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Pain and respiration: a systematic review

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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 was retrieved and analyzed. These articles were classified into four 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, asthma, and pain. Specifically in controlling pain, paced slow deep breathing 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 Mazick [37] 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 three 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, slow deep breathing 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 papers [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 the present review was to summarize the literature on the bidirectional association between pain and respiration in both clinical (pain patients), and experimental (healthy people) studies. The published articles can be categorized into four 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 four 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 Disseminations [17] 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 published studies in online databases between 1984 and 2015, covering the time 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 keyword 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 keyword 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 - December 2015. As such, 1,755 and 3,477 records were retrieved from MEDLINE and EMBASE respectively (Figure 1, identification). Duplications (1,370 records) were removed, after which the titles and abstracts of the resulting set of studies (3,477 records) were screened for relevance by the first author (H.J.), (Figure 1, screening). The main reasons for exclusion were: (1) studies that focused on cardiovascular and blood pressure 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. Out 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 (see Table 1 and Figure 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 was included in the literature review. The 31 eligible articles were categorized into four 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.

<< Please Insert Table 1 about here >>

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The first author (H.J.) extracted the following variables for both types of experimental studies: publication year, sample size, participants, type of pain, critical comparison 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, comparison 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/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 four 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 nine experimental studies summarized in Table 2, four studied the effect of a phasic, short-lasting cutaneous pain stimulus (electrocutaneous stimulation, or surgical incision of the 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].

<<<< Please Insert Table 2 about here >>>>

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 min 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 and/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 and/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 three studies (Table 3) assessing respiratory rate during a painful procedure all observed an increased respiratory rate during pain [41,54,74,75], though not necessarily in each individual [74,75]. One study also observed an

increased asynchrony with a ventilator during a painful compared to a non-painful procedure [41].

The study of Glynn et al. (1981) was the only study in which the development of a clinical pain assessment tool was not the primary aim; they documented hyperventilation in chronic pain patients, which diminished again after pain relief [46]. 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].

<<<< Please Insert Table 3 about here >>>>

3.3. Discussion

Several authors have proposed that increased ventilation / hyperventilation during acute pain reflects the respiratory component of the fight-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], though 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 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 appear 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 non-verbal individuals [41,54,72,74,75].

4. Effects of respiration on pain

Many researchers and clinicians assume that slow deep breathing 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, prior to 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

The baroreflex system

The baroreflex is a homeostatic, rapid negative feedback loop adjusting heart rate and blood pressure 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 blood pressure (BP) and relay this information (via the vagal and glossopharyngeal nerve) to neurons of the nucleus of the solitary tract (NTS) located in the medulla [28]. The NTS projects to vagal/parasympathetic and sympathetic brains stem nuclei (vagal: nucleus ambiguus, dorsal motor nucleus; sympathetic: rostral ventrolateral medulla). Efferents from these nuclei can increase (sympathetic) or decrease (vagal) heart rate. Thus, when BP increases (expansion of the arterial wall), baroreceptors are stimulated causing a decrease in heart rate (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 BRS and clinical implications, we refer to La Rovere, Pinna & Raczak (2008) [58].

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 (PAG), nucleus raphe magnus, locus coeruleus, anterior cingulate cortex, hypothalamus and thalamus [28]. Via 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.

Pain and Blood pressure

The literature describes an inverse correlation between blood pressure (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 blood pressure-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 versus non-artificial) [32], the emotional state of participants [66], and the intensity of the applied pain stimuli [77] can determine the anti-nociceptive 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].

Respiratory sinus arrhythmia (RSA)

RSA refers to oscillations in heart rate along the breathing cycle: heart rate increases during inspiration and decreases again during expiration. RSA is a major source of heart rate 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 blood pressure drops because of a decreased stroke volume, resulting in a heart rate increase through the baroreflex [69,87]. During expiration, the reverse occurs: blood pressure increases, activating baroreceptors that trigger a vagally mediated decrease in heart rate [50]. Variations in cardiac filling caused by changes in intrathoracic pressure are largely responsible for this blood pressure 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 heart rate during expiration, and making heart rate more variable across the respiratory cycle. Importantly, the magnitude of RSA (and HRV) depends on the respiratory pattern as stronger fluctuations in heart rate across the respiratory cycle have been observed with slower and/or deeper breathing volume [84]. When one slows down 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. Interestingly, fluctuations in heart rate 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 blood pressure occur.

