

# Effects of guided breathing on blood pressure and heart rate variability in hypertensive diabetic patients<sup>☆,☆☆</sup>

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## ARTICLE INFO

### Article history:

Received 14 February 2013

Received in revised form 27 June 2013

Accepted 20 August 2013

### Keywords:

Device guided breathing

RESPerATE®

Diabetes

Hypertension

Randomized controlled study

Ambulatory blood pressure monitoring

Heart rate variability

Spectral analysis

## ABSTRACT

**Objective:** Our aim was to investigate medium-term effects of device-guided breathing on blood pressure (BP) and its capacity to improve the cardiovascular autonomic balance in hypertensive diabetic patients. This feasibility study was conceived as a proof-of-concept trial under real life conditions for justification of further investigations.

**Methods:** A randomized, controlled study (RCT) of the effects of device-guided slow breathing on top of usual care against usual care alone (including non-pharmacological and pharmacological treatment). The intervention included 12-min sessions of guided breathing performed daily for 8 weeks. Treatment effects were assessed with ambulatory blood pressure monitoring (24 h ABPM) and with spectral analysis of short-term heart rate variability (HRV) obtained during standardized modified orthostatic load. Thirty-two subjects with diabetes and antihypertensive therapy were randomly assigned to both study groups.

**Results:** After 8 weeks of guided breathing, significant reductions were demonstrated in 24 h systolic BP ( $x \pm \text{SEM}$ :  $126.1 \pm 3.0$  vs  $123.2 \pm 2.7$  mm Hg,  $p = 0.01$ ), and in 24 h pulse pressure (PP,  $53.6 \pm 2.6$  vs  $51.3 \pm 2.5$  mm Hg,  $p = 0.01$ ), whereas no significant impact in the control group was shown. The differences in treatment effects (delta mm Hg, RESPerATE® vs control) were significant only for PP ( $-2.3 \pm 0.8$  vs  $+0.2 \pm 1.2$  mm Hg,  $p < 0.05$ ). Strong baseline dependence of treatment effects (delta systolic BP) was observed ( $p < 0.01$ ). Guided breathing showed a stronger treatment effect in terms of an increase in HRV, predominantly in low frequency band ( $p < 0.03$  vs. usual care).

**Conclusion:** Even in well controlled hypertensive diabetic patients, guided breathing induced relevant effects on BP and HRV, finding which should be investigated further.

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## 1. Introduction

Hypertension is a serious cardiovascular risk factor, with a prevalence of up to 28% in North America and 44% in Europe. As only 28% of patients are adequately controlled (Wolf-Maier et al., 2004), additional non-pharmacological blood pressure lowering might save complications and postpone death.

Slow, device-guided breathing has been shown to effectively reduce blood pressure. In several studies (Rosenthal et al., 2001; Viskoper et al.,

2003; Elliot et al., 2004; Meles et al., 2004; Logtenberg et al., 2007; Altena et al., 2009; Schein et al., 2009), a 12-minute daily use over 8 weeks resulted in consistent lowering of systolic and diastolic blood pressure. The pathophysiological mechanism of BP lowering with slow breathing is not fully elucidated yet. Inappropriately high sympathetic nervous outflow from the central nervous system is believed to be an important component in the development of hypertension, inducing an increase in cardiac output and peripheral resistance (Smith et al., 2004). A better understanding of the guided breathing mechanism of action would allow for an appropriate target group selection and hence for a more appropriate allocation of resources and reduction of clinical side effects when pharmacological intervention becomes necessary.

Three-dimensional spectral analysis of short-term heart rate variability using fast Fourier transform offers a unique instrument for an instantaneous quantification of sympathetic and parasympathetic cardiovascular autonomic control (Howorka et al., 1998; Pumpřla et al.,

<sup>☆</sup> Author's contributions: Kinga Howorka and Jiri Pumpřla contributed equally to the paper.

<sup>☆☆</sup> Source of funding: work funded by the non-profit Research Group Functional Rehabilitation and Group Education (registered association in Austria).

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2002; Howorka et al., 2010). Autonomic dysfunction is common in diabetes and hypertension (Gerritsen et al., 2001) and worsens the life prognosis (Ewing et al., 1985). Hypertension and diabetes mellitus are interrelated diseases, and dominate in metabolic syndrome. It is estimated that more than 60% of diabetic patients suffer from hypertension (Arauz-Pacheco et al., 2002), which increases morbidity and mortality (Morris et al., 2001). In diabetes, a near-normalization of blood pressure towards values below 130/80 mm Hg is recommended (Mogensen, 2003; ADA, 2004), since it remains the main risk factor for micro- and macrovascular diabetes complications.

