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Abstract	A dysregulated autonomic stress physiology is hypothesized to play an important role in the etiology and perpetuation of somatic symptoms that cannot be (fully) explained by an organic disease. The aim of this study was to focus on the role of the respiratory system. We examined end-tidal CO_2 concentration ($PetCO_2$) in healthy controls (n = 30), patients with panic disorder (n = 36), and patients with stress-related (overstrain; n = 35, burnout; n = 44) or functional syndromes [fibromyalgia (FM) and/or chronic fatigue syndrome (CFS); n = 36]. Participants went through a rest period and a respiratory challenge with recovery, whilst $PetCO_2$ was continuously monitored by a capnograph. Taken together, our results suggest: (1) an overactive respiratory system to be a possible transdiagnostic underlying factor of overstrain, burnout, and panic disorder, and (2) the presence of a less active respiratory fight-flight response in the more chronic and severe functional syndromes (FM/CFS).

Keywords (separated by '-')	Stress - Panic disorder - Psychophysiology - Functional syndrome - Burnout - $PetCO_2$
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End-Tidal CO_2 in Patients with Panic Disorder, Stress-Related or Functional Syndromes, Versus Healthy Controls

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Abstract

A dysregulated autonomic stress physiology is hypothesized to play an important role in the etiology and perpetuation of somatic symptoms that cannot be (fully) explained by an organic disease. The aim of this study was to focus on the role of the respiratory system. We examined end-tidal CO_2 concentration ($PetCO_2$) in healthy controls (n = 30), patients with panic disorder (n = 36), and patients with stress-related (overstrain; n = 35, burnout; n = 44) or functional syndromes [fibromyalgia (FM) and/or chronic fatigue syndrome (CFS); n = 36]. Participants went through a rest period and a respiratory challenge with recovery, whilst $PetCO_2$ was continuously monitored by a capnograph. Taken together, our results suggest: (1) an overactive respiratory system to be a possible transdiagnostic underlying factor of overstrain, burnout, and panic disorder, and (2) the presence of a less active respiratory fight-flight response in the more chronic and severe functional syndromes (FM/CFS).

Keywords Stress · Panic disorder · Psychophysiology · Functional syndrome · Burnout · $PetCO_2$

Introduction

About 40–49% of primary care patients report somatic symptoms that cannot be explained by any well-known organic disease (Haller et al., 2015). Typical examples are headache, dizziness, shortness of breath, fatigue, muscle aches, nausea, and gastrointestinal symptoms (Barsky & Borus, 1999). These bodily symptoms can occur in the context of stress-related conditions such as overstrain and burnout, but also as clusters in a more chronic form, often referred to as functional syndromes, such as fibromyalgia (FM) or chronic fatigue syndrome (CFS).

Clinically, it is widely assumed that dysregulated autonomic stress reactivity is an important mechanism underlying stress-related and functional syndromes.On the one hand, evidence in support of this assumption has been found in burnout by finding higher resting heartrate in patients with burnout compared to healthy controls (De Vente et al., 2003) and by finding burnout to be a predictor of higher blood pressure and decreased heart rate variability (HRV) (May et al., 2016). On the other hand, evidence is found within a FM/CFS population, by finding sympathetic nervous system predominance within this patient group (Martinez-Martinez et al., 2014; Meeus et al., 2013). However, research that focuses on the respiratory system

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of patients with a stress-related or functional syndrome is limited.In this study, we focus on the respiratory system, and in particular on breathing-dependent CO_2-regulation. Respiratory changes are a highly sensitive component of the stress response, typically involving an increase in frequency (Grassmann et al., 2016). However, when increased frequency is not adequately compensated by reductions in volume, hyperventilation-induced hypocapnia, an important source of bodily symptoms, may ensue (Gilbert, 1999). Hypocapnia can be measured by assessing the partial pressure of CO_2 at the end of expiration ($PetCO_2$, in mmHg) through a capnograph, which is a valid approximation of the alveolar and arterial partial pressure of CO_2 (Gardner, 1996; Pahn et al., 1987). Hypocapnia occurs when $PetCO_2$ values drop below 30 mmHg (Rafferty et al., 1992). Because hyperventilation is a context-sensitive stress response, it may occur rather irregularly rendering it difficult to objectify with laboratory testing. Nevertheless, hyperventilation can cause symptoms such as dizziness, stiff muscles, and trembling (Hornsveld et al., 1995). In addition, respiratory complaints are typically observed in overstrain and burnout (Netherlands Society of Occupational Medicine, 2011; Terluin et al., 2005). In patients with anxiety disorders and functional syndromes a progressive decrease of $FetCO_2$ during rest (without manipulation) and a delayed recovery after a hyperventilation provocation task (Han et al., 1997, 2000) have been found, while hyperventilation can complicate CFS and contribute to its symptom profile (Bogaerts et al., 2007; Natelson et al., 2007). Also, patients with panic disorder—a group in which respiratory parameters are extensively examined—appeared to have lower $PetCO_2$ values during rest, showed a higher number of sighs, reached lower $PetCO_2$ during sighing, and exhibited slower recovery after respiratory challenges compared to healthy controls (HC) (for a review, see Meuret & Ritz, 2010). Furthermore, low $PetCO_2$ at rest predicts poorer outcome of psychotherapy (cognitive behavioral therapy; acceptance and commitment therapy) across anxiety disorders, suggesting that treatment should address respiratory dysregulation directly (Davies & Craske, 2014).

