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Pain and respiration: a systematic review

Hassan Jafari^a, Imke Courtois^a, Omer Van den Bergh^a, Johan W.S. Vlaeyen^{a,b}, Ilse Van Diest^{a,*}

Abstract

Breathing techniques are commonly used to alleviate pain. Despite their frequent use, surprisingly little is known about their efficacy as well as their underlying physiological mechanisms. The purpose of this systematic review is to summarize and critically appraise the results of existing studies on the association between respiration and pain, and to highlight a potential physiological mechanism underlying the respiration–pain connection. A total of 31 publications from between 1984 and 2015 were retrieved and analyzed. These articles were classified into 4 groups: experimental and clinical studies of the effect of pain on respiration, clinical studies of the effects of breathing techniques on pain, and experimental studies of the influence of various forms of respiration on laboratory-induced pain. The findings suggest that pain influences respiration by increasing its flow, frequency, and volume. Furthermore, paced slow breathing is associated with pain reduction in some of the studies, but evidence elucidating the underlying physiological mechanisms of this effect is lacking. Here, we focus on the potential role of the cardiovascular system on the respiratory modulation of pain. Further research is definitely warranted.

Keywords: Pain, Respiration, Breathing techniques, Respiratory hypoalgesia

1. Introduction

The practice of breathing techniques is as old as Yoga, going back to about 2000 years ago. Carefully controlling one's breathing is one of the main limbs of Yoga (Pranayama).^{83,96} Even now, alongside its use in meditation and relaxation in healthy people, breathing practices are common as a therapeutic technique in controlling various symptoms and conditions including distress, anxiety, high blood pressure (BP), asthma, and pain. Specifically in controlling pain, paced slow deep breathing (SDB) has become routinely used in clinical and hospital care for patients in pain and labour. Despite the many uses of breathing techniques, their efficacy and mechanisms of action remain unclear.

A bidirectional relationship exists between pain and respiration. First, respiratory changes often occur in response to pain: An inspiratory gasp with a subsequent breath-hold in response to sudden onset, acute pain, a sigh of relief when pain is removed, or hyperventilation in the presence of persistent and uncontrollable pain. As early as 1940, Finesinger and Mazick³⁷ pioneered research on this topic, exploring the effect of painful stimuli on respiration in healthy and “psychoneurotic” patients. These authors found high variability in breathing responses elicited by pain, with the majority of the healthy participants showing an increase of respiration depth and a moderate increase in minute respiratory volume. Over the last 3 decades, studies have further investigated this relationship in experimental studies, but the

literature and findings on the topic are rather scattered across time and research domains. Second, there is evidence that respiration may influence subsequent pain severity. The instrumental application of particular breathing techniques to relief or control pain is quite common in various clinical environments. In particular, SDB has been used, either as a stand-alone therapeutic intervention or as a component of more encompassing interventions such as relaxation and yoga. Three earlier review articles^{57,76,80} have addressed the effect of relaxation on pain, but, to date, no review is available that specifically examines the effects of breathing interventions on pain.

Because a remarkable number of clinical and laboratory studies on the mutual interaction between pain and respiration were published after 1984, the aim of this review was to summarize the literature on the bidirectional association between pain and respiration in both clinical (patients with pain) and experimental (healthy people) studies. The published articles can be categorized into 4 domains: (1) experimental studies on the effect of pain on respiration, (2) clinical studies on the effect of pain on respiration, (3) experimental studies on the effect of respiration on pain, and (4) clinical studies on the effect of respiration on pain. Here, we aimed to conduct a systematic literature review on the association between pain and respiration and to summarize and critically appraise the results in each of the 4 domains of research. Based on the results of the systematic review, we outline some promising directions for future research.

2. Methods

This systematic review was conducted according to the guidelines of the Centre for Reviews and Dissemination¹⁷ and Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015.⁸² A pilot search of the databases failed to find a relevant study from before 1984 that qualified for contemporary standards of research. Also the access to older studies and databases from before 1984 turned out to be limited. Therefore, our final search strategy aimed at retrieving the

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published studies from online databases between 1984 and 2015, covering the period in which the bulk of the work that has been done on this topic. The MEDLINE and EMBASE databases were searched as they are the most commonly used databases in the area of health care interventions. The search was conducted separately for each database using pairwise key word combinations of pain, nociception, analgesia, or hypoalgesia on the one hand and respiration, respiratory, or breathing on the other hand. However, the combination of “pain” and “respiratory” was excluded as it produced too many hits, due to the very general meaning and usage of these terms in a variety of disciplines. The key word search was limited to title and abstract; the resulting records were filtered to include only studies on human subjects, written in English, and published between January 1984 and December 2015. As such, 1755 and 3477 records were retrieved from MEDLINE and EMBASE, respectively (Fig. 1, identification). Duplications (1370 records) were removed, after which the titles and abstracts of the resulting set of studies (3477 records) were screened for relevance by the first author (H.J.), (Fig. 1, screening). The main reasons for exclusion were as follows: (1) studies that focused on cardiovascular and BP without addressing respiration as a main variable of the research, (2) studies that mainly focused on the effect of painkillers and opioid medications on respiratory suppression, (3) letters to the editor and commentaries, or abstract-only publications. Of the 36 publications resulting from this screening, 6 were judged not eligible, as 3 of them were review articles, and 3 studies were lacking an explicit breathing technique mentioned in the article (Table 1 and Fig. 1, eligibility). A snowball search was conducted by scanning the reference list of the withheld 30 publications, resulting in the identification of one additional publication. Thus, a total number of 31 studies were included in the literature review. The 31 eligible

articles were categorized into 4 types of studies: (1) experimental studies on the effect of pain on respiratory outcomes, (2) clinical studies on the effect of pain on respiration, (3) clinical studies on the effect of breathing exercises on self-reported pain, and (4) experimental studies on the effect of instructed breathing patterns on the laboratory-induced pain. Figure 1 provides the diagram of the publication retrieval, screening, and categorization process.