Diabetic autonomic neuropathy is related to an increased all-cause mortality risk in diabetic patients (Ewing et al., 1985; Ziegler et al., 1992; Vinik and Erbas, 2001; Gerritsen et al., 2001; Wheeler et al., 2002). The most life threatening condition is an advanced cardiovascular autonomic neuropathy (CAN). Heart rate variability (HRV) is a measure of CAN and is partly related to the breathing rate. A lower breathing rate is associated with an increase in HRV (Pitzalis et al., 1998). Furthermore, a prolonged exhalation also results in an increased HRV (Strauss-Blasche et al., 2000). Short-term spectral analysis of HRV recorded under standardized conditions over three time segments during a modified orthostatic test, provides a fast, objective, non-invasive and reproducible method to detect even early stages of CAN and their dynamics in diabetes (Howorka et al., 1998; Pumprla et al., 2002).

Several studies have shown that controlled slow breathing results in a decrease of systolic, diastolic and mean arterial blood pressure, and also in an increase of HRV (Patel et al., 1985; Joseph et al., 2005; Pinheiro et al., 2007). Our hypothesis was that guided breathing with RESPeRATE® improves autonomic function. More specifically, we hypothesized that it would reduce blood pressure values and increase heart rate variability in diabetic patients with hypertension. We wanted to investigate guided breathing-related effects within a controlled trial (intervention vs usual care) to filter out potential placebo- (study-) related effects. More specifically, our aim was to estimate its therapeutic potential as an additional non-pharmacological treatment option in ambulatory diabetic patients with hypertension already treated by pharmacological agents.

This feasibility study was conceived as a proof-of-concept trial under real life conditions as a justification for further and more profound (and costly) investigation.

## 2. Methods

The study was carried out in accordance with the EU-GCP guideline and in accordance with the guidelines of the Declaration of Helsinki (1964), including recent revisions (Declaration of Helsinki, amended, 2008). Study protocol was approved by the local Ethics Committee (EudraCT No 2011-003839-53). Each subject signed an informed consent form before inclusion in the study.

### 2.1. Study intervention: device guided breathing with RESPeRATE® in addition to “usual care”

Guided breathing using the RESPeRATE® device was used as study intervention procedure. The device consists of a breathing sensor positioned on the chest, headphones and a computerized unit (Fig. 1). The breathing sensor analyzes the individual breathing pattern and creates a personalized melody composed of two distinct inhale and exhale guiding tones. The exhalation tone is gradually prolonged, thereby slowing down the breathing, which finally leads to less than 10 breaths per minute. An internal memory is included in the device, which registers and stores date, time, duration and effective use in each treatment session. The time the user spends with a breathing rate of less than ten breaths/min is called “effective time” and is quantified. The target time period for the use of the device is one session (at least 12 min) per day according to the recommendation of the manufacturer (based on experience from previous clinical investigations).

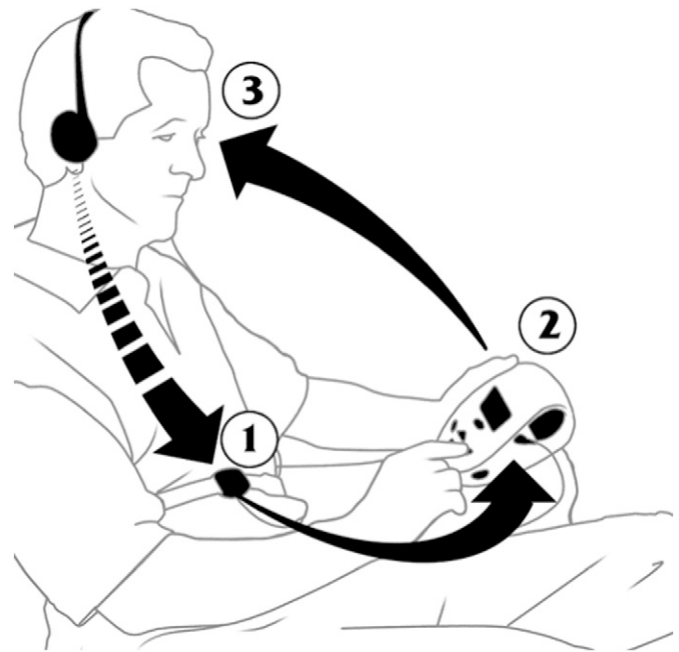


Fig. 1. Principles of device-guided paced breathing: (1) monitoring breathing movements, (2) composing breathing-guiding tones, and (3) synchronizing breathing movements with the guiding tones (by courtesy of Intercure Inc.).

