Non-invasive quantification of the effect of device-guided slow breathing with direct feedback to the patient to reduce blood pressure

Martin Bachler¹, Walter Sehnert¹, Ines Mikisek³, Siegfried Wasserteurer¹ and Thomas Mengden⁴

¹ AIT Austrian Institute of Technology, Center for Health & Bioresources, Vienna, Austria
² Institute for Clinical Research Sehnert, Dortmund, Germany
³ Ines Mikisek Coaching, Frankfurt am Main, Germany
⁴ Kerckhoff Clinic, Rehabilitation, ESH Excellence Centre, Bad Nauheim, Germany

E-mail: martin.bachler@ait.ac.at

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Abstract

Objective: Slow breathing is a relaxation exercise recommended for lowering blood pressure (BP). Biofeedback may improve patient adherence and enhance BP lowering effects. Since the pulse arrival time (PAT) is inversely proportional to BP, it can be used to estimate BP changes. Approach: In this pilot study, 30 patients (age 62.9 (SD 7.7) years, 11 F/19 M, Sys. BP 133.0 (SD 17.1) mmHg, Dia. BP 83.8 (SD 10.6) mmHg) performed a device-guided slow breathing exercise. PAT was measured by ECG and plethysmography and immediately presented to the patient, and respiratory sinus arrhythmia (RSA) was calculated retrospectively to measure the adherence to the instructed respiratory rate. Main results: Respiratory rate was 13.6 (SD 1.9) bpm at baseline and 5.4 (SD 1.0) bpm during guided breathing. PAT continuously and progressively increased from 231.5 (SD 20.3) to 237.3 (SD 18.5) ms (p < 0.001). The median deviation of RSA from the guided respiratory rate was 0.06 (IQR 0.19) bpm. In three patients, a deviation of > 0.20 bpm was detected, and two of them showed no increase in PAT. In total, 25 patients responded with increase in PAT. Significance: In this pilot study we have shown that biofeedback of PAT and RSA are feasible and can further improve motivation and adherence. Furthermore, we have shown that the exercise increased PAT, which indicates a reduction in BP. Due to its ease of use, this method is ideal for home use and self-monitoring.

1. Introduction

Hypertension represents a significant health risk that can have various causes. A chronically elevated stress level may play an important role in the development of essential arterial hypertension as it may shift the vegetative balance between the sympathetic and the parasympathetic nervous system. Such a shift in the autonomic balance may affect various organs, such as the cardiovascular system, and may result in an increase in heart rate, an increase in ventricular contraction, and a constriction of the peripheral vessels. Such a condition can lead to an acute and transient, but later chronic, increase in blood pressure, which increases the risk of events such as stroke, heart failure, and kidney failure (Brook and Julius 2000).

Non-invasive and medication-free blood pressure reduction techniques are attractive. Breathing techniques such as mantra breathing are relaxation techniques that can alleviate certain mild forms of arterial hypertension. Yoga or other relaxation techniques can also be used to influence systolic and diastolic blood pressure (Herakova et al 2017, Chaddha et al 2019, Okonta 2012, Kaushik et al 2006, Cramer 2016, Nuckowska et al 2019).

In antihypertensive therapy, medications and even life-style changes are established ways to lower blood pressure. Alternative methods of reducing blood pressure, developed over the past few decades, have been
well studied. In 2013, the American Heart Association (AHA) critically summarized and evaluated alternative antihypertensive procedures (Brook et al 2013).

Autonomic dysregulation plays an important role in the etiology of arterial hypertension. It is characterized by an increased activity of the sympathetic system (possibly combined with a reduction in parasympathetic activity) and not only in early or threshold hypertension but also in prolonged and existing and persistent hypertension (Brook and Julius 2000).

One of the mechanisms of autonomic regulatory disorder is the decreased baroreceptor sensitivity. The baroreceptor reflex is downregulated or re-adapted to elevated blood pressure levels, losing its ability to suppress increased sympathetic activity (Radaelli et al 2002, Radaelli et al 1994). A reduction in sympathetic activity and increased parasympathetic dominance with improvement in baroreceptor sensitivity appears clinically and prognostically useful in arterial hypertension. Jerath et al (2006) describe in detail the sequence of events occurring during the autonomic shift.

