>
<td>Home and clinic blood pressure</td>
<td>Last author, Dr B. Gavish, employee of InterCure Ltd</td>
</tr>
<tr>
<td>Logtenberg et al,21 2007</td>
<td>8</td>
<td>RESPeRATE 15 min/d</td>
<td>Discman 15 min/d</td>
<td>Change in office systolic BP</td>
<td>Financial support from the medical research foundation Zwolle and the Langerhans foundation</td>
</tr>
<tr>
<td>Altena et al,16 2009</td>
<td>9</td>
<td>RESPeRATE 15 min/d</td>
<td>Discman 15 min/d</td>
<td>Change in office systolic BP</td>
<td>Financial support from the medical research foundation Zwolle</td>
</tr>
<tr>
<td>Landman et al,20 2013</td>
<td>8</td>
<td>RESPeRATE 15 min/d</td>
<td>Sham device 15 min/d</td>
<td>Change in office systolic BP</td>
<td>InterCure Ltd provided sham devices Financial support from the medical research foundation Zwolle</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.
with a high risk of bias. Compared with music therapy or a sham device, the effects of DGB on systolic and diastolic blood pressure were 1.2 mm Hg (95% CI, −6.6 to 4.3; \( I^2 = 0.33 \)) and 0.3 mm Hg (95% CI, −4.0 to 5.6; \( I^2 = 0.52 \)) in favor of the control group. In studies with a high risk of bias, an effect on systolic blood pressure of 4.2 mm Hg (95% CI, −0.9 to 9.2; \( I^2 = 0.0 \)) and diastolic blood pressure of 4.0 mm Hg (95% CI, 1.3 to 6.7; \( I^2 = 0.0 \)) were found, both in favor of DGB.

### Discussion

Treatmt with DGB did not significantly influence office blood pressure compared with a sham procedure or music therapy. The results of the analysis from individual patient data and those from published articles were consistent and excluded a potential relevant effect up to 5 mm Hg in office systolic blood pressure. All 5 trials included in the analysis had a short follow-up period, and 2 had a high risk of bias. In only the analysis combining studies with a high risk of bias was a beneficial effect on short-term diastolic blood pressure found.

Hypertension treatment is ultimately aimed at preventing cardiovascular complications. Long-term sustainable reductions in blood pressure are sometimes regarded as appropriate surrogate end points for cardiovascular diseases. We found no randomized trials investigating the effects of DGB on long-term cardiovascular end points. Because of short-term inefficacy compared with other freely available relaxation techniques, combined with an absence of evidence for long-term efficacy in randomized trials, there appears to be insufficient evidence to recommend DGB to patients with hypertension.

The previous meta-analysis on DGB showed that short-term effects on blood pressure could primarily be ascribed to studies that compared DGB with usual care. In the present study, individual patient data were analyzed, studies with inadequate control groups were excluded, and 1 sham-controlled trial was included. Studies that compared DGB with usual care were specifically excluded to facilitate translation of results into recommendations for daily practice. From

### Table 3. Change in Office Measurements of Blood Pressure

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Change in Blood Pressure, mm Hg</th>
<th>( I ) (n = 51)</th>
<th>( C ) (n = 54)</th>
<th>( I-C )</th>
<th>( I-C )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>−6.7 (−10.2 to −3.2)</td>
<td>−8.9 (−12.3 to −5.4)</td>
<td>2.2 (−2.7 to 7.0)</td>
<td>1.7 (−3.1 to 6.5)</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>−4.0 (−6.2 to −1.9)</td>
<td>−3.9 (−6.0 to −1.8)</td>
<td>0.2 (−3.1 to 2.8)</td>
<td>−0.7 (−3.6 to 2.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C, control; I, intervention.

* Individual patient data were used from 3 trials. Differences in office blood pressure were analyzed with linear mixed models. Treatment group and confounders were fixed factors; patients and study number were random effect factors.