Thus, when breathing at 0.10 Hz, these spontaneous oscillations in blood pressure are synchronized with the blood pressure oscillations caused by deep breathing, thereby creating maximal fluctuations in heart rate and blood pressure [60]. Slow breathing techniques, more specifically HRV/RSA biofeedback at this resonance frequency of about 0.10 Hz, can also increase baroreflex sensitivity (BRS) [61], which is the change of heart rate per 1 mmHg change in blood pressure. Therefore, it is conceivable that not only blood pressure changes, but also higher BRS during slow deep breathing 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 and/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 appear 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 slow deep breathing (SDB) as a main component of many non-pharmacologic pain management interventions, experimental studies on the effect and underlying mechanism of SDB were lacking until recently. We could identify nine studies in the last five years that investigated the impact of breathing on different types of pain (electrical, mechanical pressure, and thermal pain) in an experimental setting. From these nine studies (see Table 4), three investigated whether pain differs between inspiration versus expiration [3,53,62], whereas six studies focused on the effect of slow breathing (low frequency) on pain in comparison with normal or higher frequencies of breathing [3,12,18,62,99,100].

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Arsenault and colleagues observed lower pain during inspiration compared to expiration [4], whereas Iwabe and colleagues reported opposite findings [53] and Martin et al. found no difference in pain between both respiratory phases [62]. 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 and colleagues [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 slow deep breathing (6 BPM) and HR biofeedback breathing compared to baseline. Fast paced breathing (16 BPM) showed no effect compared to SDB. Likewise, Zautra and colleagues (2010) reported an overall reduction in pain ratings in healthy individuals during slow breathing, but not in fibromyalgia patients [99]. In 2012, Martin and colleagues measured both the nociceptive flexion reflex (NFR) and self-reported pain during a slow breathing task [62]. Pain, but not the NFR was significantly reduced during slow breathing compared to normal and fast breathing. However, in a study with a similar design, Arsenault and colleagues could not replicate this finding [3]. In a recent study, Botha and colleagues investigated the effect of slow breathing on interoceptive pain sensitivity in the esophageal region. They showed that slow breathing compared to non-paced breathing hinders the development of esophageal hypersensitivity after infusion of acid in the region [12]. Finally, the study by Busch and colleagues investigated a possible role of relaxation in the effect of slow breathing 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 slow breathing on pain, four out of the six studies found slow breathing to significantly reduce pain. One out of two studies found that SDB also reduced the nociceptive reflex. One study found only *relaxing* instructions to be effective [15] 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 slow deep breathing 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. Importantly, 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 contribute to respiratory hypoalgesia, at least to some extent. However, further studies that investigate and manipulate expectations, attention and/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], respiratory sinus arrhythmia (RSA) [3], and baroreflex activity [78]. Thus, consensus seems to exist among many authors on the idea that slow deep breathing modulates pain perception indirectly throughout cardiovascular/autonomic changes that accompany slow deep breathing.

<<<< please Insert Figure 2 about here >>>>

Figure 2 depicts the triangular associations between pain, slow deep breathing 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 slow deep breathing have been

described elsewhere [7,48,49,91], and have been replicated in the studies on respiratory hypoalgesia (association 'B' in Figure 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 slow deep breathing on the other hand [18,62]. In a similar vein, observing that respiratory hypoalgesia is abolished by vagal blockade [12] 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 slow deep breathing is accompanied by increases in cardiac vagal tone or respiratory sinus arrhythmia, 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 and/or have attempted to study its effects independently from other intervention components. We identified only eight studies in which breathing was the only or a main component of a clinical intervention aimed at reducing pain (see Table 5).

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One older study (1987) explored the effect of a deep breathing relaxation technique on postoperative pain, blood pressure, heart rate, 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, blood pressure, heart rate, respiration rate and muscle tension. In another study on labor pain, Yilidrim and Sahin investigated the effect of a combination of three breathing techniques (slow deep inhalation at the latent phase of delivery, rapid shallow breathing in the active phase, and pant-blow abdominal breathing in the second stage of labor) plus skin massage [97]. Compared to 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 two other studies. Friesner and colleagues 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 while 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 to control group [38]. In the study by Park and colleagues, slow deep breathing was found to reduce the pain associated with changing dressing in burn patients [71]. Also, Elkreem and colleagues found a significant decrease of pain after a breathing exercise in children with cancer pain [36]. In contrast to these positive findings, Downey and Zun [21] 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 and colleagues, patients with chronic low back pain performed a daily 30 minutes 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 (non-contingent) 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 out of 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, three 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 is 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 of Downey et al., a heterogeneous group of patients were recruited in an

