Respiratory Effects on Experimental Heat Pain and Cardiac Activity

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ABSTRACT

Objective. Slow deep breathing has been proposed as an effective method to decrease pain. However, experimental studies conducted to validate this claim have not been carried out.

Design. We measured thermal pain threshold and tolerance scores from 20 healthy adults during five different conditions, namely, during natural breathing (baseline), slow deep breathing (6 breaths/minute), rapid breathing (16 breaths/minute), distraction (video game), and heart rate (HR) biofeedback. We measured respiration (rate and depth) and HR variability from the electrocardiogram (ECG) output and analyzed the effects of respiration on pain and HR variability using time and frequency domain measures of the ECG.

Results. Compared with baseline, thermal pain threshold was significantly higher during slow deep breathing ($P = 0.002$), HR biofeedback ($P < 0.001$), and distraction ($P = 0.006$), whereas thermal pain tolerance was significantly higher during slow deep breathing ($P = 0.003$) and HR biofeedback ($P < 0.001$). Compared with baseline, only slow deep breathing and HR biofeedback conditions had an effect on cardiac activity. These conditions increased the amplitude of vagal cardiac markers (peak-to-valley, $P < 0.001$) as well as low frequency power ($P < 0.001$).

Conclusion. Slow deep breathing and HR biofeedback had analgesic effects and increased vagal cardiac activity. Distraction also produced analgesia; however, these effects were not accompanied by concomitant changes in cardiac activity. This suggests that the neurobiology underlying respiratory-induced analgesia and distraction are different. Clinical implications are discussed, as are the possible cardiorespiratory processes responsible for mediating breathing-induced analgesia.

Key Words. Pain; Respiration; Heart Rate Variability; Vagal Activity; Pain Management; Acute Pain; Biofeedback; Complementary Medicine; Heat

Introduction

In medical settings, controlling breathing frequency and depth is often proposed as a complementary approach that patients can use to manage their pain [1]. In addition, slow deep breathing is often part of techniques frequently used to relieve pain such as relaxation and Qigong [2,3], but it is impossible to evaluate solely the analgesic effect of slow deep breathing from such techniques. Despite the popularity of such approaches, it is surprising to find a complete absence of experimental studies on breathing-induced analgesia.
Although experimental studies are lacking, a few clinical studies support the effectiveness of slow deep breathing to relieve pain. For example, Friesner et al. [4] found that, compared with natural breathing, slow deep breathing produced analgesia during chest tube removal post-surgery. Unfortunately, the authors did not monitor their patients’ breathing frequencies, and so cannot be sure that patient compliance was achieved and that the analgesic effects are attributable to respiration. In another clinical study that investigated breathing-induced analgesia, Hassett et al. [5] found that slow deep breathing decreased the musculoskeletal pain felt by fibromyalgia patients. Despite promising results, the authors failed to control for distraction effects (which arguably accompanies all paced breathing techniques), therefore limiting the interpretability and generalizability of their findings. Notwithstanding these potential limitations, these recent studies offer promising preliminary data that suggest that breathing-induced analgesia may serve as a clinically valid treatment approach.

Because respiration is also known to produce robust changes in cardiac activity, (i.e., respiratory sinus arrhythmia, RSA), it is thought that a common biological process may explain both respiratory-induced analgesia and respiratory-induced changes in cardiac activity [6]. Respiratory-induced changes in cardiac activity are mediated by a complex pattern of physiological responses, including variations in pulmonary volume, arterial blood pressure (BP), as well as baroreflex, brainstem, and vagal cardiac activity. These responses: 1) are relatively rapid; 2) help buffer changes in blood pressure; and 3) are thought to trigger pain inhibition. Breathing-induced analgesia, therefore, should be strongest when breathing-induced changes in heart rate (HR) are largest. Concurrently recording HR and pain sensitivity should help validate this hypothesis and should increase our general understanding of the mechanisms underlying breathing-induced analgesia.