It is assumed that 10-second cycles of breathing, corresponding to a respiratory rate of 6 breaths per minute, lead to a harmonization of breathing with the Mayer waves. More than 100 years ago the German physiologist Mayer described spontaneous blood pressure fluctuations with a 10-second cycle corresponding to a frequency of 6 breaths/min. Also slow music with a frequency of 6 breaths/min seems to have similar cardiovascular effects as slow breathing or recitations (Bernardi et al 2001).

Reducing the respiratory rate to 6 breaths per minute (slow breathing) improves the baroreflex sensitivity of normal subjects (Bernardi et al 2001) and patients with heart failure (Radaelli et al 2002), as well as hypertension (Joseph et al 2005, Irvine et al 1986). A reduction in blood pressure with improvement in baroreceptor sensitivity was found with slow breathing at 6 breaths per minute in 20 hypertensive patients compared to 26 non-hypertensive patients (Joseph et al 2005).

In the 2013 statement on alternative approaches to lowering blood pressure by the AHA, device-controlled breathing was ranked with a level of evidence of 'class II A' (ranging from I to III) with a level of evidence of 'B' (ranging from A to C), ranking it as ‘reasonable to perform the procedure’. It was ranked as being more effective than acupuncture (class III, evidence level B) in the noninvasive therapy methods examined. In general, only dynamic aerobic exercise received a better recommendation as an alternative therapy, in comparison with device-controlled breathing (Brook et al 2013).

Slow deep breathing, as used in meditation, yoga, and some other relaxation techniques, has long been reputed to have a favorable effect on blood pressure. A 1-minute episode of deep breaths (6 in 30 seconds) can reduce systolic blood pressure by 3.4 to 3.9 mmHg (Mori et al 2005). A 2019 meta-analysis furthermore suggests a reduction of systolic blood pressure of 3.73–8.03 mmHg and a reduction in diastolic blood pressure of 1.66–4.28 mmHg for daily interventions of 10–15 minutes (Chaddha et al 2019). Further recent studies confirmed the reduction of blood pressure and sympathetic activity in young normotensive individuals after 10–15 min slow breathing, and did not find any differences between women and men regarding blood pressure reduction (Adler et al 2019).

Clinical applications of slow and deep breathing with the help of automated instruction ('device guided') show a blood pressure reduction of 13/7 mmHg compared to the initial blood pressure when used for 8 to 9 weeks (Brook et al 2013). In the meta-analysis of 13 studies, this was significantly (p < 0.01) better than the reduction in blood pressure by 9/4 mmHg of other control interventions (Brook et al 2013). If these are evaluated as placebo effects, a net effect of 4/3 mmHg remains for deep breathing (Brook et al 2013). In a 2019 meta-analysis furthermore (Mahtani et al 2012), the blood pressure-lowering effect of device guided slow-breathing was investigated in 8 studies: there was a significant reduction in systolic (–3.67; 95% CI –5.99 to –1.39) and diastolic (–2.51, 95% CI –4.15 to 0.87) blood pressure in 494 adults included in the analysis. A further long-term study investigated the change of blood pressure after three, six, and twelve months of a self-administered breathing meditation program and found a reduction of systolic blood pressure of –8.0, –10.0, and –11.6 mmHg, respectively (Chandler et al 2020).

It is desirable to provide the person performing a relaxation technique feedback on its effectiveness (Henderson et al 1998, Rau et al 2003). As a result, the correct execution can be checked and the motivation increased. Conventionally, heart rate variability (HRV) derived from an electrocardiogram (ECG) signal is used as a surrogate parameter and is output as it is easily detectable. In such conventional systems, however, there is so far, no way to show the immediate effects on the blood pressure. Further, changes in HRV need not necessarily be associated with blood pressure changes. The latter can occur, for example, in a relaxation exercise only with significant delay as opposed to a change in the heart rate.