emergency situation [21]. In the study of Friesner et al., the chest tube removal occurred at three different hospital sites [38], and also the pain experienced by burn patients during change of dressing in the study of Park and colleagues may likely have varied considerably from one patient to another due to degree, site and cause of burning [71]. 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 out of 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 versus mouth, or to breath 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 slow breathing. 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 following a deep inhalation could activate the anti-nociceptive 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 (VM), 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 slow breathing 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 (see Table 5), the experimenters were not blinded to the intervention, while 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 to 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.

5. General conclusion 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 make 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 slow deep breathing 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 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 psycho-behavioral mechanisms such as attentional focus, distraction, expectation and self-

control caused by instructed breathing reduce pain? 2) Can slow deep breathing produce analgesic effects beyond those produced by psycho-behavioral mechanism? 3) Is cardiovascular activity – and baroreceptor activation in particular – a mediating link between slow deep breathing and pain? What is the role of the central branch of the baroreceptor system in relation to pain? What are the critical conditions and/or 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.

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7. References:

[1] Agarwal A, Sinha PK, Tandon M, Dhiraaj S, Singh U. Evaluating the efficacy of the valsalva maneuver on venous cannulation pain: a prospective, randomized study. Anesth. Analg. 2005;101:1230–2.

[2] Allen MT, Sherwood A, Obrist PA. Interactions of Respiratory and Cardiovascular Adjustments to Behavioral Stressors. Psychophysiology 1986;23:532–41.

[3] Arsenault M, Ladouceur A, Lehmann A, Rainville P, Piché M. Pain modulation induced by respiration: Phase and frequency effects. Neuroscience 2013;252:1–11.

[4] Bernardi L, Gabutti A, Porta C, Spicuzza L. Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. J. Hypertens. 2001;19:2221–9.

[5] Bernardi L, Porta C, Spicuzza L, Bellwon J, Spadacini G, Frey AW, Yeung LY, Sanderson JE, Pedretti R, Tramarin R. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. Circulation 2002;105:143–5.

[6] Bernardi L, Wdowczyk-Szulc J, Valenti C, Castoldi S, Passino C, Spadacini G, Sleight P. Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability. J. Am. Coll. Cardiol. 2000;35:1462–9.

[7] Berntson GG, Cacioppo JT, Quigley KS. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. Psychophysiology 1993;30:183–96.

[8] Biaggioni I. Sympathetic control of the circulation in hypertension: lessons from autonomic disorders. Curr. Opin. Nephrol. Hypertens. 2003;12:175–80.

[9] Bogaerts K, Hubin M, Van Diest I, De Peuter S, Van Houdenhove B, Van Wambeke P, Crombez G, Van den Bergh O. Hyperventilation in patients with chronic fatigue syndrome: the role of coping strategies. Behav. Res. Ther. 2007;45:2679–90.

[10] Boiten F a. The effects of emotional behaviour on components of the respiratory cycle. Biol. Psychol. 1998;49:29–51.

[11] Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain 1996;64:123–8.

[12] Botha C, Farmer AD, Nilsson M, Brock C, Gavrila AD, Drewes AM, Knowles CH, Aziz Q. Preliminary report: modulation of parasympathetic nervous system tone influences oesophageal pain hypersensitivity. Gut 2015;64:611–7.

[13] Bruehl S, Carlson CR, McCubbin JA. The relationship between pain sensitivity and blood pressure in normotensives. Pain 1992;48:463–7.

[14] Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. Neurosci. Biobehav. Rev. 2004;28:395–414.

[15] Busch V, Magerl W, Kern U, Haas J, Hajak G, Eichhammer P. The effect of deep and slow breathing on pain perception, autonomic activity, and mood processing—An experimental study. Pain Med. 2012;13:215–28.

[16] Cacioppo JT, Tassinary LG, Berntson G eds. Handbook of Psychophysiology. 3 edition. Cambridge England□; New York: Cambridge University Press, 2007.

[17] Centre for Reviews and Dissemination ed. CRD's guidance for undertaking reviews in healthcare. 3. ed. York: York Publ. Services, 2009.