The first author (H.J.) extracted the following variables for both types of experimental studies: publication year, sample size, participants, type of pain, critical comparisons made, studied outcome, and findings in terms of either pain, either respiration. For the clinical studies on respiratory effects of pain, we extracted publication year, sample size, participants, comparisons made, respiratory parameter under study, and main findings. The following variables were extracted for the clinical studies on the effect of respiration on pain: publication year, sample size, participants, type of pain, comparisons made, type of breathing intervention, presence or absence of other interventions combined with the breathing technique, intervention duration, and whether the breathing intervention was effective in reducing pain. For each of the 4 types of studies, a narrative synthesis is provided with information presented in the text and tables, summarizing qualitatively the characteristics and findings.

3. Effect of pain on respiratory outcomes

3.1. Experimental studies

From the 9 experimental studies summarized in Table 2, 4 studied the effect of a phasic, short-lasting cutaneous pain stimulus (electrocutaneous stimulation, or surgical incision of the

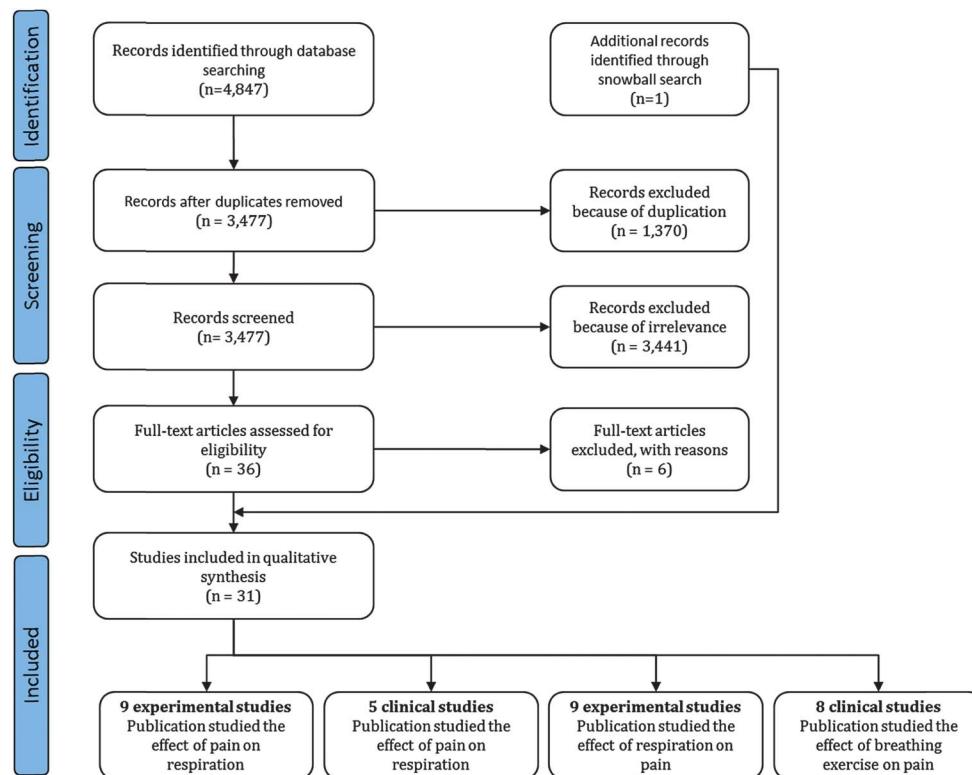


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram. The flow diagram represents publication identification, screening, selection, and categorization.

Table 1**The systematic search in MEDLINE and EMBASE databases.**

Database	MEDLINE Retrieved	EMBASE Retrieved	Total	After duplication removed
Key word combination				
Pain + respiration	454	715	1169	803
Pain + respiratory	NA	NA	NA	NA
Pain + breathing	1162	2189	3351	2461
Nociception + respiration	24	31	55	36
Nociception + respiratory	77	102	179	118
Nociception + breathing	19	29	48	31
Algesia + respiration	0	1	1	1
Algesia + respiratory	2	2	4	4
Algesia + breathing	0	0	0	0
Hypoalgesia + respiration	6	6	12	6
Hypoalgesia + respiratory	9	14	23	14
Hypoalgesia + breathing	2	3	5	3
Total	1755	3092	4847	3477

The key word combination, number of articles retrieved, total, and the article after duplication removed are shown. A total of 3477 publications found form both databases, after removing the duplications. Language: English, population: humans, publication date: 1984 to December 2015. NA, not applicable.

skin) on respiration.^{24,47,79,86} Interestingly, a consistent pattern of results emerges from those studies, showing that sudden cutaneous pain increases inspiratory flow, either by decreasing inspiratory time,²⁰ or by increasing inspiratory volume,⁸⁶ or a combination of both.⁴⁷ Inspiratory flow, or the ratio of inspiratory volume over inspiratory time, is thought to reflect the central inspiratory drive mechanism, which determines the intensity of the inspiration.⁴⁰ The findings suggest that the increase in inspiratory flow in response to acute cutaneous painful stimulation seems to occur involuntarily because it is instantaneous, it also occurs under general anaesthesia,⁸⁶ and it shows a remarkable resemblance to the respiratory component of the startle reflex.^{16,89}

Five studies investigated the effects of another form of more tonic, sustained pain. Findings in this area also are surprisingly consistent. Every study measuring both the timing and volume components of respiration under conditions of sustained pain reported an increase in minute ventilation,^{10,11,52,56,68} which is the total ventilatory output (amount of air that one breathes in and out on a 1-minute basis, calculated as the product of respiratory frequency and tidal volume). Pain-induced increases in minute ventilation seem to result from deeper breathing,^{10,11,56} faster breathing,⁶⁸ or a combination of both.⁵²