The blood pressure can be recorded and output as biofeedback using, e.g. a blood pressure cuff. However, the use of a sphygmomanometer cuff may be perceived by users as disturbing and detrimental to the effectiveness of the relaxation exercise (Steptoe and Johnston 1976, Liu et al 2013).
Changes in blood pressure lead to changes in the pulse wave velocity (PWV) via an altered transmural wall tension of the arteries. As the blood pressure increases, the pulse wave velocity increases. PWV can classically be derived as the distance travelled by the pulse wave over time. Since the distance during the measurement of one patient remains constant, changes in the PWV are inversely reflected by changes in the pulse arrival time (PAT) at a certain location on the body. Hence, falling blood pressure values lead to an increase in the PAT. Since the pulse arrival time can be measured easily and non-invasively via a 1-lead ECG and finger plethysmography, it can be used as a non-disturbing surrogate parameter indicating a blood pressure change (Steptoe and Johnston 1976, Liu et al 2013, Yang et al 2018).

In this pilot study, the main target parameter is the change in pulse arrival time (as indicator of blood pressure changes) during the 10-minute intervention and the following 5-minute cool-down phase. The main hypothesis is that device controlled slow breathing over 10 minutes will increase the short-term PAT during these 10–15 minutes compared to the baseline at the beginning of the intervention. As a secondary outcome parameter, respiratory sinus arrhythmia (RSA) was calculated retrospectively to measure compliance with the specified respiratory rate.

2. Methods

In this study, the effects of slow breathing are quantified by the PAT, calculated from the time between the R-Peak in the ECG and the arrival of the pulse wave in a finger measured by plethysmography. The respiratory rates during rest are determined and used to calculate a target respiratory rate for the slow breathing exercise. The individual target rate as well as the measured PAT of the last 20 seconds are shown on a tablet computer. This creates a device-controlled slow breathing exercise with immediate biofeedback.

The device itself consists of three parts: (1) measurement hardware, (2) guidance & feedback software, and (3) calculation of the PAT. As hardware, a ready-to-use ‘biosignals Explorer’ system (biosignalsplux, Lisbon, Portugal) was used. The guidance and feedback software was implemented as custom-made App for Android smartphones and tables. For signal processing to calculate the PAT, proven in-house algorithms were applied (Bachler et al 2013).

2.1. Slow breathing

In stress prevention and control, the targeted guidance and prolongation of breathing have a calming effect on body and mind. This relaxing effect helps to focus on resources and manage stress situation more appropriately.

The breathing cycle can be divided into four parts: (1) inhalation, (2) breath held with lungs full, (3) exhalation, and (4) breath held with lungs empty. The effect of relaxation is achieved especially in the phase of exhalation and breath holding with empty lungs. Although the four parts of a breathing cycle can be clearly separated in theory, they are functionally closely connected in practice. Breathing thus not only integrates the body and mind, but is in itself an integrative process.

The ideal breathing rate for achieving optimal therapeutic results seems to be 6/min (Bernardi et al 2001). However, our clinical experience shows that such low breathing rates are usually only achieved by young, well-trained healthy volunteers. Elderly hypertensive patients with cardiovascular diseases or untrained persons usually have difficulty in reaching such low respiratory frequencies. Hence, the ‘best fit’ breathing pattern for each patient was determined a priori in the following way.

The slow breathing exercise is carried out in a comfortable sitting position, which allows free abdominal breathing. Patients are guided to the most uniform possible breathing. This is done with the help of a short manual for ‘Right Breathing’. In the first phase (table 1), the first attempt is to adjust the exhalation to the length of the inhalation, since most people take longer to inhale in everyday life. The rhythm should be slow and even without overstraining the inexperienced user. The goal is to reach an average of 10 to 20 breaths per minute in everyday life, a maximum of 6 to 8 breaths per minute during respiratory therapy. The phase is never changed during one single exercise.