[18] Chalaye P, Goffaux P, Lafrenaye S, Marchand S. Respiratory effects on experimental heat pain and cardiac activity. Pain Med. Malden Mass 2009;10:1334–40.

[19] Dampney RAL, Coleman MJ, Fontes MAP, Hirooka Y, Horiuchi J, Li Y-W, Polson JW, Potts PD, Tagawa T. Central mechanisms underlying short-and long-term regulation of the cardiovascular system. Clin. Exp. Pharmacol. Physiol. 2002;29:261–8.

[20] D'Antono B, Ditto B, Sita A, Miller SB. Cardiopulmonary baroreflex stimulation and blood pressure-related hypoalgesia. Biol. Psychol. 2000;53:217–31.

[21] Downey LV a, Zun LS. The effects of deep breathing training on pain management in the emergency department. South. Med. J. 2009;102:688–92.

[22] Dudley DL, Holmes TH, Martin CJ, Ripley HS. Changes in respiration associated with hypnotically induced emotion, pain, and exercise. Psychosom. Med. 1964;26:46–57.

[23] Dudley DL, Martin CJ, Verhey JW, Holmes TH. Response to noxious stimulation as an indication of successful psychologic defense mechanisms in the diffuse obstructive pulmonary syndrome. Am. Rev. Respir. Dis. 1969;100:572–4.

[24] Duranti R, Pantaleo T, Bellini F, Bongianni F, Scano G. Respiratory responses induced by the activation of somatic nociceptive afferents in humans. J. Appl. Physiol. 1991;71:2440–8.

[25] Duschek S, Dietel A, Schandry R, Reyes Del Paso GA. Increased baroreflex sensitivity and reduced cardiovascular reactivity in individuals with chronic low blood pressure. Hypertens. Res. 2008;31:1873–8.

[26] Duschek S, Mück I, Reyes Del Paso GA. Relationship between baroreceptor cardiac reflex sensitivity and pain experience in normotensive individuals. Int. J. Psychophysiol. 2007;65:193–200.

[27] Duschek S, Muckenthaler M, Werner N, del Paso GAR. Relationships between features of autonomic cardiovascular control and cognitive performance. Biol. Psychol. 2009;81:110–7.

[28] Duschek S, Werner NS, Reyes del Paso GA. The behavioral impact of baroreflex function: A review. Psychophysiology 2013;50:1183–93.

[29] Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CH. Central effects of baroreceptor activation in humans: attenuation of skeletal reflexes and pain perception. Proc. Natl. Acad. Sci. USA. 1994;91:6329–33.

[30] Dworkin BR, Filewich RJ, Miller NE, Craigmyle N, Pickering TG. Baroreceptor activation reduces reactivity to noxious stimulation: implications for hypertension. Science 1979;205:1299–1301.

[31] Eckberg DL. The human respiratory gate. J. Physiol. 2003;548:339–52.

[32] Edwards L, McIntyre D, Carroll D, Ring C, France CR, Martin U. Effects of artificial and natural baroreceptor stimulation on nociceptive responding and pain. Psychophysiology 2003;40:762–9.

[33] Edwards L, McIntyre D, Carroll D, Ring C, Martin U. The human nociceptive flexion reflex threshold is higher during systole than diastole. Psychophysiology 2002;39:678–81.

[34] Edwards L, Ring C, McIntyre D, Carroll D. Modulation of the human nociceptive flexion reflex across the cardiac cycle. Psychophysiology 2001;38:712–8.

[35] Elbert T, Rockstroh B, Lutzenberger W, Kessler M, Pietrowsky R, Birbaumer N. Baroreceptor Stimulation Alters Pain Sensation Depending on Tonic Blood Pressure. Psychophysiology 1988;25:25–29.

[36] Elkreem HMA. Effect of Breathing Exercise on Respiratory Efficiency and Pain Intensity among Children Receiving Chemotherapy. J. Educ. Ldots 2014;5:18–32.

[37] Finesinger J, Mazick S. The effect of a painful stimulus and its recall upon respiration in psychonerotic patients. Psychosom. Med. 1940;2:333–368.

[38] Friesner SA, Curry DM, Moddeman GR. Comparison of two pain-management strategies during chest tube removal: relaxation exercise with opioids and opioids alone. Heart Lung J. Crit. Care 2006;35:269–76.