3.2. Clinical studies

Effects of pain on respiration have been documented also in patients confronted with clinical pain. The majority of these studies primarily aimed at developing a clinical tool to evaluate pain in nonverbal, critically ill patients or infants. Based on clinical expertise or on previous inclusion of respiratory measures in other pain assessment tools, studies reporting on the development of those tools have included changes in respiratory rate (RR) or a reduced compliance to a mechanical ventilator as potential indicators of pain.^{41,54,72,74,75} Some studies have also included an empirical validation test for the inclusion of respiratory assessments in the observation tool and studied whether or not respiration changed during a painful procedure or during pain relief in patients. The 3

studies (**Table 3**) assessing RR during a painful procedure all observed an increased RR during pain,^{41,54,74,75} although not necessarily in each individual.^{74,75} One study also observed an increased asynchrony with a ventilator during a painful compared with a nonpainful procedure.⁴¹

The study by Glynn et al.⁴⁶ (1981) was the only study in which the development of a clinical pain assessment tool was not the primary aim; they documented hyperventilation in patients with chronic pain, which diminished again after pain relief. As hyperventilation is a breathing pattern in excess of metabolic needs leading to lower levels of carbon dioxide pressure (hypocapnia),³⁹ hyperventilation associated with chronic pain is consistent with the observed increases in minute ventilation in response to sustained pain as found in the above reviewed experimental studies.^{10,11,52,56,68} Although the latter experimental studies^{10,11,52,56,68} have not measured arterial carbon dioxide pressures and cannot definitively conclude that hypocapnia was present, it is very likely to have occurred given the observed increases in minute ventilation. Taken together, the findings of both experimental and clinical studies of sustained types of pain on respiration are in accordance with the literature and studies on hyperventilation. This fits with the notion that hyperventilation is a respiratory stress response that occurs most typically in situations of uncontrollable stress, fear, and pain.^{2,22,23,63,67,90,92}

3.3. Discussion

Several authors have proposed that increased ventilation or hyperventilation during acute pain reflects the respiratory component of the fight-or-flight response, preparing the organism for a possible attack or injury.^{90,92,95} Acute hyperventilation can also activate the endogenous adrenergic and opiate system,⁹⁵ although it remains unclear whether and how hyperventilation could serve a functional goal in conditions of chronic pain. Chronic hyperventilation is generally considered a pathological condition as it dysregulates basic physiological processes in the body.^{39,45} Earlier work from our group has suggested that hyperventilation in patients suffering from chronic

Table 2

Overview of experimental studies investigating the effect of pain on respiratory variables.

Author	Year	Sample size	Participants	Type of pain	Comparison	Outcome	Finding
Duranti et al. ²⁴	1991	14	Healthy	Painful electrical stimuli/ischemic pain	Pre/post	Insp. flow Insp. time Resp. cycle time	Increase Decrease Decrease
Borgbjerg et al. ¹¹	1996	10	Healthy	Tourniquet pain at calf	Pre/post pain Pre/post opioid	Tidal volume MV	Increase
Sutherland ⁸⁶	1996	10	Under operation	Surgical incision	Pre/post	Tidal volume Insp. flow Insp. time	Increase Increase Increase
Sarton et al. ⁷⁹	1997	8	Healthy	Mild electrical cutaneous stimuli	Room air hypercapnia hypoxia	MV	Increase, similar between conditions
Boiten ¹⁰	1998	27	Healthy	Cold pressor 3°C	Pre/post	Insp. pause Exp. pause Tidal volume MV Insp. flow	Increase Increase Increase Increase Increase
Nishino et al. ⁶⁸	1999	15	Healthy	Tourniquet pain at calf during 8 min of loaded breathing	Pre/during	Insp. volume Respir. rate End-tidal CO ₂ Pressure	Increase Increase Decrease Increase
Kato et al. ⁵⁶	2001	10	Healthy	Infusion of saline into masseter muscle	Baseline Pain Placebo	Respir. rate MV Insp. rate Exp. rate	Increase Increase Increase Increase
Green et al. ⁴⁷	2008	16	Healthy	Subthreshold and suprathreshold cutaneous electrical stimulation	Inspiratory Expiratory	Insp. time Tidal volume Insp. flow	Decrease if during insp. Increase if during insp. Increase if during insp.
Hotta et al. ⁵²	2009	11	Healthy	DOMS	Pre/post	Tidal volume MV	Increase Increase

DOMS, delayed onset muscle soreness; Exp., expiratory; Insp, inspiratory; MV, minute ventilation; Resp, respiratory.

fatigue results from feelings of uncontrollability, rather than from the pain itself.⁹ In this regard, it is interesting to note that hyperventilation also occurs in anticipation of pain without any actual painful stimulation.⁸⁵ Thus, in contrast to the apparently reflexive increase in inspiratory flow in response to acute, cutaneous pain, the hyperventilation effects associated with chronic or more sustained forms of acute pain may be less specific for pain. These hyperventilation effects do not seem to depend on the stimulation of nociceptive receptors, but rather may reflect the influence of feelings of fear, panic, and uncontrollability in response to a potential or actual aversive event such as pain. Unfortunately, the precise neurophysiological mechanisms underlying respiratory responses to acute as well as to relatively sustained and chronic pain are not well understood. Studies that critically test potential mechanisms are clearly needed. Ultimately, knowledge from such studies will help foster and validate the further development of clinical tools assessing respiratory changes as indicators of pain in nonverbal individuals.^{41,54,72,74,75}

4. Effects of respiration on pain

Many researchers and clinicians assume that SDB can influence pain perception throughout cardiovascular changes. As such,

respiration may be considered a behavioral interface to change autonomic discharge patterns and central mechanisms known to modulate pain. As many of the reviewed studies suggest cardiovascular effects of breathing techniques as mediators or moderators of pain reduction, we provide the reader with an introductory background on some of the potentially relevant interactions between pain, respiration, and cardiovascular activity, before actually reviewing the clinical and experimental studies. Doing so, we hope to facilitate the unfamiliar reader's understanding of some of the hypothesized mechanisms and cardiovascular measures in the studies that will be reviewed in sections 4.2 and 4.3.