2.2. Patients

Thirty patients with treated arterial hypertension were enrolled in the study in May 2018. The protocol of the study was approved by the ethics committee of the Medical Association of Westphalia-Lippe and the University of Münster (‘Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster’, file reference 2017-733-f-S, approved on 15 March 2018), and all patients gave informed consent to participate in the study. Baseline characteristics of the patients are summarized in table 2.
Table 1. Overview of the respiratory rhythms to be used.

| Phase   | Inhalation | Exhalation | Inhalation |
|---------|------------|------------|------------|
|         | Breath held with lungs full | Breath held with lungs empty | Breath held with lungs empty |
| Phase 1 | 4 sec      | 0 sec      | 4 sec      |
| Phase 2 | 4 sec      | 0 sec      | 6 sec      |
| Phase 3 | 4 sec      | 0 sec      | 6 sec      |
| Phase 4 | 6 sec      | 0 sec      | 8 sec      |
| Phase 5 | 6 sec      | 0 sec      | 8 sec      |
| Phase 6 | 6 sec      | 0 sec      | 10 sec     |

Table 2. Baseline characteristics of the patients. Data expressed as mean (standard deviation) or in absolute numbers.

|                |            |            |
|----------------|------------|------------|
| N (#)          | 30         |            |
| Age (years)    | 62.9 (7.7) |            |
| Gender (#/#)   | 11 females / 19 males |    |
| Body height (cm) | 174.4 (10.4) |       |
| Body weight (kg) | 87.6 (18.9) |       |
| BMI            | 28.6 (4.7) |            |
| Arterial hypertension since (years) | 11.4 (10.2) |       |
| Systolic blood pressure (mmHg) | 133.0 (17.1) |       |
| Diastolic blood pressure (mmHg) | 83.8 (10.6) |       |
| Spontaneous respiratory rate (bpm) | 13.6 (1.9) |       |

2.3. Protocol
Upon arrival, the patients received information about the study and the exercise from the instructor. After they gave informed consent, patients received instructions about the slow breathing exercise and were given time to get used to wearing the measurement equipment.

The breathing rate, i.e. the phase as defined in table 1, used during the intervention was set by the investigator, based on the spontaneous respiration of the patients. The slow breathing exercise was carried out in a comfortable sitting position and consists of two stages: during the first stage, for a duration of 10 minutes, the respiration of the patient is guided by the device. It is followed by the second stage, a 5-minute cooling phase. During this second stage, the patient should continue to breathe calmly, without being guided by the device.

The patients’ ECG and pulse waves were recorded during the entire 15 minutes of the slow breathing exercise. Since the use of occlusion cuffs could disturb the patients and thus reduce the effectiveness of the relaxation exercise, we refrained from taking blood pressure measurements directly before the exercise in this feasibility study (Steptoe and Johnston 1976, Liu et al 2013).

2.4. Biosignals Explorer System
The Biosignals Explorer System by biosignalsplux (Lisbon, Portugal) is a ready-to-use wireless research kit for modular biomedical sensors. It consists of a 4-channel hub, allowing signals of four generic sensors to be recorded simultaneously. For this study, one ECG channel and one plethysmography channel with a finger clip were used, shown in figure 1. The signals were recorded synchronously at a sampling rate of 256 Hz and transferred wirelessly using Bluetooth to an Android tablet computer.

2.5. App
An app for Android systems was implemented to allow recording and analysis of ECG and pulse wave data from a biosignals Explorer system.

The application is divided into two main views. The first view is used to establish a Bluetooth connection to the measurement device. The second view provides a live display of the incoming data, the guidance for the slow breathing exercise, and the results of the exercises. It further can record and share the data, PAT, and heart rates via email, to allow the post-hoc analysis for this study.

After the Bluetooth connection between the biosignals Explorer and the Android app has been established, and the signal quality was confirmed, the user can start the breathing exercise. To get an initial (baseline) value for the exercise, an average value for the PAT is calculated over the first 40 seconds, indicated to the user via a progress bar. During the exercise, the user breaths in accordance with a balloon shown on the screen. As the balloon rises, the user inhales. As it sinks, the user exhales. Holding the breath is indicated by the balloon stopping at the top or bottom (figure 1).

After ten minutes of exercise time (also visible as progress bar), the main part of the relaxation exercise is complete. It is followed by a 5-minute cooling phase. During this phase, the patients should try to continue...
to breathe calmly, without being guided by the balloon going up and down. For this purpose, the balloon is completely hidden in this phase. The progress during this phase is indicated by a blue progress bar at the top of the screen.

After the cooling down phase is completed, the recorded data (signals, PAT, breathing settings, and heart rates) are collected to allow post-hoc analyses.