Despite this evidence, literature tends to underestimate the role of respiration in most stress-related or functional syndromes (Sikter et al., 2009). This may be due to the fact that there is no one-to-one relationship between the presence of hypocapnia and the presence of symptoms (Hornsveld et al., 1996). This argument has played a critical role in dismissing hyperventilation as a causal mechanism in panic disorder and in the so-called hyperventilation syndrome, leading researchers to consider it at best as an epiphenomenon of panic and—by extension—of stress-related disorders (Hornsveld & Garssen, 1997). However, the argument of a poor correspondence between physiological dysfunction and self-reported symptoms is mistaken because it overlooks the important role of symptom perception processes. Substantial evidence exists that repeated respiratory challenges (through CO_2-enriched air inhalation or through voluntary hyperventilation) can act as a source of learning of symptoms. During these challenges, the correspondence between actual hypocapnia and symptoms of hyperventilation gradually becomes loose (Bresseleers et al., 2010; Van den Bergh et al., 1997, 2002; Van Diest et al., 2006). This means that even in the absence of a one-to-one relationship between the presence of symptoms and the presence of hypocapnia, respiratory responses in response to stress remain an important source of information to understand somatic symptoms without objectifiable disease.

The goal of the present study is to examine $PetCO_2$ in patients diagnosed with overstrain, burnout and FM/CFS. Since core symptoms of overstrain and burnout like perspiration, shortness of breath and chest pain (Terluin et al., 2005) are remarkably similar to symptoms of panic disorder, and since the latter is one of the few patient groups in which the role of $PetCO_2$ has been the subject of extensive investigation, we included panic disorder patients as an extra control group. In the present study, we assessed $PetCO_2$ at rest, during and after a mild respiratory challenge. Since breathing abnormalities have been recorded in patients with functional syndromes (Bogaerts et al., 2007; Han et al., 1997, 2000), and in panic disorder (see for a review: Meuret & Ritz, 2010), we hypothesize that the different patient groups show a stronger decline of $PetCO_2$ during rest, exhibit on average a significantly lower $PetCO_2$ in response to a respiratory challenge and have a less steep recovery slope after a respiratory challenge compared to HC. In addition, we will explore the differences between the different patient groups in $PetCO_2$ during rest, during the respiratory challenge and during recovery.

Method

Participants

Outpatients at Tumi Therapeutics, a multidisciplinary diagnostic and treatment center that specializes in stress-related and functional syndromes (Heusden-Zolder, Belgium), participated in the study between January 2017 and July 2019. As part of their intake procedure, all patients completed an examination assessing physiological parameters, consisting of -amongst others- the respiratory challenge, and filled out a series of questionnaires at the onset of their trajectory. All patients gave consent that they have taken note that this expertise center conducts research in collaboration with the university and that their data may be processed anonymously for research purposes. Patients with panic disorder were diagnosed according to DSM-IV criteria via the MINI 'International Neuropsychiatric Interview' (Overbeek