In our study, RESPeRATE® was used as an add-on on top of the usual pharmacological and non-pharmacological treatment. All study subjects had a history of participation in a structured patient group education on diabetes and hypertension (Howorka et al., 2009; Pumprla, 2008).

### 2.2. Control intervention: “usual care”

The control intervention included the usual treatment as taught during structured hypertension education (Howorka et al., 2009), which includes the ‘classical’ recommended non-pharmacological measures (salt reduction, DASH diet, weight reduction, endurance and or muscle hypertrophy training, Chobanian et al., 2003), and – if necessary – individual pharmacotherapy (usually 1–3 agents; mainly ACE inhibitors and/or sartans, if necessary other agents), and at least two self-BP-measurements per week.

### 2.3. Research design

Randomized, controlled trial (RCT) of effects of guided breathing with RESPeRATE® on top of usual care against usual care alone, while “standard” treatment and usual care remained unchanged (non-pharmacological and pharmacological treatment based on structured group education and individual counseling). Intraindividual and intergroup comparison of ambulatory blood pressure monitoring (24 h ABPM) as well as HRV target parameters between baseline and values obtained after 8 weeks of either intervention (systematic, daily use of guided breathing) or no intervention (“usual care”). Randomization was performed using [www.randomization.com](http://www.randomization.com). Patients were randomly allocated to one of the two groups as described in study protocol submitted to the local Ethics Committee. The study was conducted in a way that patients were kept blinded regarding their group assignment.

### 2.4. Inclusion and exclusion criteria

#### 2.4.1. Inclusion criteria

Clinical manifestation of diabetes mellitus (types 1 and 2) for at least three months, age 18–78 years, history of hypertension

(>130/80 mm Hg) and concomitant antihypertensive medication, acceptable level of hypertension control (at least 50% of BP self measurements within target limits, i.e. below 130/80 mm Hg in diabetes), structured education, at least sedentary compliance, capability of self-monitoring and recording the values, and understanding the informed consent.

#### 2.4.2. Exclusion criteria

Uncontrolled hypertension with acute need for medication adjustment, insufficiently controlled diabetes with acute need for additional pharmacological intervention, inability for systematic use of guided breathing, severe autonomic neuropathy (total cumulative power below 100 ms<sup>2</sup>/total Ewing Score > 3), pregnancy planning or current pregnancy, extraordinary circumstances and/or treatment which might severely influence blood pressure control and/or heart rate and/or heart rate variability during the study, circumstances which might interfere with applicability of study instruments, any history of disease which could interfere with the objectives of the study, e.g. severe psychological disorders including drug abuse and/or self-destructive behavior, deafness, severe symptomatic cardiac insufficiency, atrial fibrillation or clinically apparent coronary heart disease.

#### 2.5. Concomitant medication and study related restrictions

Study participants could not receive any other treatment than that for diabetes, hypertension and hyperlipidemia or for another stable chronic condition (such as thyroid replacement for hypothyroidism) throughout the whole study period. Concomitant medication for all chronic conditions remained unchanged during the study.

In accordance with the study protocol, subjects had to abstain from atypical strenuous physical activity or atypical life circumstances for at least one day before the investigation days, as well as from other activities which might interfere with the study-related questions. Patients kept their usual dietary habits consistent throughout the study. They were educated in intensified treatment of diabetes (Functional Insulin Treatment, Howorka, 1996) and hypertension as described (DiabetesFIT® Curriculum, Howorka et al., 2009). A usual frequency of blood glucose self-monitoring (approx. five daily measurements in insulin-treated diabetes) and at least two blood pressure self-measurements per week were asked for during the study. Patients' records including documentation of self-monitoring and interventional sessions with RESPeRATE® were kept. The primary compliance endpoint quantifying "appropriate use" of the device, was the "effective time" accumulated over the 8-week treatment period, using the data-logging capability of the device.