4.1. Interactions between pain, respiration, and cardiovascular changes

4.1.1. The baroreflex system

The baroreflex is a homeostatic, rapid negative feedback loop adjusting heart rate (HR) and BP in the body.²⁸ Located in the lung vessels, wall of the aortic arch, and carotid sinuses and chambers of the heart, baroreceptors sense changes in BP (BP) and relay this information (through the vagal and glossopharyngeal nerves) to neurons of the nucleus of the solitary tract (NTS) located in the medulla.²⁸ The NTS projects to vagal/parsympathetic and

Table 3**Overview of clinical studies on respiratory changes in patients experiencing pain.**

Author	Year	Sample size	Participants type of pain	Comparisons	Respiratory parameter	Finding
Glynn et al. ⁴⁶	1981	52 patients with chronic pain	Low back pain, cancer pain and other causes	Pre vs post pain relief	Arterial CO ₂ level	Decreased hyperventilation upon pain relief
Puntillo et al. ^{74,75}	1997	31 patients, 114 assessments	surgical patients	Pre vs post intravenous dose of an opioid	Change in RR	Increased RR prior to the drug in 21% of the patients
Payen et al. ⁷²	2001	30 patients, 269 assessments	Mechanically ventilated patients in trauma unit	None	Compliance with ventilator	Poor compliance/fighting with ventilator when in pain
Gélinas and Johnston ⁴¹	2007	30 conscious, 25 unconscious	ICU patients	Pre/post a non-nociceptive/nociceptive procedure	RR	Increase in RR during nociceptive procedure
Kabes et al. ⁵⁴	2009	64 patients, 121 assessments	ICU patients	Pre vs during vs post painful procedure	Change in RR of 10 or 20 breaths/min over the past 4 h RR increase of 10-20 above baseline Asynchrony with ventilator	Inclusion in a pain assessment tool Increases during painful procedure Inclusion in a pain assessment tool

ICU, intensive care unit; RR, respiratory rate.

sympathetic brain stem nuclei (vagal: nucleus ambiguus, dorsal motor nucleus; sympathetic: rostral ventrolateral medulla). Efferents from these nuclei can increase (sympathetic) or decrease (vagal) HR. Thus, when BP increases (expansion of the arterial wall), baroreceptors are stimulated causing a decrease in HR and vascular tone. Conversely, a decrease in BP inhibits the baroreceptors, resulting in an increase in HR and vascular tone. This pathway is described as the cardiovascular branch of the baroreceptor system.^{81,93} For an overview of measurements of baroreflex sensitivity (BRS) and clinical implications, we refer to La Rovere et al.⁵⁸ (2008).

Interestingly, the baroreceptor system also has a central nervous branch, connecting the NTS with other regulatory centers in the brain stem and higher cerebral regions related to pain and autonomic control such as the periaqueductal gray, nucleus raphe magnus, locus coeruleus, anterior cingulate cortex, hypothalamus, and thalamus.²⁸ Through these connections, information from cardiovascular activity can also impact higher cerebral regions involved in emotion and cognition (insulae, hippocampus, amygdala, left prefrontal cortex), which may reciprocally modulate autonomic outflow and characteristics of baroreceptor function.^{19,44,77} However, knowledge about the central nervous branch of the baroreceptor system remains sparse.

4.1.2. Pain and blood pressure

The literature describes an inverse correlation between BP levels and pain sensitivity.^{13,20,28,33-35,43,71} Such an association may be functional in that it works to reduce the impact of pain in stressful and threatening situations.¹⁴ Several mechanisms have been proposed for the association, including stimulation of baroreceptors, lowering cerebral arousal,^{14,29,73} or endogenous opioids and noradrenergic pathways as a crucial component of descending inhibitory activity.^{43,98} Although opioids and noradrenergic pathways play a prominent role in pain modulation, human data on their potential role in the BP-pain sensitivity relationship are still sparse, whereas the role of the baroreceptors has been investigated more thoroughly.¹⁴ The NTS—the first synapse in the baroreflex—is an important interface between autonomic centers in the brainstem and the central nervous nociceptive system,^{14,28} allowing for central modulation of both cardiorespiratory and nociceptive activity.¹⁸

Data consistently suggest that baroreceptors can have a role in pain dampening. However, the potential antinociceptive effects of baroreceptor stimulation seem to depend on several experimental and individual factors. For instance, the mode of baroreflex stimulation (artificial vs nonartificial),³² the emotional state of participants,⁶⁶ and the intensity of the applied pain stimuli⁷⁷ can determine the antinociceptive effect size. To complicate the picture, the research literature demonstrates that baroreceptor activity can be modified in the elderly,⁴² in pathological situations such as systemic hypertension and heart failure,^{8,25,70} and can be overridden at various levels of the central nervous system under some circumstances such as mental stress,²⁵ cognitive activity,^{25,27} and experimental pain induction.²⁶

4.1.3. Respiratory sinus arrhythmia

Respiratory sinus arrhythmia (RSA) refers to oscillations in HR along the breathing cycle: Heart rate increases during inspiration and decreases again during expiration. Respiratory sinus arrhythmia is a major source of HR variability (HRV). Central cardiorespiratory rhythm generators (ventral and dorsal respiratory groups), chemoreceptor, cardiac and pulmonary stretch reflexes, local mechanical and metabolic factors are all thought to contribute to RSA, but a major mechanism is the baroreflex.⁴⁻⁷ During inspiration, systolic BP drops because of a decreased stroke volume, resulting in a HR increase through the baroreflex.^{69,87} During expiration, the reverse occurs: Blood pressure increases, activating baroreceptors that trigger a vagally mediated decrease in HR.⁵⁰ Variations in cardiac filling caused by changes in intrathoracic pressure are largely responsible for this BP variability.^{59,69,87} Thus, efferent parasympathetic activity to the heart ("cardiac vagal tone") is elevated during expiration relative to inspiration, not only because of a potentially central respiratory gating of vagal outflow,³¹ but also especially because of a stronger peripheral stimulation of the baroreceptors during the expiratory phase. A relative increase in vagal tone during exhalation inhibits the heart's primary pacemaker, slowing down HR during expiration, and making HR more variable across the respiratory cycle. Of importance, the magnitude of RSA (and HRV) depends on the respiratory pattern as stronger fluctuations in HR across the respiratory cycle have been observed with slower and deeper breathing volume.⁸⁴ When one slows down