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et al., 1999; Sheehan et al., 1998). Patients with overstrain and burnout were diagnosed according to the multidisciplinary guidelines for overstrain and burn-out for first line professionals of the Netherlands Society of Occupational Medicine (2011). According to these guidelines, overstrain is characterized by the following symptoms: disturbed or restless sleep, irritability, not being able to stand commotion/ noise, emotional lability, feeling stressed or rushed, not being able to relax, and difficulty concentrating and/ or forgetfulness with a duration of 3 months. Burnout occurs when symptoms of overstrain persist for more than 6 months, and feelings of fatigue and exhaustion become prominent. The patient experiences significant limitations in professional and/or social functioning. (NVAB, 2011). The same criteria for overstrain and burnout were used in a recent study by Bogaerts et al. (2022). Patients with CFS were diagnosed using the CDC criteria (Centers for Disease Control and Prevention; Fukuda et al., 1994) while patients with FM were diagnosed using the ACR criteria (American College of Rheumatology; Wolfe et al., 2010). For all patient groups, psychiatric disorders—other than panic disorder for the panic disorder group and somatization or somatoform disorder for the FM/CFS group—were excluded by use of the semi-structured psychiatric interview (MINI). Organic diseases were excluded based on doctor's reports, physical examination, and medical tests.

Healthy controls were recruited through the distribution of flyers and on social media and matched on age, gender, educational level, and body mass index using a frequency sampling method, so that the distributions were similar in the patient and HC sample. HC were selected based on their scores on the Checklist for Symptoms in Daily life (CSD; Walentynowicz et al., 2018) and the Dutch trait version of the Positive and Negative Affect Schedule (PANAS-trait; Watson et al., 1988), since symptom-reporting is associated with higher trait negative affect (Van Diest et al., 2005). Only participants with a score equal or lower than 75 on the CSD and equal or lower than 21 on trait negative affect were included in the study. These cut-off scores represent the upper quartiles in a large healthy sample and show favorable discriminative power (see also Bogaerts et al., 2008, 2010a, 2010b). Other exclusion criteria were any self-reported medical conditions, such as cardiovascular, gastrointestinal, neuromuscular, pulmonary, acute illnesses or psychiatric conditions, and pregnancy. The study was approved by the local ethics committee and all participants provided written informed consent.

Capnography

End-tidal PCO_2 (expressed in mmHg) was monitored using a nasal CO_2-sampling cannula connected to a calibrated Oridion Microcap® Handheld Capnograph, with a sampling flow rate of 50 ml/min. The monitor uses Microstream non-dispersive infrared (NDIR) spectroscopy to continuously measure the partial pressure of CO_2 ($PetCO_2$). We focused on $PetCO_2$ because it is a relevant indicator of hypocapnia. The normal range of resting $PetCO_2$ is 35–45 mmHg (Litchfield, 2003), physical symptoms typically appear below 30 mmHg (Rafferty et al., 1992).

Procedure

All participants filled out the questionnaires and went through a resting phase (300 s), a mild respiratory challenge (sighing) and a recovery phase (300 s). During the entire physiological examination, participants were instructed to sit on a chair with their feet on the ground, back against the backrest and hands placed on their lap. First, $PetCO_2$ was continuously assessed during a five-minute resting phase where subjects were instructed to simply breathe through the nose. Second, participants were instructed to take five natural sighs in a row at their own pace as they would in daily life, which constituted the mild respiratory challenge. Participants raised their hand after their last sigh, thereby initiating the five-minute recovery phase. Participants were instructed to breathe through the nose whilst $PetCO_2$ was continuously measured. The original protocol also consisted of a subsequent phase where hypocapnia was elicited by voluntary hyperventilation by means of a hyperventilation provocation task (HVPT). However, due to clinical and safety considerations, participants were not allowed to participate in the HVPT when they showed signs of acute hypocapnia (< 30 mmHg; Rafferty et al., 1992) during rest. Participants could also choose not to participate in the HVPT due to personal reasons (e.g., fear of the test, practical concerns). The HVPT was not carried out in 58.33% of patients with panic disorder, 34.29% of patients with overstrain, 43.18% of patients with burnout, 22.22% of patients with FM/CFS, and in 23.33% of HC. Since the sample participating in the HVPT is an unrepresentative subset of the complete study sample, we chose not to analyze HVPT-data in our study.

Self-report measures

Responses to an extensive battery of questionnaires were collected in the context of diagnostics and treatment plan (see Supplement).