### Table 4. Results From the Secondary Meta-analysis in 5 Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Experimental Group</th>
<th>Control Group</th>
<th>Weight, %</th>
<th>Mean Difference in IV, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schein 2001 et al,27 2001</td>
<td>15.2 (13.4) 32</td>
<td>11.3 (12.8) 33</td>
<td>24.8</td>
<td>3.9 (−2.5 to 10.3)</td>
</tr>
<tr>
<td>Grossman et al,6 2001</td>
<td>7.5 (12.0) 18</td>
<td>2.9 (12.1) 15</td>
<td>17.1</td>
<td>4.6 (−3.7 to 12.9)</td>
</tr>
<tr>
<td>Logtenberg et al,21 2007</td>
<td>7.5 (9.4) 15</td>
<td>12.2 (9.4) 15</td>
<td>23.0</td>
<td>−4.7 (−11.4 to 2.0)</td>
</tr>
<tr>
<td>Altena et al,16 2009</td>
<td>9.8 (11.3) 15</td>
<td>5.6 (10.4) 15</td>
<td>18.7</td>
<td>4.2 (−3.6 to 12.0)</td>
</tr>
<tr>
<td>Landman et al,20 2013</td>
<td>6.0 (14.5) 21</td>
<td>8.4 (15.4) 24</td>
<td>16.5</td>
<td>−2.3 (−10.7 to 6.2)</td>
</tr>
<tr>
<td>Total</td>
<td>...</td>
<td>...</td>
<td>100</td>
<td>1.1 (−2.8 to 5.0)</td>
</tr>
</tbody>
</table>

Abbreviation: IV, inverse variance.

* The secondary meta-analysis also included data from 2 studies that could not provide individual patient data.
a patient’s perspective, the question whether to buy a time-consuming and costly device or to perform freely available relaxation techniques is more relevant than whether DGB is more effective than doing nothing. This meta-analysis provides no evidence that slow breathing is either responsible for blood pressure-lowering effects or that DGB is more effective than listening to music. The absence of benefit compared with music therapy or a sham device does not necessarily negate the value of DGB. However, the lowering of breathing frequency is the presumed physiologic mechanism through which DGB affects blood pressure and for which it is marketed.5 Furthermore, there is no evidence of better (or acceptable) long-term compliance of DGB compared with other relaxation techniques.

A limitation of this meta-analysis was the absence of the inclusion of randomized trials with sufficient follow-up. Therefore, a hypothesized long-term beneficial effect of DGB on hypertension could not be excluded. Also, from the 5 studies selected for this meta-analysis, none used structurally trained relaxation techniques as a comparator group.

Two trials6,27 did not provide individual patient data. Inclusion of these results in the primary analyses could have led to different conclusions; however, the results of the secondary analyses, which included all 5 trials, provided some evidence that the results would not likely have been different. Not all studies reported whether adverse events occurred, and 1 trial20 showed that DGB could potentially have unanticipated adverse effects, although these findings could also be coincidental. Some heterogeneity in the secondary efficacy analysis was observed, which was explained by 1 study.21 Although we performed a meta-analysis in 3 trials with individual patient data, the contribution of participants’ baseline characteristics to the effect estimates were not investigated in the meta-analysis using the results from published articles. Exclusion of trials with high risk of bias in a sensitivity analysis did not relevantly alter the results of the main analysis.

Conclusions

This study shows that DGB has no relevant short-term effects on office blood pressure compared with a sham procedure or listening to music. The results of one sham-controlled trial questions the validity of the presumed physiologic mechanism through which DGB exerts effects on blood pressure. Furthermore, the use of DGB is possibly not free from adverse effects. This meta-analysis could be a basis for the American Heart Association to reconsider their recommendation regarding the use of DGB.

ARTICLE INFORMATION

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Author Contributions: Dr Landman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Landman, van Dijk, Houweling, Groenier, Kleefstra. Acquisition, analysis, or interpretation of data: Landman, van Hateren, Logtenberg, Groenier, Bilo, Kleefstra.

Drafting of the manuscript: Landman, van Dijk, Groenier, Kleefstra. Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Landman, van Dijk, Groenier.

Obtained funding: Bilo.

Administrative, technical, or material support: van Hateren, van Dijk.

Study supervision: Houweling, Bilo, Kleefstra.

Conflict of Interest Disclosures: None reported.

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