Table 4**Review of experimental studies investigated the effect of respiration on pain intensity and NFR.**

Author	Year	Participants (sample size)	Type of pain	Comparisons	Outcome	Findings
Chalaye et al. ¹⁸	2009	Healthy (20)	Thermal pain (heat)	Baseline, 6 BPM, 16 BPM, HR biofeedback, computer game	Pain threshold and tolerance	Higher pain threshold and tolerance in SDB and HR biofeedback compared with baseline. No sig. change during 16 BPM. Computer game increased only the threshold of pain.
Zautra et al. ⁹⁹	2010	Healthy (25), Fibromyalgia (27)	Thermal pain (heat)	Normal resp. rate, 50% of normal rate	Pain	Less pain especially during moderate pain in healthy control. No effects in patients with fibromyalgia.
Busch et al. ¹⁵	2012	Healthy (16)	Thermal pain (cold and hot)	Attentive SDB, relaxing SDB	Pain threshold	Increase of pain threshold in relaxing SDB, but not attentive SDB.
Martin et al. ⁶²	2012	Healthy (30)	Electrocuteaneous stimuli on sural nerve	Normal/slow/fast breathing, insp. vs exp.	Pain, NFR	Reduced pain during slow breathing; NFR not influenced by breathing; no effects of breathing phase
Arsenault et al. ³	2013	Healthy (20)	Electrocuteaneous stimuli on sural nerve	SB with slow insp, SB with fast insp, normal breathing, insp. vs exp.	Pain, NFR	No effect of breathing pattern on pain, but NFR modulated. Pain lower during inspiration. NFR lower during expiration.
Zunhammer et al. ¹⁰⁰	2013	Healthy (20)	Thermal pain (cold and hot)	Breathing at 0.14 Hz, breathing at 0.10 Hz, breathing at 0.06 Hz, resting frequency	Pain threshold, intensity, unpleasantness	No effects
Iwabe et al. ⁵³	2014	Healthy (10)	Intraepidermal electrical stimulation	Insp. vs exp.	Pain intensity, skin conductance, and brain activity	Expiration < inspiration
Botha et al. ¹²	2015	Healthy (37)	Electrical stimulation of proximal oesophagus	SDB, nonpaced breathing	Pain threshold, skin conductance, and vagal tone	Deep breathing increases cardiac vagal tone and decreases skin conductance responses. Deep breathing prevents the development of oesophageal hypersensitivity
Reyes del Paso et al. ⁷⁸	2015	Healthy (38)	Pressure algometer	Slow inhalation, breath-hold	Pain intensity	Less pain during breath-hold comparing with slow inhalation regardless of pressure intensities.

BPM, breath per minute; HR, heart rate; NFR, nociceptive flexion reflex; SB, slow breathing; SDB, slow deep breathing.

breathing, a compensatory increase in volume typically occurs. Deeper breathing causes larger fluctuations in BP as it is associated with larger fluctuations in intrathoracic pressure. Of interest, fluctuations in HR across the respiratory cycle increase to its maximum around a breathing frequency of 0.10 Hz (6 breaths per minutes),^{60,61,94} which is also the frequency around which spontaneous fluctuations in BP occur.

Thus, when breathing at 0.10 Hz, these spontaneous oscillations in BP are synchronized with the BP oscillations caused by deep breathing, thereby creating maximal fluctuations in HR and BP.⁶⁰ Slow breathing (SB) techniques, more specifically HRV/RSA biofeedback at this resonance frequency of about 0.10 Hz, can also increase BRS,⁶¹ which is the change of HR per 1 mm Hg change in BP. Therefore, it is conceivable that not only BP changes, but also higher BRS during SDB could modulate pain.

In summary, although direct central mechanisms could also play critical roles in the integration of pain and breathing, the baroreceptor system seems to play an essential role in the

relationship between cardiovascular, respiratory activity, and pain dampening through the cardiovascular or central branch of the system. The exact role and (inter)actions of the central branch of the baroreceptor system remain unclear, however. First, many mentioned neuroanatomical regions seem directly or indirectly involved in modulating a large number of physiological actions. Second, multiple conditions and modulating factors seem to determine the baroreceptor-mediated hypoalgesic effects in a rather complex way. Last but not least, other central mechanisms such as endogenous opioids, noradrenergic ascending and descending systems, as well as placebo or distraction effects cannot be excluded, and may contribute importantly to the overall respiratory hypoalgesic effect.

4.2. Experimental studies

Despite the popularity of SDB as a main component of many nonpharmacologic pain management interventions, experimental studies on the effect and underlying mechanism of SDB were

lacking until recently. We could identify 9 studies in the last 5 years that investigated the impact of breathing on different types of pain (electrical, mechanical pressure, and thermal pain) in an experimental setting. From these 9 studies (**Table 4**), 3 investigated whether pain differs between inspiration vs expiration,^{3,53,62} whereas 6 studies focused on the effect of SB (low frequency) on pain in comparison with normal or higher frequencies of breathing.^{3,12,18,62,99,100}

Arsenault et al. observed lower pain during inspiration compared with expiration,⁴ whereas Iwabe et al.⁵³ reported opposite findings and Martin et al.⁶² found no difference in pain between both respiratory phases. Taken together, the existing studies indicate there is no (consistent) effect of respiratory phase on pain.