In the current study, we investigated the effects of breathing on experimental heat pain and autonomic cardiac activity. We compared natural breathing (baseline) with slow deep breathing (6 breaths/minute), rapid breathing (16 breaths/minute), distraction (playing a video game), and a biofeedback condition where patients had to synchronize breathing and HR (i.e., HR biofeedback). This latter condition was included because past studies suggest that biofeedback explicitly targets the respiratory frequency that will cause maximal variations in HR [7,8]. Because of the preliminary results obtained in previous clinical studies [4,5], we expected that slow deep breathing and HR biofeedback would produce the largest cardiac changes and the strongest analgesic responses.

**Methods**

**Subjects**

Twenty healthy adults (11 men, 9 women, mean age = 25.1 years, standard deviation [SD] = 5.6 years) were recruited for this study. None suffered from chronic pain, cardiac, or respiratory problems. The protocol was approved by the ethics committee of Centre Hospitalier Universitaire de Sherbrooke.

**Thermal Pain**

A 3 cm × 3 cm thermode (Medoc TSA-II, Ramat Yishai, Israel) was used to evaluate thermal pain threshold and thermal pain tolerance. Thermal pain threshold was obtained by increasing the temperature from 37°C at a fixed rate of 0.3°C/second until the stimulation first became painful (i.e., the lowest painful temperature). Thermal pain tolerance was obtained by increasing the temperature to the point where participants judged that they could no longer sustain it. For safety reasons, temperatures never exceeded 50°C. The thermode was placed on the volar part of each participant’s left forearm. To avoid peripheral receptor sensitization, different, but adjacent, locations were used for successive applications of the thermode. Prior to testing, the thermode was placed in the palm of the left hand so that participants could become accustomed to our test stimulus, and so that they could practice rating experimental heat pain.

**Physiological Measures**

**Breathing**

Respiratory rate and depth were measured with a Piezo electric respiratory belt transducer (AD Instruments, Colorado Springs, CO). Data were recorded with a PowerLab 8/30 amplification system (AD Instruments) and analyzed with the Chart software (AD Instruments).

**Electrocardiogram**

Electrocardiogram (ECG) activity was monitored to determine cardiac activity. ECGs were recorded
using a standard 3-lead montage and sampled at a frequency of 1,000 Hz using the PowerLab system with Chart software (AD Instruments). Instantaneous R-R intervals were calculated from the ECG waveform using a peak detection algorithm to detect successive R-waves and obtain a continuous R-R tachogram. All data were manually checked to ensure that only normal-to-normal (NN) intervals were analyzed. Once checked, we obtained time and frequency indices of the variability in HR response. In the time domain, we measured SDNN (standard deviation of the NN interval) and a peak-to-valley index of HR change (i.e., normalized RSA amplitude: mean difference between maximum and minimum NN intervals for each breathing cycle divided by mean NN interval). SDNN was used as a measure of general HR variability and the peak-to-valley index was used to quantify breathing-induced oscillations in HR, a phenomenon largely dependent on efferent vagal cardiac activity [9,10]. In the frequency domain, fast Fourier transforms were used to calculate the power spectral density of HR oscillations. Two components are usually distinguished from short term cardiac recordings: a low frequency (LF) (0.04–0.15 Hz) and a high frequency (HF) (0.15–0.4 Hz) component. The two components (LF and HF) are generally associated with two peaks in the cardiac power spectrum. A first peak is observed in the LF range (0.05–0.15 Hz). It reflects naturally occurring slow oscillations of blood pressure, known as Mayer waves, which translate (via the baroreflex arc) into slow cardiac oscillations. These slow, baroreflex-mediated oscillations are dependant on vagal cardiomotor responses, but are also influenced by slow adrenergic (sympathetic) responses [11]. Under normal breathing conditions, LF power is unrelated to respiration [8]. A second peak is observed in the HF range (0.15–0.4 Hz) and reflects the vagal activity responsible for mediating RSA [11]. It is important to point out that when breathing slows down (to about 6 breaths/minute), HF oscillations shift to the LF range, creating a sharp increase in LF power. This is a robust phenomenon that occurs because of the resonant characteristics of the cardiovascular system [7,8].