#### 2.6. Patients

Thirty two diabetic patients with hypertension and/or already using hypertensive treatment were recruited. The potential study participants who met inclusion criteria were selected by the principal investigator and co-investigators. The final study population included  $n = 32$  diabetic patients with hypertension and antihypertensive treatment (male: 17, age:  $49.3 \pm 11.7$ /SD/, diabetes duration:  $25.8 \pm 12.6$  year, HbA1c:  $7.7 \pm 0.9\%$ , type 1 diabetes  $n = 25$ , insulin therapy and FIT-educated  $n = 31$ , hypertension-educated  $n = 32$ , number of antihypertensive agents/day  $1.6 \pm 1.1$ , normoalbuminuria:  $n = 30$ , history of previous hyperalbuminuria  $n = 4$ , currently increased albumin excretion rate  $n = 2$ ).

#### 2.7. Main methods of assessment

Ambulatory blood pressure monitoring (ABPM) over a 24 h period, and spectral analysis of short-term heart rate variability (HRV) in time- and frequency-domains as obtained with VariaCardio TF5 during standardized modified orthostatic load (supine1–standing–supine2).

#### 2.8. Ambulatory blood pressure monitoring (ABPM)

ABPM was performed using a BoSo TM-2420 PC system according to the recommendations of the Austrian Hypertension Society (Slany et al., 2008). Additional outcome variables such as mean systolic and diastolic blood pressure, pulse pressure, mean heart rate, and night-time dipping were assessed as described.

#### 2.9. Spectral analysis of HRV

Short-term spectral analysis of HRV was calculated from recordings obtained during the modified orthostatic load consisting of 15 min of artifact-free records, using a VariaCardio TF5® system (Advanced Medical Diagnostics Group, UK) (Howorka et al., 1998; Salinger et al., 1999; Pumprla et al., 2002; Howorka et al., 2010). R–R intervals were recorded with sampling rate of 1000 Hz. Computational method was based on modified fast Fourier transform (FFT). Recordings were obtained in three consecutive positions (supine–standing–supine), each lasting 300 s in recording time. Artifacts were labeled, and a specific algorithm imputed beat-to-beat intervals throughout an artifact period to preserve time relationships of the adjacent, uncorrupted heart rate data (Pumprla et al., 2002). The final results were immediately displayed on the monitor as three-dimensional running spectra (see Fig. 2).

Parameters of frequency-domain HRV were measured in every position within the very-low frequency (VLF, 0.01–0.05 Hz), correlating among others with activity of baro- and thermoreceptors, low frequency (LF, 0.05–0.15 Hz) mirroring the combined sympathetic and parasympathetic control, and high-frequency bands (HF, 0.15–0.40 Hz), corresponding exclusively to parasympathetic tone, as well as total spectral power (TF, 0.01–0.40 Hz) representing the degree of cardiac autonomic dysfunction in diabetes (Malik and Task Force, 1996; Howorka et al., 1998). Main outcome variables were total spectral power [unit ms<sup>2</sup>] and spectral power in all three frequency bands individually. To assess even small intraindividual changes in global autonomic tone during the trial, we used cumulative indices (spectral power of frequency bands with its main frequency components obtained over all three positions during the orthostatic load, Howorka et al., 1998). Time-domain analysis included the averaged R–R intervals (ms), RMSSD, root of the mean square of difference of successive R–R intervals (ms) as well as SDNN, standard deviation of all normal intervals. Because of the skewness of the frequency-domain data distribution, a natural log (LN) transformation was performed to produce a normal distribution before the final results were analyzed.

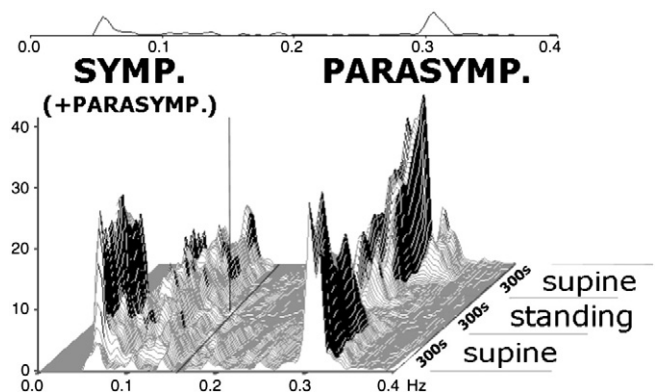


**Fig. 2.** Three-dimensional display of HRV pattern was obtained during a modified orthostatic load (standardized assessment by VariaCardio TF4® in positions supine–standing–supine, each position 300 s). Horizontal axis: frequency of fluctuations of R–R intervals (Hz); vertical axis: power spectral density (ms<sup>2</sup>/Hz); z-axis: time elapsed (s), modified after Salinger et al., 1999; Pumprla et al., 2002.