Data analysis

Evolution of $PetCO_2$ during rest

Average $PetCO_2$ levels were calculated for every 60 s of the resting phase, hereafter referred to as time segments [0–60 s (1); 60–120 s (2), 120–180 s (3), 180–240 s (4),

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240–300 s (5)]. Since a progressive decrease of $FetCO_2$ during rest (without manipulation) has been found within patients with both anxiety disorders and functional symptoms (Han et al., 1997, 2000), a random intercept random slope linear mixed model analysis was performed on the resting phase with $PetCO_2$ levels as dependent variable. Group (five levels: HC, panic disorder, overstrain, burnout, FM/CFS) and time (five time segments) were used as independent variables. Apart from comparing all different groups in planned contrasts, we also compared the HC group to the total patient group. A false discovery rate (FDR)-correction was applied on the p-values of the planned contrast to correct for multiple testing.

Differences in lowest $PetCO_2$ reached during the mild respiratory challenge

In addition, a one-way ANOVA on the lowest $PetCO_2$ values during the mild respiratory challenge as dependent variable and the different subgroups as independent variable was conducted. In case of inequality of variances, a Satterthwaite correction was performed. In case significant differences were found, Tukey post-hoc analyses were used to determine which groups were significantly different from each other. A planned contrast was additionally performed to compare the mean lowest value $PetCO_2$ during the respiratory challenge between the entire patient group and the HC group. The same one-way ANOVA was repeated with the last $PetCO_2$ value during rest as a covariate.

Evolution of $PetCO_2$ during the recovery of the mild respiratory challenge

Average $PetCO_2$ levels were calculated for every 60 s of the recovery phases of the mild respiratory challenge, hereafter referred to as time segments [0–60 s (1); 60–120 s (2), 120–180 s (3), 180–240 s (4), 240–300 s (5)]. A separate random intercept random slope linear mixed model analysis was performed on the recovery from mild respiratory challenge with $PetCO_2$ levels as dependent variables. Group (five levels: HC, panic disorder, overstrain, burnout, FM/CFS) and time (five time segments) were used as independent variables. Apart from comparing all different groups in planned contrasts, we also compared the HC group to the total patient group. An FDR-correction was applied on the p-values of the planned contrasts to correct for multiple testing. All analyses were carried out with SAS 9.4 (SAS Institute, Cary, NC, USA). Prism 9 was used to create the artwork.

Results

Sample characteristics and questionnaires

Our sample consisted of a total of 181 white participants of Belgian nationality (125 women) with an age range of 18–67 year (HC; n = 30, panic disorder; n = 36, overstrain; n = 35, burnout; n = 44, FM/CFS; n = 36). Anxiety-related questionnaire scores indicate significantly higher anxiety in the panic disorder group, compared to the other patient groups and HC. Somatization scores were higher in all patient groups—experiencing bodily symptoms in daily life—compared with HC. A more extensive description of our different patient groups can be found in Supplement.

Evolution of $PetCO_2$ during rest

Planned pairwise comparisons of $PetCO_2$ slopes revealed a steeper decline in overstrain patients compared to FM/CFS patients, $t(531) = -2.78$, $p = 0.006$, and in panic disorder patients compared to the FM/CFS group, $t(531) = -2.21$, $p = 0.028$; time*group interaction $F_{4,531} = 2.4$, $p = 0.05$. However, no significant difference in slope appeared between the total patient group and HC, $t(531) = 0.98$, $p = 0.33$, or between other subgroups. $PetCO_2$ values overall decreased during rest (main effect of time, $F_{1,172} = 42.02$, $p < 0.001$), whereas the main group differences in $PetCO_2$ levels did not reach significance at the intercept (time = 1; main effect of group, $F_{4,531} = 0.36$, $p = 0.84$; Fig. 1a).

Differences in lowest $PetCO_2$ reached during the mild respiratory challenge

Patients versus HC

As expected, a planned contrast showed that the lowest $PetCO_2$ values reached during the mild respiratory challenge were significantly lower in the patient group than in HC, $F_{1,171} = 12$, $p < 0.001$ (Fig. 2a).

Differences between all groups

A one-way ANOVA indicated that the lowest $PetCO_2$ values during the respiratory challenge did not differ significantly between overstrain, burnout, FM/CFS, and panic disorder. However, $PetCO_2$ values in overstrain ($p = 0.002$), burnout ($p = 0.032$), and panic disorder ($p = 0.011$), were significantly lower than in HC (one-way ANOVA: $F_{4,171} = 4.69$, $p = 0.001$). Interestingly, there was no significant difference in lowest $PetCO_2$ levels during sighing between FM/CFS and HC ($p = 0.48$) (Fig. 2b).