### 2.6. Calculation of the pulse arrival time

Since only relative changes in blood pressure are of interest in this project, neither the determination of the absolute blood pressure values nor the determination of the absolute PWV values is necessary. Usually, the pulse wave velocity is determined using the time difference between two measurement points and calculated as \( \text{path} \times \text{time}^{-1} \). Thus, since the length of the path stays constant over the measurement period, it is sufficient to determine changes in the pulse transit time (PTT) to detect blood pressure changes within a patient. This requires measurement of the pulse wave at two locations along the arterial tree. The distal measurement point is often determined on the extremities, preferably on the finger or on the toe or ear. In this study, plethysmography is used as a measuring technique. Since this recording technique is difficult for proximal measuring points, alternative methods such as ballistocardiography, impedance cardiography, or the phonocardiogram can be used instead. However, these methods are currently not suitable for everyday mobile use. Therefore, ECG is used to determine the proximal reference time in this project (Bachler et al 2013, Bachler et al 2013, Griggs et al 2016, Mukkamala et al 2015, Selvaraj 2016).

The R-wave of the ECG can usually be well determined and represents the electrical stimulation of the heart, which must be distinguished from the mechanical ejection start. Thus, in the measurement, the pulse arrival time (PAT), which is the sum of the pre-ejection period (PEP) and the pulse transit time (\( \text{PAT} = \text{PEP + PTT} \)) is determined. The inverse relationship between changes in pulse wave arrival time and blood pressure has been demonstrated in many studies. It turned out that especially the correlations to the systolic blood pressure are strong. It is believed that with elevated systolic blood pressure not only the PTT but also the PEP decreases and thus the PAT represents a good measure of relative variations in systolic blood pressure (Griggs et al 2016, Mukkamala et al 2015, Selvaraj 2016).

To determine the PAT, the device first determines the time of the R waves of the ECG signal, as illustrated in figure 2, left (Bachler et al 2013). To determine the time of arrival of the pressure or volume pulse, the device determines the time at which the rising edge of the pulse wave signal begins. This is done by determining the point of intersection between the tangent to the rising edge of the pulse wave signal and a line passing through the minimum of the pulse wave signal (figure 2, right). The time corresponding to this intersection represents the arrival time of the pulse. The PAT then is the time difference between the R wave of the ECG signal and the arrival time of the pulse (Bachler et al 2013).

The algorithm determines the PAT for each individual heart beat during the breathing exercise. For biofeedback and post-hoc analysis, moving average calculations (20 seconds for biofeedback, 3 minutes for post-hoc analysis) and filtering of metrological outlier values are employed to reduce short-term fluctuations.
Figure 2. Determination of the pulse arrival time. Left: Simultaneous recording of electrocardiogram (ECG) and pulse waves. Dashed lines mark the R waves in the ECG, dotted lines mark the arrival of the pulse wave. The time between those two is the pulse arrival time (PAT). Right: Close-up of the rising edge of the pulse wave with the point of intersecting tangents (IT) by lines passing through the maximum systolic upstroke (MSU) and the minimum of the pulse wave (Bachler et al 2013).

2.7. Post-hoc analysis
To remove metrological outlies in the post-hoc analysis, recordings were filtered according to the criteria by Suzuki et al (2012). Hence, PAT values and heart rates were removed, if the heart rate was below 30 or above 200 beats per minute. Furthermore, the time between consecutive R-Peak-detections may not change by more than 0.2 seconds, otherwise the related PAT and heart rate values were removed as well (Suzuki et al 2012).

Heart rate and PAT were then averaged within a 3-minute moving window to remove short-term fluctuations. The results were plotted as functions over time as difference from the baseline value, and boxplots as well as ladder plots of the absolute values for direct comparison of baseline, end of guided breathing (average of minutes 7–10), and end of cooling phase (average of the last 3 minutes).

Data were checked for normality using a Kolmogorow–Smirnow–Lilliefors-Test and by investigating the skewness, kurtosis, mean-median difference, and their empirical cumulative distribution.

Since all paired data were found to be distributed normally (see subsection 3.1), paired-sample t-tests were used to evaluate statistical significance at the 5% level, and location and spread are reported as mean and standard deviation (SD). For data not distributed normally, median and interquartile range (IQR) are reported.