### 2.10. Statistical methods

Treatment effects were quantified by generation of delta values, calculated intraindividually as the arithmetic difference between values after and before treatment. Intraindividual intervention-related differences to baseline values were determined using paired t-tests, differences between study groups were detected through unpaired t-tests or Wilcoxon tests where appropriate. One-tailed t-tests were applied to detect differences in treatment effects between groups (superiority comparison, Sackett, 2004; Schein et al., 2009). Normality of frequency distributions was assessed by Kolmogorov–Smirnov goodness-of-fit tests. Correlations between baseline values and intervention effects were described with a linear correlation model using Pearson coefficients. All statistical tests used an alpha level of  $p < 0.05$ . Initial data processing and calculations were run with Microsoft Excel 2007, statistical analyses were performed with IBM SPSS Statistics 18.0 and SYSTAT 12 (SYSTAT Software Inc. San Jose, CA, USA).

### 3. Results

#### 3.1. Guided breathing performance and compliance analysis

Patients in the intervention group demonstrated sufficient compliance with the prescribed method for use of the guided breathing device. We found that for a stable, reproducible session performance, patients' experience with five and more guided breathing sessions was needed. Patients spent most of their time (86%) at slow breathing rate (in average around 6 breaths per minute, while values below 10 breaths per minute were indicated earlier as the therapeutic effect threshold, Elliott et al., 2004.). In a typical session, taking at least 12 min, a trend of slowing down the breathing rate from 9–10 to 5–6/min could be consistently observed, which finding corresponds with recorded prolonged exhalation time and excellent compliance. An average exhalation time was about 50% longer than inhalation time. The average degree of synchronization between breathing movements and the guiding tones, as provided by the device, was 72%. These results indicate good performance with the device guiding instructions.

#### 3.2. ABPM

With exception for heart rate, no differences between treatment groups were found at baseline (see Table 1 and Fig. 3). Subjects already displayed a fair or good control of their blood pressure even before the study.

In the intervention group, the guided breathing induced a significant overall reduction of systolic 24 h BP ( $x \pm \text{SEM}$ :  $126.1 \pm 3.0$  vs  $123.2 \pm 2.7$  mm Hg,  $p = 0.01$ ), non-significant reduction of systolic day time blood pressure ( $129.3 \pm 3.0$  vs  $127.1 \pm 2.7$ ,  $p = 0.06$ ), a significant reduction of pulse pressure (PP) in 24 h ( $53.6 \pm 2.6$  vs  $51.3 \pm 2.5$  mm Hg,  $p = 0.01$ ), and daytime PP ( $54.8 \pm 2.8$  vs  $52.8 \pm 2.6$  mm Hg,  $p = 0.04$ ), as well as non-significant reduction of 24 h mean arterial pressure ( $90.3 \pm 1.7$  vs  $89.0 \pm 1.5$  mm Hg,  $p = 0.08$ ),

**Table 1**  
Patient characteristics at baseline in both treatment groups.

|                                            | Resperate + usual care | Usual care       | p=   |
|--------------------------------------------|------------------------|------------------|------|
| N                                          | 16                     | 16               |      |
| Age (years)                                | $49.9 \pm 11.3$        | $48.8 \pm 12.4$  | 0.78 |
| Sex                                        | M = 8/F = 8            | M = 9/F = 7      | 0.75 |
| Type of diabetes                           | t1d = 11/t2d = 5       | t1d = 14/t2d = 2 | 0.19 |
| Weight (kg)                                | $80.0 \pm 16.9$        | $76.3 \pm 17.0$  | 0.54 |
| Waist circumference (cm)                   | $92.1 \pm 15.2$        | $90.0 \pm 11.5$  | 0.67 |
| Diabetes duration (years)                  | $26.6 \pm 11.5$        | $25.1 \pm 14.0$  | 0.73 |
| Proteinuria (median/Q1/Q3; $\mu\text{g}$ ) | 5/5/8.25               | 5.5/5/7.5        | 0.57 |
| Initial heart rate in 24 h ABPM (bpm)      | $71 \pm 7$             | $78 \pm 9$       | 0.02 |