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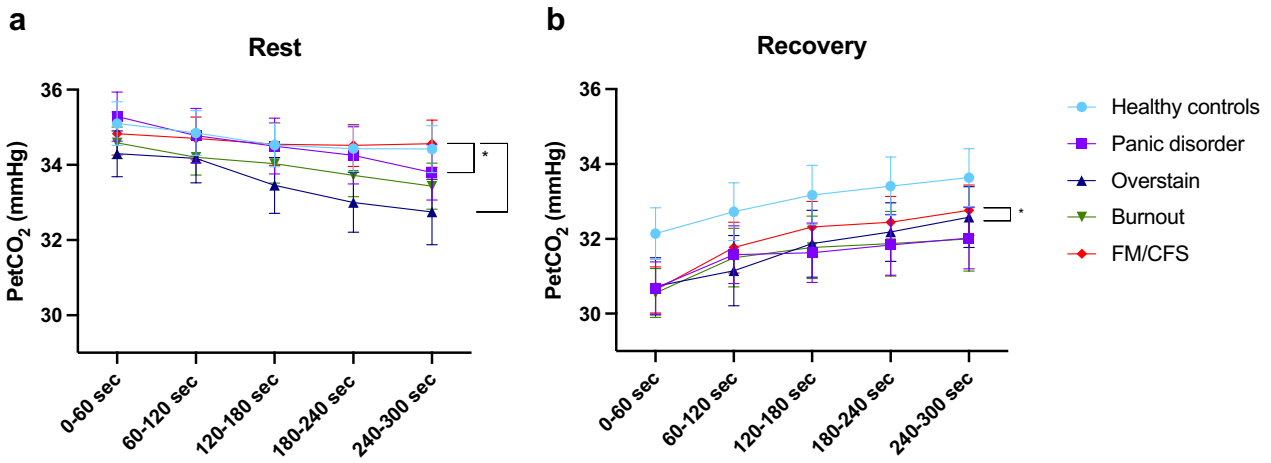
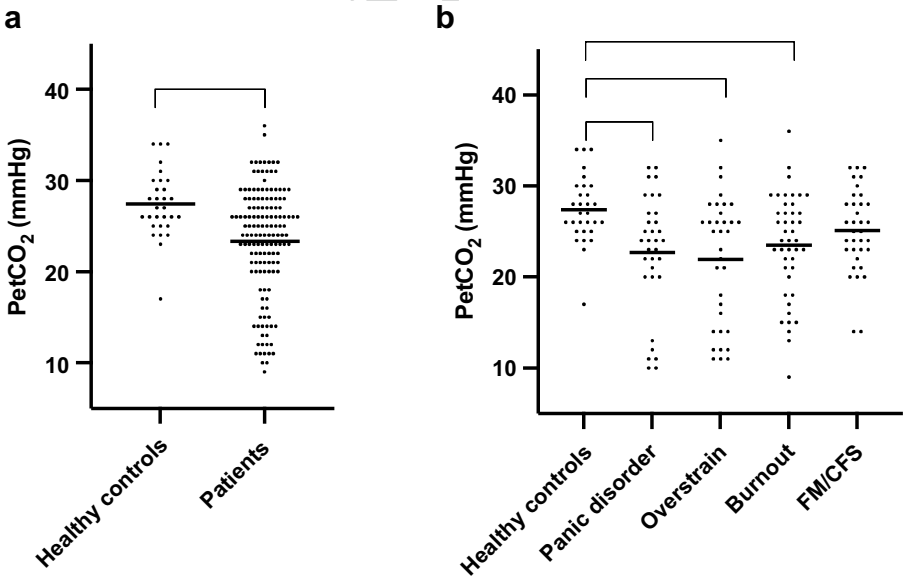


Note. Error bars represent standard errors of the mean

Fig. 1 Graphic representation of the mean $PetCO_2$ values for each time segment, during rest (**a**) and during the recovery of the respiratory challenge (**b**). *Note* Error bars represent standard errors of the mean

Fig. 2 Graphic representation of lowest $PetCO_2$ values during the respiratory challenge comparing the HC group to the patient group (**a**) and comparing all groups (**b**). *Note* The raw means are displayed for interpretational purposes



Note. The raw means are displayed for interpretational purposes

Repeating this analysis with the last $PetCO_2$ value of rest as a covariate, results indicate that the effect of group (one-way ANOVA: $F_{4,171} = 5.09$, $p < 0.001$) and the difference between HC and patients with overstrain ($p = 0.005$) and with panic disorder ($p = 0.016$) remains significant. With the last value of rest as a covariate, the difference between HC and patients with burnout became marginally significant ($p = 0.078$).