2.8. Calculation of respiratory sinus arrhythmia
The deviation of the respiratory sinus arrhythmia (RSA) from the instructed respiratory rate was calculated retrospectively. The RSA is detected as most prominent frequency in the power spectral density estimate of the intervals between heartbeats (Kluge et al 1988).

In the first step, equal to the determination of the PAT, the time of the R waves of the ECG signal is determined and false positive detections are removed (Bachler et al 2013, Suzuki et al 2012). From this time series of consecutive R waves, the interbeat intervals are calculated as successive differences and shown as beat-to-beat heart rate in figure 3 on the left. Using the method described by Lomb (1976), Scargle (1982), these interbeat intervals are transformed to the frequency domain. Since the Lomb–Scargle-periodogram considers not only the values of the interbeat intervals, but also the times of their occurrence, a small number of missed beats or a short loss of signal continuity has no effect on the results (Lomb 1976, Scargle 1982). In the generated spectrum, the most prominent frequency in the low frequency range (0.04–0.15 Hz (American Heart Association Inc. 1996)) is detected as RSA. Figure 3 illustrates this process in a time series from this study, showing strong RSA in the time- and frequency domain.

3. Results

3.1. Testing for normality
Data were checked for normality using a Kolmogorow–Smirnow–Lilliefors-Test and by investigating the skewness, kurtosis, mean-median difference, and their empirical cumulative distribution. The results of these investigations are presented in table 3.

In the table, ‘p(ks test)’ refers to the p-value of the Kolmogorow–Smirnow–Lilliefors-Test, for the null hypothesis that the data comes from a normal distribution. Since all p-values are well above 0.05, this null hypothesis cannot be rejected at the 5% significance level.
Figure 3. Determination of the respiratory sinus arrhythmia (RSA). Left: Instantaneous heart rate derived from the intervals between consecutive R waves in the ECG. The RSA, i.e. the change of the heart rate with respiration, can be easily seen. Right: Power spectral density estimate of the left signal. The prominent peak at 0.083 Hz represents the RSA with a respiratory rate of 5 breaths per minute.

Table 3. Results of the investigation for normality. ‘p(kstest)’ is the p-value of the Kolmogorow–Smirnow–Lilliefors-Test, 'Diff' refers to the difference between mean and median value. Skewness and kurtosis include their 95% confidence interval.

| Dataset       | p(kstest) | Skewness        | Kurtosis       | Mean [95% CI] | Median [95% CI] | Diff |
|---------------|-----------|-----------------|----------------|---------------|-----------------|------|
| PAT, Baseline | 0.79      | 0.41 [1.25, -0.43] | 3.55 [5.19, 1.92] | 231.54        | 229.94          | 1.60 |
| PAT, After guidance | 0.88 | 0.22 [1.06, -0.61] | 2.59 [4.23, 0.96] | 237.27        | 236.51          | 0.76 |
| PAT, After cooling | 0.92 | 0.14 [0.98, -0.70] | 2.48 [4.12, 0.85] | 239.24        | 237.97          | 1.27 |
| HR, Baseline  | 0.62      | -0.36 [0.48, -1.19] | 2.19 [3.82, 0.56] | 68.73         | 71.37           | -2.64|
| HR, After guidance | 0.88 | -0.23 [0.61, -1.07] | 2.02 [3.65, 0.39] | 71.02         | 71.58           | -0.56|
| HR, After cooling | 0.90 | -0.15 [0.68, -0.99] | 2.33 [3.97, 0.70] | 70.23         | 70.44           | -0.21|

Additionally, we evaluated the means, medians, and their differences for the datasets. Table 3 shows that mean and median values are very similar and their differences relatively small. Therefore, we conclude that the data distribution is not substantially skewed.

Furthermore, skewness and kurtosis are reported including their 95% confidence intervals (CI) in table 3. The skewness of a normal distribution is 0, its kurtosis is 3. Since all CIs of the skewness cover the value 0, and all CIs of the kurtosis cover the value 3, we cannot reject the null hypothesis that the data comes from a normal distribution at the 5% significance level.

Finally, the empirical cumulative distribution with their 95% CIs were investigated together with their fitted normal distribution. The results are shown in figure 4. Since all fits are within the CIs for all distributions, the null hypothesis that the data comes from a normal distribution cannot be rejected at the 5% significance level.