[39] Gardner WN. The pathophysiology of hyperventilation disorders. Chest 1996;109:516–34.

[40] Gautier H. Control of the pattern of breathing. Clin. Sci. Lond. Engl. 1979 1980;58:343–8.

[41] Gélinas C, Johnston C. Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin. J. Pain 2007;23:497–505.

[42] Gerritsen J, TenVoorde BJ, Dekker JM, Kostense PJ, Bouter LM, Heethaar RM. Baroreflex sensitivity in the elderly: influence of age, breathing and spectral methods. Clin. Sci. Lond. Engl. 1979 2000;99:371–381.

[43] Ghione S. Hypertension-Associated Hypalgesia Evidence in Experimental Animals and Humans, Pathophysiological Mechanisms, and Potential Clinical Consequences. Hypertension 1996;28:494–504.

[44] Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD. Brain systems for baroreflex suppression during stress in humans. Hum. Brain Mapp. 2012;33:1700–16.

[45] Gilbert C. Hyperventilation and the body. Accid. Emerg. Nurs. 1999;7:130–40.

[46] Glynn CJ, Lloyd JW, Folkhard S. Ventilatory response to intractable pain. Pain 1981;11:201–11.

[47] Green D a, Bowtell J, Turner DL. Electrical percutaneous tibial stimulation modulates within-a-breath respiratory drive in man. Respir. Physiol. Neurobiol. 2008;161:214–7.

[48] Grossman E, Grossman A, Schein MH, Zimlichman R, Gavish B. Breathing-control lowers blood pressure. J. Hum. Hypertens. 2001;15:263–9.

[49] Grossman P, Taylor EW. Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. Biol. Psychol. 2007;74:263–85.

[50] Guz A, Innes JA, Murphy K. Respiratory modulation of left ventricular stroke volume in man measured using pulsed Doppler ultrasound. J. Physiol. 1987;393:499–512.

[51] Hotta N, Sato K, Sun Z, Katayama K, Akima H, Kondo T, Ishida K. Ventilatory and circulatory responses at the onset of exercise after eccentric exercise. Eur. J. Appl. Physiol. 2006;97:598–606.

[52] Hotta N, Yamamoto K, Katayama K, Ishida K. The respiratory response to passive and active arm movements is enhanced in delayed onset muscle soreness. Eur. J. Appl. Physiol. 2009;105:483–91.

[53] Iwabe T, Ozaki I, Hashizume A. The respiratory cycle modulates brain potentials, sympathetic activity, and subjective pain sensation induced by noxious stimulation. Neurosci. Res. 2014:1–13.

[54] Kabes AM, Graves JK, Norris J. Further Validation of the Nonverbal Pain Scale in Intensive Care Patients. Crit. Care Nurse 2009;29:59–66.

[55] Kapitza KP, Passie T, Bernateck M, Karst M. First Non-Contingent Respiratory Biofeedback Placebo versus Contingent Biofeedback in Patients with Chronic Low Back Pain: A Randomized, Controlled, Double-Blind Trial. Appl. Psychophysiol. Biofeedback 2010;35:207–17.

[56] Kato Y, Kowalski CJ, Stohler CS. Habituation of the early pain-specific respiratory response in sustained pain. Pain 2001;91:57–63.

[57] Kwekkeboom KL, Gretarsdottir E. Systematic review of relaxation interventions for pain. J. Nurs. Scholarsh. 2006;38:269–77.

[58] La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. Ann. Noninvasive Electrocardiol. Off. J. Int. Soc. Holter Noninvasive Electrocardiol. Inc 2008;13:191–207.

[59] Larsen PD, Tzeng YC, Sin PYW, Galletly DC. Respiratory sinus arrhythmia in conscious humans during spontaneous respiration. Respir. Physiol. Neurobiol. 2010;174:111–8.

[60] Lehrer PM, Vaschillo E, Vaschillo B. Resonant Frequency Biofeedback Training to Increase Cardiac Variability: Rationale and Manual for Training. Appl. Psychophysiol. Biofeedback 2000;25:177–191.

[61] Lehrer PM, Vaschillo E, Vaschillo B, Lu S-E, Eckberg DL, Edelberg R, Shih WJ, Lin Y, Kuusela TA, Tahvanainen KUO, Hamer RM. Heart Rate Variability Biofeedback Increases Baroreflex Gain and Peak Expiratory Flow: Psychosom. Med. 2003;65:796–805.