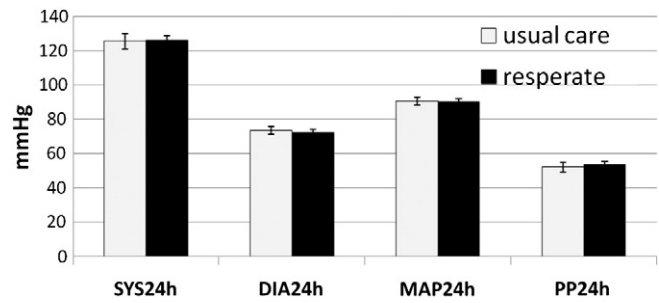


**Fig. 3.** Comparison of baseline values ( $x \pm \text{SEM}$ ) between treatment groups. No differences for systolic (SYS 24 h), diastolic (DIA 24 h) BP, mean arterial pressure (MAP 24 h) and pulse pressure (PP 24 h) were found before the study.

whereas in the control group the non-intervention (“usual care” alone) induced no significant changes. The effects of both intervention types – i.e. RESPerATE® use vs. usual care alone – are summarized in Fig. 4.

Even though guided breathing induced more pronounced effects on systolic blood pressure, the differences between groups for the impact of treatment (delta mm Hg, Fig. 4) were not significant, the only exception being pulse pressure ( $-2.3$  vs.  $+0.2$  mm Hg,  $p < 0.05$ ). Similarly, no differences between group-specific treatment effects were found neither for daytime nor for night-time blood pressure, as well as for night-time dipping, probably due to the high variability of these target variables. A strong dependence of treatment effect (delta systolic mm Hg) on baseline blood pressure values in both groups was found ( $r = 0.59$ ,  $n = 32$ ,  $p = 0.01$ ), see Fig. 5. Significant baseline dependence was given for 24 h daytime systolic ( $p < 0.001$ ), 24 h total diastolic blood pressure ( $p = 0.013$ ), and 24 h total and daytime pulse pressure (both  $p = 0.008$ ).

#### 3.3. Heart rate variability

At baseline no significant differences between treatment groups were found for all target variables of heart rate variability (all  $p > 0.13$ ).

##### 3.3.1. Frequency domain analysis

In comparison with ‘usual care’ alone, guided breathing induced a significantly stronger treatment effect in low-frequency (LF,  $p = 0.02$ ), in combined low and high frequency bands (LFHF,  $p < 0.05$ ) as well as a non-significant effect in total spectral power over all three frequency bands ( $p = 0.06$ ), always as cumulative value over three positions supine–standing–supine. Fig. 6 summarizes treatment effects (delta

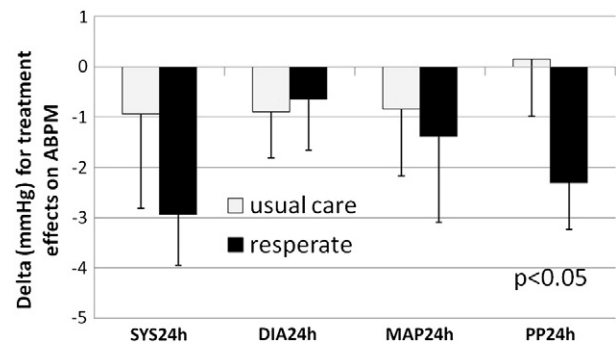


**Fig. 4.** Comparison of treatment effects ( $x \pm \text{SEM}$ ) after 8 weeks of guided breathing vs. usual care alone: The pulse pressure was significantly reduced (PP 24 h,  $p < 0.05$ ), while the differences between the treatment impacts on systolic blood pressure (SYS 24 h,  $p = 0.18$ ), diastolic BP (DIA 24 h,  $p = 0.43$ ) and mean arterial pressure (MAP 24 h,  $p = 0.36$ ), did not reach significance in ambulatory BP monitoring.

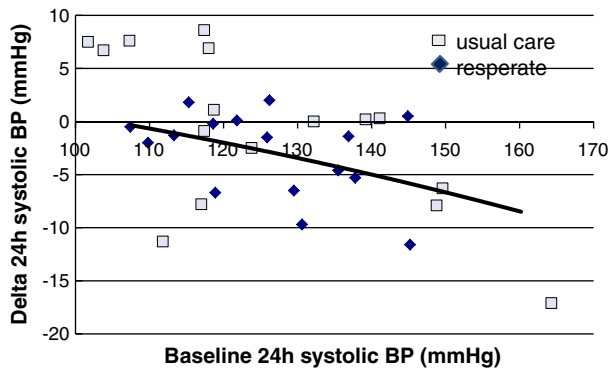


**Fig. 5.** Baseline dependence: Correlation between treatment effect as delta (mm Hg) and 24 h baseline systolic BP values,  $p = 0.01$  for both groups,  $y = -0.0022x^2 + 0.3269x - 8.3058$ ,  $r = 0.59$ .