**Experimental Protocol**

Testing was carried out over a single, 1-hour visit. Participants were seated in a comfortable chair and had to refrain from moving or talking during testing. Participants were not explicitly asked to relax. Five different conditions were tested using a repeated measures design: 1) natural breathing (baseline); 2) slow deep breathing (six breaths per minute or 0.1 Hz); 3) rapid breathing (16 breaths per minute or 0.26 Hz) (conditions 2 and 3 were done in randomized order); 4) distraction (playing a video game); and 5) HR biofeedback. Slow deep breathing and rapid breathing were the only randomized conditions while the other conditions were done in the order listed above. In the baseline condition, participants were asked to breathe naturally. For the slow and rapid breathing conditions, participants were asked to breathe following a paced breathing program called EZ-air™ (Thought Technology, Montreal, Québec, Canada), which uses a moving bar graph that can be adjusted to different breathing rates. For the distraction condition, participants were asked to play the video game Tetris Xp (Intelore, Seattle, WA) on a laptop computer using only their right hand to play the game (their left arm was reserved for thermal stimulations). To reduce anxiety, participants were informed their performance at playing the game was not important. For the HR biofeedback condition, we used a computerized program called Freeze-frame™ (Institute of Heartmath, Boulder Creek, CA) and followed the administration protocol described by Vashillo et al. and Lehrer et al. [7,8]. During HR biofeedback, participants were instructed to synchronize their breathing with the fluctuations of their HR (fed response). When their HR was rising, participants were asked to slowly breathe in and when their HR started to decrease, they had to slowly exhale. Participants were exposed to the experimental heat pain stimulus only once the target breathing frequency was reached and maintained for at least 2 minutes. As breathing was not explicitly paced during the natural breathing and distraction conditions, this prerequisite was not necessary for these conditions. Nevertheless, the 2-minute delay was applied to ensure comparability between all conditions. Importantly, participants were asked to follow the instructions appropriate for each condition during application of the noxious stimulus. Heat pain was applied twice (in rapid succession and on adjacent forearm locations): once to determine pain threshold and once to determine pain tolerance. For each condition, thermal pain threshold was always tested before thermal pain tolerance.

**Statistical Analyses**

Friedman tests were used to test for condition effects on thermal pain threshold, thermal pain
tolerance, and the various time and frequency domain measures of the cardiac response. Raw scores were used for these analyses. Post hoc analyses comparing condition effects were decomposed using Wilcoxon signed ranks tests. All comparisons were made relative to the baseline condition (i.e., natural breathing). Mann–Whitney tests were conducted to determine if carryover effects were present in the two breathing conditions or could have affected the results of the distraction condition. To appreciate the degree of change between conditions, we also calculated the difference score between the baseline condition and each other condition. This difference score was calculated for all of our dependent variables, except for respiratory variables, which were only compared with baseline condition. Difference scores were analyzed using Friedman tests. Holm’s corrections for multiple comparisons were applied to all comparisons, and \( P < 0.05 \) (two-tailed) was considered statistically significant.

### Results

All participants completed our experiment. None reported signs of hyperventilation and none reported undesirable side-effects.

### Respiration

As expected, significant differences in breathing rate were observed for the different conditions (\( \chi^2 = 65.203, P < 0.001 \); Table 1). Compared with natural breathing (baseline), breathing rate was significantly slower during slow deep breathing and HR biofeedback conditions (both \( P < 0.001 \)), whereas it was significantly faster during rapid breathing and distraction conditions (both \( P_S < 0.009 \)). Significant differences in breathing depth were also observed (\( \chi^2 = 43.4, P = 0.001 \); Table 1). Compared with baseline, breathing depth was significantly greater during slow deep breathing and HR biofeedback (both \( P_S < 0.001 \)).

#### Thermal Pain Threshold and Tolerance

Testing conditions significantly affected thermal pain threshold and tolerance (both \( \chi^2 s \geq 30.56, \text{both } P_S < 0.001 \); Table 2). Compared with natural breathing, threshold values were significantly higher during slow deep breathing, HR biofeedback, and distraction conditions (all \( P_S < 0.006 \)), and tolerance scores were significantly higher during slow deep breathing and HR biofeedback (both \( P_S < 0.003 \)).

