Effects of guided breathing on blood pressure and heart rate variability in hypertensive diabetic patients ☆,☆☆

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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 ± SEM: 126.1 ± 3.0 vs 123.2 ± 2.7 mm Hg, p = 0.01), and in 24 h pulse pressure (PP, 53.6 ± 2.6 vs. 51.3 ± 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 ± 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.

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; Pumprla et al.,

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 (Morrish 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).
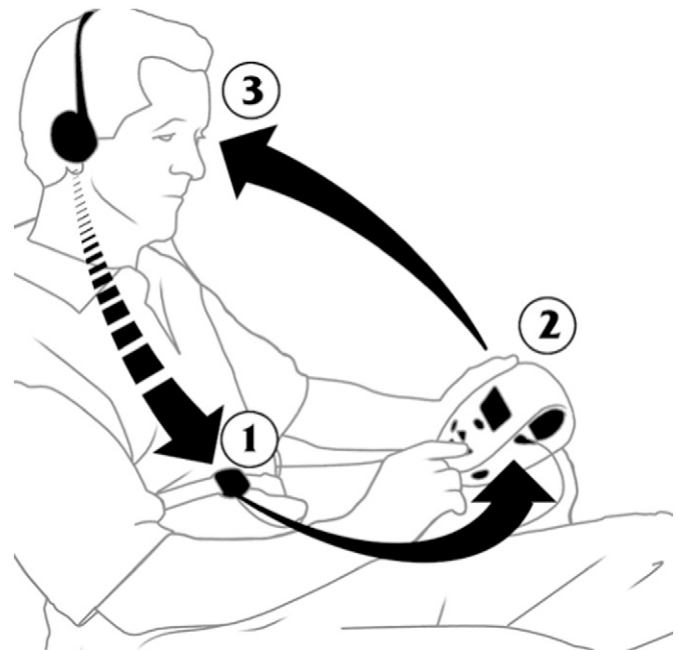

Fig. 1. Principles of device-guided paced breathing: (1) monitoring breathing movements, (2) composing breathing-guiding tones, and (3) synchronizing breathing movements with the guiding tones (by courtesy of Intercure Inc.).

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. 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