'after' – 'baseline' LN spectral power in individual frequency bands) in both study groups.

The intervention group showed a significant reduction of centroid frequency in the high frequency band (HF,  $x = -13 \pm 11$  mHz vs.  $+8 \pm 7$  mHz,  $p = 0.04$ ) which correlates with a slower spontaneous respiration rate induced by the guided breathing intervention.

### 3.3.2. Time domain analysis

At baseline, no significant differences for time domain parameters (mean R–R interval, SDNN, RMSSD) were found, although the intervention group displayed non-significantly longer mean R–R intervals  $906 \pm 137$  ms as compared to the non-intervention group  $836 \pm 97$  ms, corresponding to slightly slower heart rate in the intervention group in 24 h ABPM. No significant differences were found for treatment effects between both study groups.

## 4. Discussion

Our study is the first randomized controlled trial that reports effects of device-guided breathing in diabetic patients, using 24 h ABPM. In previous trials, either only a casual/office BP was measured (Schein et al., 2009) or ABPM was used in non-diabetic individuals (Rosenthal et al., 2001). Our hypotheses, that guided breathing would positively influence autonomic control and further improve of blood pressure control, have been confirmed in our setting: in already well controlled hypertensive diabetic patients, a consistent use of the device for a

time period of eight weeks resulted in small but measurable effects. Systolic blood pressure was further lowered by  $-2.9$  and the pulse pressure  $-2.3$  mm Hg by guided breathing whereas no significant effect could be seen in the control group with usual care alone. Since 24 h ambulatory BP is not biased by the white coat effect, the observed reduction by 3 mm Hg is clinically important (Mancia et al., 1995). In contrast to office BP, mean 24 h ABPM values are generally accepted to be mostly free of placebo effect (Mancia et al., 1995) and of the statistical artifact called "regression to the mean" (O'Brien et al., 1991; Coats et al., 1992) due to the large number of measurements involved.

Our study was conceived as a RCT to filter out a possible placebo effect in "usual care" group. Study-related effects (placebo of the "usual care" group) did not reach statistical significance, whereas the systolic BP and PP reductions in the treatment group are significant and not related to placebo effect. According to JNC7 (JNC 7th report, 2003) "every mm Hg counts": a 3 mm Hg reduction in systolic BP is associated with 8% reduction in the mortality from stroke and with 5% reduction from coronary artery disease. In diabetes, the gains seem even more relevant. Therefore, the 3 mm Hg systolic BP reduction observed in the treatment group is both clinically and statistically significant, placebo-free benefit. As elevated pulse pressure is increasingly being recognized as a risk factor for cardiovascular – particularly coronary – disease (Dart and Kingwell, 2001), the beneficial effect of guided breathing in the intervention group is particularly relevant.

These results are supported by increase of cumulative power in HRV predominantly in low frequency corresponding to combined sympathetic and parasympathetic components. This finding correlates with the observed shift-to-left of centroid frequency component of the (parasympathetic) HF band which implies slowing down of respiration rate by guided breathing.

These significant effects have been achieved for both, blood pressure and heart rate variability despite the fact that diabetic patients recruited for this study already displayed almost optimal blood pressure control at baseline. Recent recommendations (Mogensen, 2003, JNC 7th report 2003) for diabetes target high normal or even (in younger patients) normal blood pressure values. In a similar study about guided-breathing (Elliott et al., 2004) where the group using the RESPeRATE® device achieved a blood pressure lowering of  $-15.0 \pm 1.8$  compared to the non-intervention group with a blood pressure lowering of "only"  $-9.2 \pm 1.6$  mm Hg, while the initial blood pressure values were around  $150 \pm 9/86 \pm 9$  mm Hg, with only 77% of patients using pharmacological treatment. According to these studies, and taking into account the usual standard deviations of blood pressure values, sample size of 30 patients appeared sufficient (Lenth, 2006). However, the pre-study blood pressure control in our diabetes and hypertension educated patients was much better than in previous studies. Further blood pressure lowering effect was small but still achievable in our patients who were already using 1.6 pharmacological agents per day and were educated (Howorka et al., 2009) about another means for non-pharmacological blood pressure reduction like endurance and muscle hypertrophy training, DASH diet, weight control and sodium restriction (JNC 7th report 2003). This fact underlines the efficacy of the method and – considering the demonstrated baseline dependence of therapeutic effects – illustrates its potential for patients with insufficient blood pressure control. Adjuvant non-pharmacological treatment is simply a need. In many patients, simple life style modification provides a potential for sufficient initial treatment. Guided breathing seems to provide such an additional and complementary option for treatment.