HR biofeedback, slow deep breathing, and distraction conditions produced larger increases (from baseline) in pain threshold than did rapid breathing (\( P_S < 0.009 \)), whereas slow deep breathing and HR biofeedback conditions produced larger increases in pain tolerance than did rapid breathing (both \( P_S < 0.001 \)). Slow deep breathing and HR biofeedback also produced larger increases in pain tolerance than did the distraction condition (\( P_S < 0.021 \)).

The analgesic effects of slow deep breathing were equivalent, whether slow deep breathing was conducted prior to or after rapid breathing (\( P_S \geq 0.734 \)). Rapid breathing had no effect on pain whether it was done before or after slow deep breathing (\( P_S \geq 0.521 \)), and the analgesic effect of distraction was not affected by the order of the previous breathing conditions (\( P_S \geq 0.97 \)).

### Table 1

<table>
<thead>
<tr>
<th>Breathing parameters mean (± standard error)</th>
<th>Baseline</th>
<th>Six breaths/minute</th>
<th>Sixteen breaths/minute</th>
<th>Distraction</th>
<th>HR biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing rate (RPM)</td>
<td>13.03 (0.78)</td>
<td>5.78 (0.08)</td>
<td>15.48 (0.09)</td>
<td>17.23 (1.2)</td>
<td>5.7 (0.19)</td>
</tr>
<tr>
<td>Breathing depth (mV)</td>
<td>10.37 (0.97)</td>
<td>21.38 (2.46)</td>
<td>15.16 (1.96)</td>
<td>8.74 (0.99)</td>
<td>21.43 (2.68)</td>
</tr>
</tbody>
</table>

HR = heart rate; mV = millivolt; RPM = respirations per minute.

### Table 2

<table>
<thead>
<tr>
<th>Mean thermal pain threshold and tolerance for the different conditions (± standard error)</th>
<th>Baseline</th>
<th>Six breaths/minute</th>
<th>Sixteen breaths/minute</th>
<th>Distraction</th>
<th>HR biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain threshold (°C)</td>
<td>43.8 (0.5)</td>
<td>44.8 (0.4)</td>
<td>1.0* (0.3)</td>
<td>43.6 (0.5)</td>
<td>-0.2 (0.3)</td>
</tr>
<tr>
<td>Pain tolerance (°C)</td>
<td>47.7 (0.3)</td>
<td>48.2 (0.3)</td>
<td>0.5** (0.2)</td>
<td>47.8 (0.3)</td>
<td>0.0 (0.1)</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \); ** \( P < 0.005 \).

DS = difference score, the difference between a given condition and the baseline (natural breathing) condition; HR = heart rate; RS = raw score.
Heart Rate Variability

Time Domain Measures
Testing conditions significantly affected mean HR, SDNN, and peak-to-valley indices (all $\chi^2$s > 19.2, all $P$s < 0.001). Mean HR was significantly higher during rapid breathing than during natural breathing ($P = 0.003$; Table 3). SDNN and peak-to-valley indices were significantly higher during slow deep breathing and HR biofeedback conditions than during natural breathing (all $P$s < 0.003; Table 3; Figure 1).

Rapid breathing produced larger increases (from baseline) in HR than did slow deep breathing and HR biofeedback (both $P$s < 0.001). Distraction produced larger increases (from baseline) in HR than did the HR biofeedback condition. Finally, slow deep breathing and HR biofeedback produced larger increases in peak-to-valley amplitude and SDNN than did the rapid breathing and distraction (all $P$s < 0.001).

Frequency Domain Measures
Testing conditions significantly affected the LF component of the power spectrum ($\chi^2 = 62.68, P < 0.001$; Table 3). LF power was significantly higher during slow deep breathing and HR biofeedback conditions than during natural breathing (both $P$s < 0.001). There were no significant differences in HF power ($\chi^2 = 4.96, P = 0.291$; Table 3).