Regarding the question whether SDB in particular could reduce pain, Chalaye et al.¹⁸ were likely the first to address this with an experimental study. In their study, participants reported significantly higher thermal pain threshold and tolerance (1°C on average) during SDB (6 breath per minutes) and HR biofeedback breathing compared with baseline. Fast paced breathing (16 breath per minutes) showed no effect compared with SDB. Likewise, Zautra et al.⁹⁹ (2010) reported an overall reduction in pain ratings in healthy individuals during SB, but not in patients with fibromyalgia. In 2012, Martin et al.⁶² measured both the nociceptive flexion reflex and self-reported pain during a SB task. Pain, but not the nociceptive flexion reflex, was significantly reduced during SB compared with normal and fast breathing. However, in a study with a similar design, Arsenault et al.³ could not replicate this finding. In a recent study, Botha et al. investigated the effect of SB on interoceptive pain sensitivity in the esophageal region. They showed that SB compared with nonpaced breathing hinders the development of esophageal

hypersensitivity after infusion of acid in the region.¹² Finally, the study by Busch et al. investigated a possible role of relaxation in the effect of SB on pain. These authors compared pain thresholds between “attentive” SDB (respiratory feedback provided by a computer) and “relaxing” SDB (verbal instruction by experimenter). Pain thresholds were significantly increased during relaxing SDB but not during attentive SDB.¹⁵

4.2.1. Discussion

Among the studies that have experimentally investigated^{3,12,18,62,99,100} the effect of SB on pain, 4 of the 6 studies found SB to significantly reduce pain. One of the 2 studies found that SDB also reduced the nociceptive reflex. One study found only relaxing instructions to be effective¹⁵ and in another study it was observed that breath-holding reduces pain. Overall, the findings are not very consistent, and we could not detect any obvious and systematic methodological difference between the studies that observed and those that failed to observe respiratory hypoalgesia. Therefore, an important challenge for future research will be to identify the critical conditions under which SDB can and cannot produce such “respiratory hypoalgesia.” It is evident that a deeper understanding of underlying mechanisms should be a focus in research on the conditions and boundaries of the respiratory hypoalgesia effect. Of importance, the studies that have investigated the effects of SDB on pain not only yield inconsistent findings, they also have assumed quite different mechanisms that could contribute to pain reduction. Behavioral modulators that have been studied or hypothesized to underlie respiratory hypoalgesia include relaxation,¹⁵ distraction from pain,¹⁸ and expectation.⁹⁹ The available evidence is scarce, but supports the idea that both relaxation and distraction may

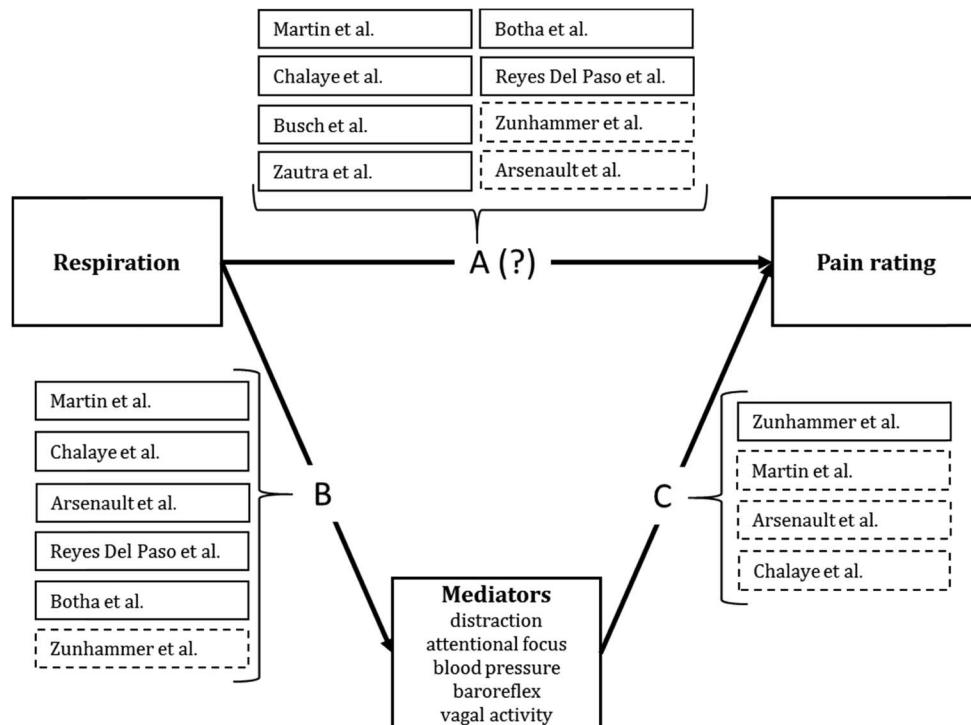


Figure 2. Diagram summarizing the experimental studies which focused on the direct (A) and indirect (B and C) associations between respiration and pain. In the indirect pathway (B and C), other psychological/physiological mechanisms mediate the analgesic effect of respiration. Solid-line boxes indicate that the association was observed for the specified link, whereas dashed-line boxes indicate a lack of evidence for the association. No study could provide evidence for both parts of the indirect association link.

Table 5
Overview of clinical studies.

Author	Year	Sample size	Participants type of pain	Comparisons	Breathing technique	Intervention combination*	Intervention duration	Finding: effective?
Miller ⁶⁵	1987	15	Coronary bypass surgery	Pre/post study	Abdominal deep SB	N	Short time effect	"yes," but no P value reported
Yildirim and Sahin ⁹⁷	2004	40; E = 20, C = 20	Labour pain	C: no intervention, E: breathing technique	Slow deep breathing, rapid shallow breathing, pant-blown breathing	Y	Short time effect	Yes
Agarwal et al. ¹	2005	75, 25 per group	Venous cannulation pain before elective surgery	C: control, V: valsalva, B: press a rubber ball	Valsalva manoeuvre	N	20 s	Yes
Friesner et al. ³⁸	2006	40; E = 19, C = 21	Chest tube removal pain after heart surgery	C: opioid, E: opioid + deep SB breathing	Slow nose inhaling and slow mouth exhaling	N	immediate + 15 min	Yes
Downey and Zun ²¹	2009	159; C = 84, E = 75	All type (emergency department) breathing	C: medication, E: medication + deep breathing	SB with meditation and focus on breathing	Y	Short time effect	No
Kapitza et al. ⁵⁵	2010	42; E = 21, C = 21	Chronic low back pain	C: placebo biofeedback, E: biofeedback breathing	Respiratory biofeedback	Y	30 min for 15 d	No
Park et al. ⁷¹	2013	64; E = 34, C = 30	Burn patients	C: medication, E: breathing and medication	Slow abdominal with 2:4 inhalation/ exhalation ratio	N	3 sessions	Yes
Elkrem et al. ³⁶	2014	70	Children with cancer	Pre/post study, breathing exercise	Not specified	N	1 session	Yes

* Intervention combination refers to only breathing technique (N) or breathing in combination with other relaxation techniques (Y).