[62] Martin SL, Kerr KL, Bartley EJ, Kuhn BL, Palit S, Terry EL, DelVentura JL, Rhudy JL. Respiration-Induced Hypoalgesia: Exploration of Potential Mechanisms. J. Pain 2012;13:755–63.

[63] Masuda M, Dudley DL. Physiologic responses to noxious head stimuli. J. Psychosom. Res. 1968;12:205–14.

[64] Mehling WE, Hamel K a, Acree M, Byl N, Hecht FM. Randomized, controlled trial of breath therapy for patients with chronic low-back pain. Altern. Ther. Health Med. 2005;11:44–52.

[65] Miller KM. Deep Breathing Relaxation. AORN J. 1987;45:484–8.

[66] Mini a, Rau H, Montoya P, Palomba D, Birbaumer N. Baroreceptor cortical effects, emotions and pain. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 1995;19:67–77.

[67] Morgan EJ, Baidwan B, Petty TL, Zwillich CW. The effects of unanesthetized arterial puncture on PCO2 and pH. Am. Rev. Respir. Dis. 1979;120:795–8.

[68] Nishino T, Shimoyama N, Ide T, Isono S. Experimental pain augments experimental dyspnea, but not vice versa in human volunteers. Anesthesiology 1999;91:1633–8.

[69] Novak V, Novak P, de Champlain J, Le Blanc AR, Martin R, Nadeau R. Influence of respiration on heart rate and blood pressure fluctuations. J. Appl. Physiol. 1993;74:617–26.

[70] Parati G, Di Rienzo M, Bertinieri G, Pomidossi G, Casadei R, Groppelli A, Pedotti A, Zanchetti A, Mancia G. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension 1988;12:214–22.

[71] Park E, Oh H, Kim T. The effects of relaxation breathing on procedural pain and anxiety during burn care. Burns J. Int. Soc. Burn Inj. 2013:1–6.

[72] Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit. Care Med. 2001;29:2258–63.

[73] Pickering TG. Effects of stress and behavioral interventions in hypertension. Pain and blood pressure. J. Clin. Hypertens. Greenwich Conn 2003;5:359–61.

[74] Puntillo KA, Miaskowski C, Kehrle K, Stannard D, Gleeson S, Nye P. Relationship between behavioral and physiological indicators of pain, critical care patients' self-reports of pain, and opioid administration. Crit. Care Med. 1997;25:1159–66.

[75] Puntillo KA, Stannard D, Miaskowski C, Kehrle K, Gleeson S. Use of a pain assessment and intervention notation (P.A.I.N.) tool in critical care nursing practice: Nurses' evaluations. Heart Lung J. Acute Crit. Care 2002;31:303–14.

[76] Reis P. Cochrane review: relaxation and yoga may decrease pain during labour and increase satisfaction with pain relief, but better quality evidence is needed. Evid. Based Nurs. 2012;15:105–6.

[77] Reyes del Paso GA, Montoro C, Muñóz Ladrón de Guevara C, Duschek S, Jennings JR. The effect of baroreceptor stimulation on pain perception depends on the elicitation of the reflex cardiovascular response: Evidence of the interplay between the two branches of the baroreceptor system. Biol. Psychol. 2014;101:82–90.

[78] Reyes del Paso GA, Muñoz Ladrón de Guevara C, Montoro CI. Breath-Holding During Exhalation as a Simple Manipulation to Reduce Pain Perception. Pain Med. Malden Mass 2015;16:1835–41.

[79] Sarton E, Dahan A, Teppema L, Berkenbosch A, van den Elsen M, van Kleef J. Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. Anesthesiology 1997;87:289–96.

[80] Seers K, Carroll D. Relaxation techniques for acute pain management: a systematic review. J. Adv. Nurs. 1998;27:466–75.

[81] Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Psychol. Clin. Settings 2014;5:1040.

[82] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Systematic Reviews. 2015;4:1.

[83] Sitharamiah A. Outline of history of Yoga. Bull. Indian Inst. Hist. Med. Hyderabad 1980;10:15–22.

[84] Strauss-Blasche G, Moser M, Voica M, McLeod D, Klammer N, Marktl W. Relative Timing Of Inspiration And Expiration Affects Respiratory Sinus Arrhythmia. Clin. Exp. Pharmacol. Physiol. 2000;27:601–6.