Evolution of $PetCO_2$ during the recovery of the mild respiratory challenge

Overall, $PetCO_2$ values increased during the recovery phase of the mild respiratory challenge (main effect of time, $F_{1,144} = 59.41$, $p < 0.001$), but groups did not differ significantly from each other at the intercept (time = 1; main effect of group: $F_{4,441} = 0.73$, $p = 0.57$; Fig. 1b). Moreover,

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although we found no significant time*group interaction effect ($F_{4,441} = 1.45$, $p = 0.22$), planned pairwise comparisons of $PetCO_2$ slopes revealed a steeper increase of $PetCO_2$ in FM/CFS patients compared to overstrain patients, $t(441) = -2.34$, $p = 0.02$. No other significant differences were found.

Discussion

The present study aimed to investigate $PetCO_2$ as a respiratory parameter that is particularly sensitive to physiological overreactivity, and which may act as a source of somatic symptoms that cannot be (fully) organically explained. The current study investigates whether there are differences in end-tidal CO_2 between different patient groups with stress-related or functional syndromes. Specifically, we measured $PetCO_2$ levels during rest, during a mild respiratory challenge, and during recovery of this respiratory challenge. During rest, we found a stronger decline of $PetCO_2$ in patients with panic disorder and overstrain compared to patients with FM/CFS. No other differences were found. During the mild respiratory challenge, we found that the patient group as a whole reached a significantly lower level of $PetCO_2$ compared to HC. Interestingly, when looking at groups separately, we found that patients with overstrain, burnout, and panic disorder, but not FM/CFS, reached significantly lower $PetCO_2$ during this challenge compared to HC. Next, we found a stronger increase of $PetCO_2$ during the recovery of the respiratory challenge in patients with FM/CFS compared to the overstrain group.

Results showed that patients reached significantly lower $PetCO_2$ values during a mild respiratory challenge than HC. Further, no differences could be found between patients with panic disorder and patients with a stress-related syndrome (overstrain and burnout). This is interesting since respiratory dysfunctions are often seen as a specific characteristic of panic disorder (see for a review: Meuret & Ritz, 2010), a disorder which distinguishes itself from typical stress-related disorders due to intermittent bouts of anxiety as a core component. Rather, our results show that it could be a transdiagnostic feature for both. Further, our data also confirm that panic disorder patients reached significantly lower $PetCO_2$ values during sighing than HC, in keeping with Wilhelm et al. (2001). However, no differences were found during recovery when comparing patients with panic disorder with a HC group.

Although previous literature found dysfunctional ANS activity in burnout (De Vente et al., 2003; May et al., 2016), FM and CFS (Martinez-Martinez et al., 2014; Meeus et al., 2013), research that focuses on the respiratory system of patients with stress-related or functional syndromes is limited. Our study contributes to a better understanding of the psychophysiology of stress within these different patient groups by looking at hypocapnia as a form of feedforward regulation eliciting physiological symptoms. $PetCO_2$ seems particularly sensitive to stress responses characterized by (anticipated) physiological arousal (Van Diest et al., 2001). This also means that when a fight-flight response becomes less active, a gradual reduction of physiological overreactivity may ensue, resulting in more normalized PetCO2 values. Interestingly, this would be similar to what is found in anxiety disorders: researchers refer to an anxiety-continuum, where an exaggerated eye-blink startle reflex indicating activation of the defensive response system is found in conditions characterized by focal fears, but defensive response mobilization gradually becomes blunted along with more chronic, long-lasting and generalized anxiety (Lang et al., 2018; McTeague & Lang, 2012). An intriguing analogy with the abovementioned anxiety literature (Lang et al., 2018; McTeague & Lang, 2012) can be found in our current findings, placing overstrain, burnout, and FM/CFS on a stress-continuum regarding increasing levels of severity and chronicity (Fukuda et al., 1994; NVAB, 2011; Terluin et al., 2005; Van der Klink & Van Dijk, 2003; Wolfe et al., 2010). For instance, an active fight-flight strategy characterized by high arousal may be present in patients with overstrain, but a chronic course of the stress problem may result in a less active fight-flight in FM/CFS, with burnout as an intermediate state. This would be consistent with finding a steeper decline of $PetCO_2$ in patients with overstrain compared to FM/CFS during rest, and a significantly less adaptive increase of $PetCO_2$ in overstrain compared to FM/CFS during the recovery of the respiratory challenge. In addition, our results also showed that overstrain and burnout patients, but not FM/CFS patients, reached lower $PetCO_2$ values during the mild respiratory challenge compared to the HC group. These results suggest that $PetCO_2$ can be interpreted as a readout of the level of arousal/activity involved in the fight-flight response of the patients. During active fight-flight, which may characterize overstrain patients, behaviorally driven feedforward regulation of breathing overrules metabolic regulation resulting in tendencies to overbreathe. However, interestingly, as syndromes become more chronic and severe, the fight-flight response may become less active, which reduces overbreathing and normalizes $PetCO_2$. The proposed stress-continuum should be seen as a new hypothesis that should be tested in further research.