C, control; E, experimental or intervention group; SB, slow breathing.

contribute to respiratory hypoalgesia, at least to some extent. However, further studies that investigate and manipulate expectations, attention, or stress levels during instructed breathing are required to understand and evaluate their relative importance in pain reduction during instructed SDB. Physiological variables that have been proposed or investigated as a potential modulator of respiratory hypoalgesia mainly include vagal activity or tone,^{18,62,99} RSA,³ and baroreflex activity.⁷⁸ Thus, consensus seems to exist among many authors on the idea that SDB modulates pain perception indirectly throughout cardiovascular/autonomic changes that accompany SDB.

Figure 2 depicts the triangular associations between pain, SDB, and potential mediators (behavioral/physiological) that have been proposed in the reviewed literature. In addition, it summarizes the available evidence for each of the associations based on the studies listed in **Table 4**. The cardiovascular effects of SDB have been described elsewhere,^{7,48,49,91} and have been replicated in the studies on respiratory hypoalgesia (association "B" in **Fig. 2**). However, there is currently no clear evidence for a moderating, mediating, or causal role of these autonomic modulators in respiratory hypoalgesia. Indeed, a few studies have looked at, but failed to find a correlation between the magnitude of the respiratory hypoalgesia effect on the one hand, and the cardiovascular changes accompanying SDB on the other hand.^{18,62} In a similar vein, observing that respiratory hypoalgesia is abolished by vagal blockade¹² does not necessarily mean that efferent vagal activity (or: vagal tone) is causing the observed antinociceptive effects of SDB. Both vagal activity and respiratory hypoalgesia may well be a "read-out" of other, correlated central processes, without necessarily implying causation. In conclusion, many studies have shown that SDB is accompanied by increases in cardiac vagal tone or RSA, but failed to critically show or to investigate to which extent the respiratory hypoalgesia effect depends on such cardiovascular changes.

4.3. Clinical studies

Many relaxation and meditation techniques include instructions to alter one's breathing pattern. This might be a reasonable approach because of the functional interactions between respiration, cardiovascular activity, and pain regulatory system.¹⁴ However, only a limited number of clinical studies have explicitly and specifically addressed the effects of breathing as an intervention technique or have attempted to study its effects independently from other intervention components. We identified only 8 studies in which breathing was the only or a main component of a clinical intervention aimed at reducing pain (**Table 5**).

One older study (1987) explored the effect of a deep breathing relaxation technique on postoperative pain, BP, HR, respiration rate, and muscle tension in patients who underwent coronary artery bypass surgery.⁶⁵ Although the published study fails to report statistics, the author concludes that slow rhythmic breathing resulted in a significant reduction in pain, BP, HR, respiration rate, and muscle tension. In another study on labor pain, Yıldırım and Sahin⁹⁷ investigated the effect of a combination of 3 breathing techniques (slow deep inhalation at the latent phase of delivery, rapid shallow breathing in the active phase, and pant-blown abdominal breathing in the second stage of labor) plus skin massage. Compared with a control group receiving no intervention, the group of women who received the intervention reported less pain.

The effects of instructed deep breathing during painful procedures have been addressed in 2 other studies. Friesner

et al. studied pain associated with chest tube removal (a flexible catheter that is inserted through the chest wall into the pleural space, to remove air or fluid from the intrathoracic space). The control group received an opioid, whereas the experimental group received an additional deep breathing intervention during the painful procedure, which caused significantly lower pain reports after and up to 15 minutes later of tube removal compared with control group.³⁸ In the study by Park et al.,⁷¹ SDB was found to reduce the pain associated with changing dressing in burn patients. Also, Elkreem et al.³⁶ found a significant decrease of pain after a breathing exercise in children with cancer pain. In contrast to these positive findings, Downey and Zun²¹ found no effect of instructed deep breathing on pain in patients who consulted at an emergency department with different types of pain as the principal complaint.

In the study by Kapitza et al., patients with chronic low back pain performed a daily 30-minute breathing exercise, making use of a respiratory biofeedback portable device. The intervention group received contingent feedback of their slow deep abdominal breathing signal, whereas the control group received placebo (noncontingent) feedback of a constant signal with a rate of 8 breaths per minute. Pain levels did not differ significantly between both groups, although the pain reduction in the experimental group was more pronounced when comparing pain levels before with those of 3 months after the intervention.⁵⁵

4.3.1. Discussion

The majority of the clinical studies reviewed (6 of the 8, or 75%) report a beneficial effect of some type of breathing intervention on pain. Although these numbers are promising, a research bias (experimenter bias and patients' expectation) towards positive findings could be at play here. In addition, 3 of the reviewed studies did not apply the breathing technique independently from other potentially active therapeutic ingredients such as relaxation, massage, listening to the relaxing sound of the sea, meditation, etc.^{21,55,97} In those studies, it is not clear how much each of the different interventions contributed to the pain reduction, or, whether the breathing intervention contributed to the effect at all.