[85] Suess WM, Alexander AB, Smith DD, Sweeney HW, Marion RJ. The effects of psychological stress on respiration: a preliminary study of anxiety and hyperventilation. Psychophysiology 1980;17:535–40.

[86] Sutherland RW, Drummond GB. Effects of surgical skin incision on respiration in patients anaesthetized with enflurane. Br. J. Anaesth. 1996;76:777–9.

[87] Toska K, Eriksen M. Respiration-synchronous fluctuations in stroke volume, heart rate and arterial pressure in humans. J. Physiol. 1993;472:501–12.

[88] Triedman JK, Saul JP. Blood pressure modulation by central venous pressure and respiration. Buffering effects of the heart rate reflexes. Circulation 1994;89:169–79.

[89] Van Diest I, De Peuter S, Devriese S, Wellens E, Van de Woestijne KP, Van den Bergh O. Imagined risk of suffocation as a trigger for hyperventilation. Psychosom. Med. n.d.;67:813–9.

[90] Van Diest I, Proot P, Van De Woestijne KP, Han JN, Devriese S, Winters W, Van Den Bergh O. Critical conditions for hyperventilation responses. The role of autonomic response propositions during emotional imagery. Behav. Modif. 2001;25:621–39.

[91] Van Diest I, Verstappen K, Aubert AE, Widjaja D, Vansteenwegen D, Vlemincx E. Inhalation/Exhalation Ratio Modulates the Effect of Slow Breathing on Heart Rate Variability and Relaxation. Appl Psychophysiol Biofeedback. 2014;39(3-4):171-80.

[92] Van Diest I, Winters W, Devriese S, Vercamst E, Han JN, Van de Woestijne KP, Van den Bergh O. Hyperventilation beyond fight/flight: respiratory responses during emotional imagery. Psychophysiology 2001;38:961–8.

[93] Van Roon AM, Mulder LJM, Althaus M, Mulder G. Introducing a baroreflex model for studying cardiovascular effects of mental workload. Psychophysiology 2004;41:961–981.

[94] Vaschillo E, Lehrer P, Rishe N, Konstantinov M. Heart rate variability biofeedback as a method for assessing baroreflex function: a preliminary study of resonance in the cardiovascular system. Appl. Psychophysiol. Biofeedback 2002;27:1–27.

[95] Wilhelm FH, Gevirtz R, Roth WT. Respiratory Dysregulation in Anxiety, Functional Cardiac, and Pain Disorders: Assessment, Phenomenology, and Treatment. Behav. Modif. 2001;25:513–45.

[96] Wren AA, Wright MA, Carson JW, Keefe FJ. Yoga for persistent pain: new findings and directions for an ancient practice. Pain 2011;152:477–80.

[97] Yildirim G, Sahin NH. The effect of breathing and skin stimulation techniques on labour pain perception of Turkish women. Pain Res. Manag. J. Can. Pain Soc. J. Société Can. Pour Trait. Douleur 2004;9:183–7.

[98] Zamir N, Maixner W. The relationship between cardiovascular and pain regulatory systems. Ann. N. Y. Acad. Sci. 1986;467:371–84.

[99] Zautra AJ, Fasman R, Davis MC, Craig ADB. The effects of slow breathing on affective responses to pain stimuli: an experimental study. Pain 2010;149:12–8.

[100] Zunhammer M, Eichhammer P, Busch V. Do cardiorespiratory variables predict the antinociceptive effects of deep and slow breathing? Pain Med. 2013;14:843–54.

Figures Captions:

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

Fig. 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 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 1: The systematic search in Medline and EMBASE databases. The keyword combination, number of articles retrieved, total and the article after duplication removed are shown. The total of 3477 publications found form both databases, after removing the duplications. language: English, population: humans, publication date: 1984 – December 2015

Database	Medline	EMBASE		After Duplication
Keyword combination	Retrieved	Retrieved	Total	removed
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