Slow deep breathing and HR biofeedback produced larger increases (from baseline) in LF power than did rapid breathing and distraction (all $P$s < 0.001).

Discussion
As expected, slow deep breathing and HR biofeedback were characterized by slower and deeper breathing compared with baseline (natural breathing), whereas rapid breathing and distraction were characterized by faster breathing. These findings confirm that participants followed the testing instructions unique to each condition. As a result, we can be confident that our effects are attributable to our experimental manipulations (i.e., paced breathing or distraction).

Thermal pain threshold and tolerance were higher during slow deep breathing and HR biofeedback conditions than during natural breathing. These analgesic effects were not systematically seen in the other conditions. In fact, the distraction condition was the only other condition which procured an analgesic effect (increased pain threshold). On average, thermal pain threshold and tolerance values increased by 1°C when breathing slowed down. This increase may appear trivial; however, given the exponential function linking temperature and pain, a 1°C increase will logically produce important changes in perceived pain (more importantly for pain tolerance) [12]. In fact, the entire intensity range, from pain threshold to pain tolerance, spanned only 3.3°C in our experiment. Our findings, therefore, corroborate anecdotal reports that suggest that slow deep breathing yields analgesic effects.

We initially hypothesized that a common biological process might explain breathing-induced

Table 3  Mean cardiac parameters (± standard error)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six breaths/minute</th>
<th>Sixteen breaths/minute</th>
<th>Distraction</th>
<th>HR Biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean heart rate (BPM)</td>
<td>71 (2.5)</td>
<td>71 (1.7)</td>
<td>75 (2.2)*</td>
<td>73 (2.0)</td>
<td>70 (1.7)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>52.1 (5.4)</td>
<td>99.8 (8.2)*</td>
<td>43.4 (4.7)</td>
<td>51.7 (4.4)</td>
<td>96.4 (7.8)*</td>
</tr>
<tr>
<td>Peak-to-valley amplitude</td>
<td>0.099 (0.012)</td>
<td>0.296 (0.021)*</td>
<td>0.079 (0.008)</td>
<td>0.077 (0.007)</td>
<td>0.288 (0.025)*</td>
</tr>
<tr>
<td>LF power (ms²)</td>
<td>1,524 (422)</td>
<td>9,194 (1433)*</td>
<td>751 (229)</td>
<td>1,155 (293)</td>
<td>8,463 (1180)*</td>
</tr>
<tr>
<td>HF power (ms²)</td>
<td>879 (213)</td>
<td>1,214 (398)</td>
<td>874 (264)</td>
<td>535 (124)</td>
<td>623 (142)</td>
</tr>
</tbody>
</table>

* $P < 0.005$ for all baseline comparisons.

BPM = beats per minute; HF = high frequency (0.15–0.4 Hz); HR = heart rate; LF = low frequency (0.04–0.15 Hz); ms = milliseconds; ms² = squared milliseconds; SDNN = standard deviation of the normal-to-normal interval.
analgesia and breathing-induced changes in HR. In support of this hypothesis, we found that slow deep breathing and HR biofeedback produced the largest decrease in pain sensitivity, while also producing the largest variability in HR (SDNN). A rise in peak-to-valley amplitude (indices of vagal activity) during slow deep breathing and HR biofeedback supports the idea that slow breathing (at about 6 breaths/minute) increases vagal activity.

Furthermore, frequency domain analyses of the ECG output revealed a sharp increase in LF power during slow deep breathing and HR biofeedback. This rise naturally occurs when breathing slows down and happens because the oscillations associated with RSA (which are usually expressed in the HF component) overlap with the slow HR oscillations (LF component). This phenomenon is directly tied to breathing oscillations and also indexes vagal cardiac activity.