Interestingly, repeated overbreathing contributes to somatic symptoms in two ways. First, actual hypocapnia results directly in a large array of symptoms (Gilbert, 1999), and, secondly, repeated overbreathing acts as a source of "symptom learning" during which symptoms of hyperventilation become uncoupled from hypocapnia over time (Bresseleers et al., 2010; Van den Bergh et al., 1997, 2002; Van Diest et al., 2006). This is in line with observations that physical symptoms in FM/CFS are less driven by actual

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ANS-dysfunction, but rather depend on central processes (Van den Bergh et al., 2017 for a review). In a broader sense, these findings underline the importance of an integrative psychophysiological model of stress-related and functional syndromes, in which (psycho)physiological reactivity as well as central processes such as the role of learning in symptom perception should be investigated. For instance, earlier we established a (learned) association between a negative affect and elevated symptom reporting in healthy high habitual symptom reporters (Bogaerts et al., 2010a, 2015): experimental induction of negative affective states led to elevated symptoms in the latter group, but also in patients with FM/CFS (Van Den Houte et al., 2018). Additionally, we showed that symptom reporting was less strongly related to actual physiological responses in participants within these groups (Bogaerts et al., 2010a; Van Den Houte et al., 2018) compared to HC. Future research to understand stress-related physical symptoms should therefore focus on the interaction between psychological and physiological variables and on the dynamic changes in their relationship over time.

Some limitations of the study should be mentioned. Because of the cross-sectional design of our study, the data does not allow us to draw conclusions about directionality or causality of the found effects. Another limitation is that we only studied one respiratory parameter without including respiratory frequency and/or volume and without self-report respiratory covariates. As such, the present findings are a first indication to detect differences in respiratory physiology in patients with stress-related or functional syndromes. Further research—including multiple psychophysiological parameters and additional patient groups—is needed to confirm the specificity of the current findings.

The study results have theoretical and clinical implications. Since dysfunctional breathing has been seen as an important component within panic disorder, respiratory biofeedback-assisted therapy has already been proposed (Meuret et al., 2004) and proven useful in this patient group (Meuret et al., 2001). Furthermore, this method has also been proven to be effective in medically unexplained dyspnea (Han et al., 2004). Since psychophysiological arousal appears to be a prominent feature in different stress-related disorders, and not only within panic disorder, the effectiveness of capnometry-assisted breathing therapy embedded in psychotherapy of stress-related and functional syndromes should be tested. Psychophysiological treatment—consisting of amongst others psychoeducation and biofeedback—has already been proven effective in patients with medically unexplained physical symptoms (Katsamanis et al., 2011). Effectiveness may be further enhanced by adding capnometry-assisted breathing therapy, in particular because hypocapnia-related symptoms and subsequent symptom learning may provide a convincing rationale for these patients.

Conclusion

In summary, although respiratory dysfunctions are often seen as a specific characteristic of panic disorder, the present study found indications for an overactive respiratory system to be a possible transdiagnostic underlying factor of overstrain, burnout, and panic disorder. Further, our results may suggest the presence of a less active respiratory fight-flight response in the more chronic and severe functional syndromes (FM/CFS). However, this research is only a first step and lays a foundation for future studies on respiratory psychophysiology within these populations. Further research is needed to investigate the interaction between physiological and psychological mechanisms and the dynamic changes of their relationship over time. In addition, our findings suggest that respiratory biofeedback may complement treatment approaches of stress-related and functional syndromes.

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Data availability The datasets and code generated during this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Approval was obtained from the Social and Societal and Ethical Committee of KU Leuven (Leuven, Belgium). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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