As demonstrated previously, only two non-pharmacological measures are known to improve heart rate variability in various stages of autonomic neuropathy in diabetes so far: food restriction or fasting (Howorka et al., 1997b) and systematic endurance training (Howorka et al., 1997a). As shown in our current study, guided breathing provides one more option for influencing autonomic nervous control in diabetes in a positive way. As many patients require multiple combinations of

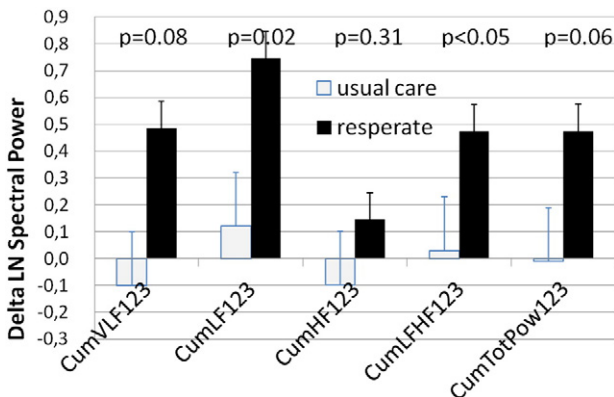


**Fig. 6.** Comparison of treatment effects (delta LN spectral power  $\pm$  SEM) between groups. Target variables: cumulative spectral power over 3 positions – CumVLF123 (very low frequency band), CumLF123 (low frequency band), CumHF123 (high frequency band), CumLHF123 (low and high frequency bands), and CumTotPow123 (total frequency band).

pharmacological agents, which per se could diminish heart rate variability, guided breathing seems to provide an important, complementary adjuvant treatment affecting both, blood pressure as well as autonomic function, in an advantageous way. In our study, the 8-week systematic use of guided breathing induced a slowing of spontaneous breathing rate in intervention group, which is declared to be the main treatment effect of the device (Schein et al., 2001; Viskoper et al., 2003; Elliot et al., 2004).

Beyond the specific necessity for optimal control for diabetes, international guidelines recommend applying lifestyle modification in hypertension therapy (JNC 7th report, 2003). Additional non-pharmacological treatment could enhance antihypertensive treatment strategy, as they could be used to reduce the amount of drugs needed to control hypertension and therefore reduce side effects. In diabetes, hypertension after decades of therapy duration requires usually 3–4 pharmacological agents. Treatment adherence remains very low (Poluzzi et al., 2007), so that further approaches to complement the complex pharmacological therapy are necessary to reach the therapeutic goal.

## 5. Conclusions

Even in already well controlled diabetic patients, guided breathing had beneficial influences on cardiovascular autonomic control and a measurable impact on BP control. It enriches available options for non-pharmacological blood pressure and pulse pressure reduction. If consistently used, guided breathing enhances restoration of physiological autonomic balance in patients with diabetes and hypertension. Our initial investigation reveals findings relevant enough to justify further investigation of the impact of guided breathing in hypertensive diabetic patients.

### List of abbreviations

|              |                                                                          |
|--------------|--------------------------------------------------------------------------|
| ABPM         | Ambulatory blood pressure monitoring                                     |
| ACEI         | Angiotensin-converting enzyme inhibitor                                  |
| ANOVA        | Analysis of variance                                                     |
| BP           | Blood pressure                                                           |
| CAN          | Cardiovascular autonomic neuropathy                                      |
| DASH         | Dietary approaches to stop hypertension                                  |
| DIA          | Diastolic (blood pressure)                                               |
| ECG          | Electrocardiogram                                                        |
| FIT          | Functional Insulin Treatment                                             |
| HbA1c        | Hemoglobin A1c                                                           |
| HF band      | High frequency band                                                      |
| HRV          | Heart rate variability                                                   |
| LF band      | Low frequency band                                                       |
| LN           | Natural logarithm                                                        |
| MAP          | Mean arterial pressure                                                   |
| RMSSD        | Root of the mean square of difference of normal successive R–R intervals |
| PP           | Pulse pressure                                                           |
| R–R interval | Interval between two normal successive R waves                           |
| RCT          | Randomized controlled trial                                              |
| SDNN         | Standard deviation of all normal R–R intervals                           |
| SYS          | Systolic (blood pressure)                                                |
| VLF band     | Very low frequency band                                                  |

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