Our findings clearly support our original hypothesis regarding the effects of slow deep breathing on pain and cardiac activity. Although our study was not designed to chart the precise neurobiological mechanisms underlying breathing-induced analgesia and HR variability, the pattern of results obtained here allows us to speculate on the nature of the mechanisms involved. Slow deep breathing is known to produce a sharp increase in intrathoracic pressure, venous return, and systolic BP [13]. BP fluctuations are detected by stretch sensitive baroreceptors that send action potentials via the IX and X cranial nerves to the nucleus tractus solitarius (NTS) located in the brainstem. Following afferent baroreceptor signaling, the NTS sends excitatory projections to the nucleus ambiguous, a medullary structure responsible for controlling parasympathetic (vagal) cardiac activity. Thus, a rise in arterial BP is translated into vagal cardiovascular responses through the modulatory activity of brainstem nuclei. Interestingly, peripheral baroreceptors activation also exerts powerful excitatory effects on the pain inhibitory relays in the NTS [14]. The NTS, in fact, is part of a network of interconnected areas (including the lateral parabrachial nucleus, the ventrolateral medulla, and periaqueductal gray) involved in pain modulation [15]. NTS activity, therefore, offers an opportunity for the central modulation of both cardiorespiratory and nociceptive activity.

One possible limitation of this study is worth noting. Although we assume that respiration induces changes in BP and activates baroreceptors, we did not directly measure BP, baroreceptor stimulation, or NTS activity, but instead used vagal cardiac outflow measures (peak-to-valley and LF power) as surrogates. Despite this limitation, surrogate cardiac measures are regularly used to index baroreceptors/vagal reflex activity [10]. More importantly, these measures change following graded doses of phenylephrine, a vasopressor agent that increases baroreflex activity [16]. This means that a relationship likely exists between baroreceptor activity and breathing-induced changes in cardiac response. Future studies using continuous BP monitors and functional imaging should help delineate the precise mechanisms responsible for mediating respiratory-induced analgesia.

While cardiopulmonary processes likely explain the analgesic effects observed during slow deep breathing, attentional factors may have also contributed. For example, participants were instructed to keep constant breathing rhythms using an exogenous pacer. This necessarily required the mobilization of attentional resources, and may have produced pain relief because of distraction effects. Despite this possibility, we believe that the analgesia produced during slow deep breathing was not entirely caused by distraction effects, as slow deep breathing produced a greater increase (from baseline) in pain tolerance than the distraction condition. Moreover, all of our paced breathing conditions required comparable levels of attention, yet rapid breathing failed to produce analgesia. Although lower stimulus or pacing frequencies could be more analgesic than faster frequencies [17], it is not clear if this was the case in our study. More importantly, however, the analgesia observed during the distraction condition (increased pain threshold) was not accompanied by the cardiac effects observed during slow deep breathing. This suggests that distraction may decrease pain, but the mechanisms underlying this effect are likely different from those underlying respiratory-induced analgesia. This hypothesis is consistent with recent functional imaging studies that show that distraction-induced pain relief is primarily a cortical phenomenon, involving increased activity in prefrontal and sensory-discriminative regions of the cortex [18,19].

Another potential limit is the fact that not all conditions were randomized. However, no carryover effects were observed for the two randomized breathing conditions and in the distraction condition. Thus, carryover effects could have only influenced the HR biofeedback condition.
Slow deep breathing is a simple and easy to use method to relieve acute pain that could easily be used for painful medical procedures (shots, punctures, dressing change, childbirth, etc.), to help alleviate acute painful crisis or as a complementary pain treatment for chronic pain. Studies evaluating the effect of slow deep breathing in chronic painful conditions are required.

In conclusion, this is the first experimental study to systematically control for breathing frequency and distraction effects and to show that respiratory-induced analgesia reduces pain in healthy subjects. The combined cardiorespiratory and antinociceptive effects observed during slow deep breathing suggest that the modulation of HR and pain share a common neurophysiological pathway. Our results, therefore, support the use of slow deep breathing as an inexpensive and valuable adjunct to the current treatment of pain.

Acknowledgments
This research was supported by Dr. Marchand’s research grants from the Canadian Institutes of Health Research and by a postdoctoral scholarship from the Fond de la Recherche en Santé du Québec given to Philippe Goffaux. The authors wish to thank all subjects for their participation.

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