3.2. Breathing exercise
The average spontaneous respiratory rate, measured shortly prior the exercise, was 13.6 (SD 1.9) bpm. During the guided slow breathing exercise, the average respiratory rate was 5.4 (SD 1.0) bpm, which further decreased during the unguided cooling phase to 4.7 (SD 1.2) bpm.

In the course of the guided 10-minutes breathing exercise, we observed a continuous and progressive increase in PAT from 231.5 (SD 20.3) to 237.3 (SD 18.5) ms (p < 0.001). This trend continued during the unguided cooling phase, though somewhat slower, were the PAT increased further to 239.1 (SD 18.5) ms (p < 0.001 compared to baseline), as shown in figure 5, figure 6, and figure 7. Of the 30 patients enrolled in this study, 25 responded with an increase in PAT during the 10 minutes of guided breathing. During the unguided cooling phase, the PAT further increased in 18 out of the 30 patients.

We further observed significant changes in the heart rate of the patients during both stages of the breathing exercise. In contrast to the PAT, however, these changes were neither continuous nor progressive. During the first 6 minutes of the guided breathing, the average heart rate increased from 69.6 (SD 10.3) to 71.2 (SD 11.1) beats per minute (p < 0.001). The last 4 minutes of the guided breathing, however, did not result in any further significant change of the heart rate, as shown in figure 7. During the unguided cooling phase during the last 5 minutes, the average heart rate significantly decreased from 71.2 (SD 11.1) to 70.4 (SD 10.6) beats per minute (p < 0.05), approaching, but not reaching, the value at baseline. Out of the 30
patients, 24 responded with an increase in heart rate during the first 10 minutes of guided breathing. In 19 of 30 patients, the heart rate decreased during the cooling phase.

In the post-hoc analysis, the RSA was calculated and compared to the target respiratory rate. Figure 7 shows the differences between the RSA and target respiratory rate together with the change in PAT at the end of the 10 minutes guided breathing exercise. We observed a median deviation of RSA from the guided respiratory rate of 0.06 (IQR 0.19) bpm. In only three patients, an individual deviation of more than 0.20 bpm was detected (marked with squares in figure 7). Two of those three patients did not respond with increased PAT, but instead showed a slightly decreased PAT.

4. Discussion

We found that device-guided slow breathing with biofeedback increased the pulse arrival time in patients with treated arterial hypertension by 5.8 (SD 6.0) ms, and further increased during subsequent unguided slow breathing to a total increase of 7.6 (SD 10.6) ms.
Figure 6. Ladder plots of the pulse arrival times and heart rates at baseline, end of guided breathing (average of minutes 7–10), and end of cooling phase (average of the last 3 minutes). Increasing values are shown in green, decreasing values in red.

**Figure 7.** Left: Differences of pulse arrival time (PAT) and heart rate (HR) from baseline for all patients as function over time, smoothed using a 3-minute moving average, shown as mean value with 95% confidence interval. The 10-minute-mark is the transition from guided to unguided slow breathing. Right: The x-axis shows the deviation of the respiratory sinus arrhythmia (RSA) from the target respiratory rate, while the y-axis shows the differences of the PAT after 10 minutes of guided breathing. In three patients, a deviation of more than 0.20 bpm was detected (marked with squares).

While the precise connection between PAT and blood pressure depends on several factors and is individual for all people, estimates of the average relationship suggest that an increase of 7.6 ms in the PAT corresponds roughly to a decrease of 7–16 mHg in mean pressure (Proenca et al 2010). These findings are in line with previous studies directly investigating the effect of slow breathing on the blood pressure (Chaddha et al 2019, Buby et al 1990, Elliott and Izzo 2006, Joseph et al 2005, Rau et al 2003).