Several other factors in the reviewed clinical studies render it difficult to draw a general conclusion on the effectiveness of breathing interventions, as well as on the mechanisms that may have caused a hypoalgesic effect. First, it is evident that the quality, type, and intensity of pain studied are very heterogeneous in the reviewed clinical studies. Slow breathing exercises are unlikely to have the same outcome in different conditions including burn pain,⁷¹ musculoskeletal pain,⁵⁵ emergency acute pain,²¹ or labor pain.⁹⁷ For several studies, the diversity of pain seems considerable even within a patient sample of the same study. For example, in the study by Downey et al.,²¹ a heterogeneous group of patients were recruited in an emergency situation. In the study by Friesner et al.,³⁸ the chest tube removal occurred at 3 different hospital sites, and also the pain experienced by burn patients during change of dressing in the study by Park et al.⁷¹ may likely have varied considerably from one patient to another because of degree, site, and cause of burning. Applying exactly the same protocol for every patient could be a challenge given such diversity, which may further add to uncontrolled error variance hindering statistical inference. Obviously, there is a tension between scientific and clinical goals in this respect. Scientifically, future clinical studies would benefit from more controlled inclusion criteria, leading to more homogeneous patient groups in terms of pain and illness characteristics, and from statistically controlling remaining variation caused by

diversity in the sample. However, clinically it may not be feasible to control for every source of variance, and the clinical relevance of breathing techniques for pain conditions would be limited if the effects would not emerge robust across various clinical conditions.

A second factor limiting the conclusions that can be drawn from the studies summarized in **Table 5** is that the applied breathing patterns seem rather diverse. Slow abdominal breathing seems to be the most commonly applied technique (5 of the 8 studies,^{21,55,65,71,97}), but often the breathing technique is poorly described.^{21,36,65} For example, several studies remain unclear as to whether or not patients received explicit instructions regarding respiratory frequency.^{21,36,65} It is recommendable that future clinical studies standardize and carefully report the applied breathing technique, as well as how it is instructed to the patients. Breathing patterns can be characterized in a basic way by specifying the targeted timing (breathing frequency, inspiration/expiration ratio) and volume (breathing depth) components of a breathing cycle. Another relevant characteristic that should be reported is whether patients received specific instructions to breathe through the nose vs mouth, or to breathe abdominally. In addition, monitoring the patients' breathing (using pneumography or respiratory belt) could be valuable for several reasons. First, it allows monitoring how well patients comply with the instructed breathing pattern. Second, recording the respiratory signal allows the identification of compensatory changes in breathing depth that often are associated with SB. For example, to maintain a stable level of ventilation, an increased breathing depth often compensates reduced breathing frequency. It is conceivable that breathing depth, rather than respiratory frequency may play a key role in pain reduction, as deep breathing and breath-holding after a deep inhalation could activate the antinociceptive effects of baroreceptor stimulation^{29,30} and concomitant increases in vagal activation.^{14,88} An increase in inspiratory flow and volume has been described as a reaction to acute pain,^{24,51,52,56,79} and may be functional to reduce pain. Voluntary deep breaths may be able to reduce pain as well. Consistent with this idea, the valsalva maneuver, a forceful attempted exhalation against a closed airway, has been found to decrease acute pain.¹

Third, clinical studies may want to better control for expectation, demand, and distraction effects caused by a breathing intervention. Anecdotally, many persons seem to assume and accept that SB is relaxing and helpful to alleviate pain. In situations where a patient is in pain and a clinician offers a strategy that is announced to be helpful, such expectation effects may grow stronger and also demand effects may easily arise. In the studies mentioned above (**Table 5**), the experimenters were not blinded to the intervention, whereas some authors acknowledged this as a limitation of their study.^{37,64} Although it may be unfeasible to blind the therapist and experimenter to the intervention, reducing or documenting expectation bias can be achieved in clinical studies. Besides carefully designing and standardizing the instructions, one can also measure patients' expectations about the effectiveness of the to-be-delivered intervention, or design studies in which expectations are experimentally manipulated.

Aside from expectation and demand effects, any breathing task demands attention and can, therefore, distract from the pain. Also, the therapist is likely a source of distraction, as patients receiving the breathing intervention receive more attention and care from the therapist compared with control groups who often only receive conventional medical treatment.^{21,38,65,71,97} Some of the reviewed clinical studies implemented commendable attempts to control for effects of distraction by giving a distracting

task to the control group, such as placebo biofeedback,⁵⁵ sham breathing (counting the breath),¹² or pressing a rubber ball as a distracting task.¹

In summary, several clinical studies suggest a beneficial effect of SDB on pain, but more well-documented studies on homogeneous patient groups that control for expectancy, demand characteristics, and distraction effects are clearly needed.

5. General conclusions and directions for future research

The outcomes of studies on the association between respiration and pain were presented and psychophysiological mechanisms underlying these associations discussed. Pain and respiration are integrated in a complex way, which makes research advancements challenging and ambitious. Acute pain augments respiratory frequency, flow, and volume, but the clinical impact of chronic pain on respiration remains unclear and needs consideration in future studies. The majority of clinical studies document the usefulness of breathing techniques, especially SDB to alleviate pain, but experimental studies have not consistently establish such a pain dampening effect, nor have studies revealed the precise mechanism that would produce such effect. The experiments on respiratory-related hypoalgesia proposed diverse mechanisms but did not yield consistent findings. Although it would be clinically useful to understand respiratory hypoalgesia, the evidence currently does not support a direct causal association between respiration and pain. A more indirect mediation through cardiovascular and autonomic changes is plausible. Nevertheless, several questions need to be answered. (1) Do psychobehavioral mechanisms such as attentional focus, distraction, expectation, and self-control caused by instructed breathing reduce pain? (2) Can SDB produce analgesic effects beyond those produced by psychobehavioral mechanism? (3) Is cardiovascular activity—and baroreceptor activation in particular—a mediating link between SDB and pain? What is the role of the central branch of the baroreceptor system in relation to pain? What are the critical conditions and modulating factors for a baroreceptor-mediated hypoalgesic effect? (4) Which other central mechanisms may produce respiratory hypoalgesia and what can we learn from the animal literature in this respect? Other possible mechanisms cannot be excluded, and may be part of an overall mechanism.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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