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 [24]	1991	14	Healthy	Painful electrical stimuli/ischemic pain	pre / post	insp. flow	increase
						insp. time	decrease
						resp. cycle time	decrease
Borgbjerg [11]	1996	10	Healthy	Tourniquet pain at calf	pre / post pain pre / post opioid	tidal volume	increase
						MV	
Sutherland [87]	1996	10	Under operation	Surgical incision	pre / post	tidal volume	increase
						insp. flow	increase
						insp. time	increase
Sarton et al [80]	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	increase
						exp. pause	increase
						tidal volume	increase
						MV	increase
						insp. flow	increase
Nishino [68]	1999	15	Healthy	Tourniquet pain at calf during 8 min	pre / during	insp. volume resp. rate end-tidal CO_2	increase increase decrease

				of loaded breathing		pressure	increase
Kato et al [56]	2001	10	Healthy	Infusion of saline into masseter muscle	baseline pain placebo	resp. rate	increase
						MV	increase
						insp. rate	increase
						exp. rate	increase
Green et al [47]	2008	16	Healthy	Sub-threshold and supra- threshold cutaneous electrical stimulation	inspiratory expiratory	insp. time	decrease if during insp.
						tidal volume	increase if during insp.
						insp. flow	increase if during insp.
Hotta et al [52]	2009	11	Healthy	DOMS	pre / post	tidal volume	increase
						MV	increase

Resp: respiratory; Insp: inspiratory; Exp.: expiratory; MV: minute ventilation; DOMS: Delayed onset muscle soreness

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 chronic pain patients	low back pain, cancer pain and other causes	pre vs post pain relief	arterial CO2 level	decreased hyperventilation upon pain relief
Puntillo et al. [74,75]	1997	31 patients 114 assessment	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 assessment	mechanically ventilated patients in trauma unit	none	compliance with ventilator	poor compliance/ fighting with ventilator when in pain
Gélinas et al. [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 hours	inclusion in a pain assessment tool
					RR increase of 10-20 above baseline	increases during painful procedure
					asynchrony with ventilator	inclusion in a pain assessment tool

RR: respiratory rate; ICU: intensive care unit

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 6BPM 16 BMP HR biofeedback computer game	pain threshold and tolerance	Higher pain threshold and tolerance in SDB and HR biofeedback compared to baseline. No sig. change during 16 BPM. Computer game increased only the threshold of pain.
Zautra et al [100]	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 fibromyalgia patients.
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)	Electrocutaneous stimuli on sural nerve	normal/slow/fast breathing insp. versus 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)	Electrocutaneous stimuli on sural nerve	slow breathing with slow insp. slow breathing with fast insp. normal breathing insp. versus exp.	pain, NFR	No effect of breathing pattern on pain, but NFR modulated. Pain lower during inspiration. NFR lower during expiration.
Zunhammer et al [101]	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. versus exp.	pain intensity	expiration < inspiration

					skin conductance brain activity	
Botha et al [12]	2014	Healthy (37)	Electrical stimulation of proximal oesophagus	slow deep breathing non-paced breathing	pain threshold skin conductance 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 [79]	2015	Healthy (38)	Pressure algometer	slow inhalation breath-hold	pain intensity	Less pain during breath-hold comparing to slow inhalation regardless of pressure intensities.

NFR: nociceptive flexion reflex, BPM: breath per minutes, HR: heart rate, SDB: slow deep breathing, NFR: nociceptive flexion reflex, SB: slow breathing

Table 5: Overview of clinical studies

Author	Year	Sample size	Participants Type of pain	Comparisons	Breathing technique	Intervention combination[i]	Intervention duration	Finding: Effective?
Miller[65]	1987	15	coronary bypass surgery	pre/post study	Abdominal deep slow breathing	N	short time effect	'yes', but no p-value reported
Yildrim & Sahin[98]	2004	40 E=20, C=20	labour pain	C: no intervention E: breathing technique	Slow deep breathing Rapid shallow breathing Pant-blow 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 seconds	yes
Friesner et al[38]	2006	40 E=19, C=21	chest tube removal pain after heart surgery	C: opioid, E: opioid + deep slow breathing	Slow nose inhaling and slow mouth exhaling	N	immediate + 15 min	yes
Downey & Zun[21]	2009	159 C=84, E=75	all type (emergency department)	C: medication E: medication + deep breathing	Slow breathing 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 days	no
Park et al[71]	2013	64 E=34, C=30	burn patients	C: medication E: breathing & medication	Slow abdominal with 2:4 inhalation/ exhalation ratio	N	3 sessions	yes
Elkreem et al[36]	2014	70	children with cancer	pre/post study, breathing exercise	Not specified	N	1 session	yes

E: experimental or intervention group, C: Control, [i] intervention combination refers to only breathing technique (N) or breathing in combination with other relaxation techniques (Y)