PAT is known to be a surrogate of BP, but it is also related to other parameters such as vascular smooth muscle tone or pre-ejection period (PEP). Previous studies have revealed a change in the relationship between BP and PAT that depends on whether subjects rest, exercise, or recover from exercise (Liu et al 2013). For example, during exercise, the vascular smooth muscle tone is higher than during recovery, leading to stiffer arteries (Liu et al 2013). Another effect was found in relation to PEP, which changes immediately at the end of an exercise, while PTT and blood pressure show a delayed response (Lee et al 2018). However, these effects can only be observed if the activity of the subjects changes suddenly and rapidly. In contrast, the activity of the patients in the present study does not change at all during the relaxation exercises. It was even found that in subjects at rest the SD of the PEP only accounts for about 1.0–1.5% of the PAT (Kortekaas et al 2018). Since the effect found in the present study is substantially stronger, we conclude that the effect of the low variability of PEP at rest is negligible.

The different stages of the slow breathing exercise are clearly visible in the progression of the measured data (figure 7). The increase of the PAT progresses continuously during the first 10 minutes and only shows a
short constant phase at the change from guided to unguided breathing, before increasing further. In contrast, the increase in heart rate reaches a constant value already after approximately 6 minutes, and even reverses during the unguided breathing. This suggests, that different mechanisms contribute to the changes of the cardiovascular system in the course of the relaxation exercise to a varying degree and with varying delay.

Slow, deep breathing leads to a synchronization of the heart rate variability with the respiratory rate, suppressing high frequency fluctuations and increasing the amplitude of the low frequency components, as RSA becomes more prominent. This effect is usually seen within the first minute of deep breathing (see figure 3) and is then followed by the increase in average heart rate. While the amplitude of the heart rate fluctuations increases, the blood pressure fluctuations remain unchanged in the beginning. This enhances arterial baroreflex sensitivity, contributing to the blood pressure lowering effect with some delay (Parati and Esler 2012). After the end of the guided slow breathing exercise and during the 5 minutes cooling phase, the fluctuations of the heart rate as well as the short-term average heart rate begin to return to their normal state, as is suggested by figure 7. The increase of the PAT and therefore likely the decrease of blood pressure, however, further progresses.

The analysis of the RSA further adds to this explanation. In three out of the 30 patients, the heart rate variability did not synchronize with the respiratory rate, visible as large negative deviation in figure 7. It is noticeable that two of those three also show no increase in PAT, suggesting that the arterial baroreflex sensitivity is not enhanced in those individuals. Of course, the number of patients with this irregularity (three) is too small to draw tangible conclusions, so further studies are needed to better investigate this phenomenon. Furthermore, since the RSA can also be derived almost in real-time, with a short delay of about 1 minute, it is possible to include the RSA in the biofeedback to the patient during the exercise.

4.1. Limitations

It should be mentioned as a minor limitation that the in-house algorithms used for the calculation of the PAT have so far only been presented in conference publications, where they were successfully used for the evaluation of signals from the established Multi-parameter Intelligent Monitoring for Intensive Care (MIMIC) Database (Moody and Mark 1996).

Furthermore, the ECG signal was used to determine the proximal reference time. Physiologically, this is not the ideal choice because the ECG signal can change between phases. However, more reliable methods are not suitable for everyday, real-life use. This compromise was therefore unavoidable.

In this study, we investigated the effect of slow breathing as a relaxation exercise on PAT. However, due to limitations in time and budget, no control group was enrolled that performed these measurements without an assigned breathing pattern. Hence, it is not verified that the breathing pattern was indeed the main reason for the lengthening of PAT.

Another limitation to this study is, that the vital parameters of the patients were recorded only for 5 minutes past the end of the guided slow breathing exercise. Hence, future studies will include a longer recording period after the exercise in order to further investigate the mechanisms influencing the cardiovascular system during deep breathing.

In this pilot study, the feasibility of slow breathing as a non-invasive and medication-free blood pressure reduction technique was investigated. Therefore, the selection of subjects was limited to patients with essential hypertension. Hence, these results cannot be extended to the general population.

5. Conclusion

In this study we have shown that device-assisted slow breathing with real-time biofeedback of PAT is feasible for essential hypertensives. Significant short-term improvement of PAT was shown for almost all patients, while no serious adverse effects were detected. Therefore, this approach can be used in future studies to investigate long-term effects over weeks or months. Furthermore, real-time biofeedback of RSA is possible and adds more information about the arterial baroreflex sensitivity of the user. Hence, this method is ideal for home use and self-monitoring due to its ease of use and unobtrusive nature of the measurement.

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