The influence of affective state on respiratory muscle activity

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Short title: EMGpara and affective state

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Research was carried out at: Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences, King's College London, London, UK

Word Count: 1909 words

Tables: 1

Figures: 2

Summary

Measures of neural respiratory drive through the use of electromyography of the parasternal intercostal muscles (EMGpara) are accurate markers of respiratory load and are reflective of pulmonary function. A previous observation of a significant reduction in EMGpara from a first to second measurement occasion was attributed to participants' acclimatisation to the laboratory environment and a reduction in anxiety. This study therefore aimed to investigate whether manipulation of participants' affective state would influence EMGpara and related variables. Healthy adult participants underwent measurement of EMGpara and respiratory flow and volume during exposure to four conditions: no stimulus, music, and tense and calm videos. Respiratory rate (RR), raw neural respiratory drive index (rawNRDI, the product of EMGpara in microvolts and RR) and minute ventilation (VE) differed significantly across conditions: RR and VE were significantly higher in the tense condition than all other conditions (all $p<0.05$); rawNRDI was higher in the tense compared to the calm video condition ($p=0.03$). There was also a significant relationship between EMGpara and subjective tension ratings (measured via visual analogue scale) in the tense condition (Spearman's rho = 0.508, p = 0.016), with multivariate modelling indicating significant interactions between rawNRDI and subjective ratings of both tension and calmness. This suggests that anxiety could contribute to elevated respiratory muscle activity and ventilation. Greater consideration should be given to the influence of anxiety when undertaking measurement of respiratory muscle activity to ensure data accurately represent underlying respiratory load.

Key Words: Mood, anxiety, parasternal intercostals, neural respiratory drive, ventilation

Introduction

Measures of neural respiratory drive through the use of electromyography of the parasternal intercostal muscles (EMGpara) are a non invasive, accurate marker of respiratory load and are reflective of pulmonary function (Reilly *et al*., 2011). In a previous study we showed significantly lower EMGpara obtained from the second of two recordings within a single measurement session (MacBean *et al*., 2016). We attributed this to the unfamiliar laboratory environment inducing mild feelings of anxiety, which reduced with familiarisation. Certain circumstances and participant populations may be associated with an exaggeration of this anticipatory anxiety; respiratory disease and anxiety are known to be highly comorbid (Katon *et al*., 2004; Mikkelsen *et al*., 2004), and anxiety before tests, appointments or operations has previously been demonstrated (Kindler *et al*., 2000). Emotional responses prior to dyspnea-inducing activities have also been observed in people with COPD (Esser et al, 2017). Any impact of affective state on EMGpara activity and respiratory behaviour is therefore important to understand. Falsely elevated values due to anxiety could erroneously indicate presence or greater severity of respiratory disease, and would make detection of subtle increases within the same testing session more challenging.

Research has shown that external stimuli, such as videos or games can have an effect on physiological arousal (Anderson *et al*., 2001) heart rate and sleep quality (Ivarsson *et al*., 2003). It is therefore plausible to hypothesise that such stimuli could also have a differential effect on EMGpara and respiratory flow parameters. We therefore sought to investigate whether exposure to extrinsic stimuli would induce changes in EMGpara and ventilatory parameters, and whether any changes were related to subjective ratings. Given our previous findings of a reduction in EMGpara in healthy subjects, we investigated the influence of stimuli designed to subtly increase or decrease anxiety levels.

Methods

Ethical Approval: This study was granted ethical approval by King's College London Research Ethics Office, and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from participants before commencing the experiment.

Participants: 22 young healthy humans (median (IQR) age 17 (16-21) years, 17 female, median (IQR) height 162.5 (159.6 – 179.9)cm, median (IQR) mass 59.1 (55.9 – 69.2)kg) were recruited via word of mouth and university platforms. Participants had screening spirometry performed prior to testing to confirm absence of respiratory disease; all were within +/-1.96 z scores of predicted normal values based on sex, age, height and ethnicity (Quanjer *et al*, 2012).

Measurements: EMGpara was recorded using surface electrodes placed over the second intercostal space as previously described in MacBean *et al* (2016). Respiratory flow and volume were determined using a pneumotachograph (Fleisch model, PK Morgan Ltd, Rainham, Kent, UK) and spirometer (ADInstruments Ltd, Castle Hill, Australia) as previously described in MacBean *et al* (2016) attached to a full face mask (Hans Rudolph Inc, Kansas City, KS, USA). Subjective measurements of how tense and relaxed participants were feeling were recorded using two separate 100mm visual analogue scales (VAS), with anchor points at 0mm (‘not tense/relaxed at all’) and 100mm (‘as tense/relaxed as I could possible be’). Participants were asked to indicate their response to the question ‘how tense/relaxed are you feeling at this moment?’ by drawing a mark on the line of the VAS.

Stimuli: Music was from the top 50 charts in the UK on Spotify. Tense and calm videos were a selection of clips from the David Attenborough Africa Series (2013, British Broadcasting Corporation). All participants were shown the same clips on a laptop computer, with the position of the screen and sound volume consistent across all measurement sessions.

Protocol: Subjects were exposed to four conditions: no stimulus, music, tense videos, and calm videos, in a randomised order. Each condition lasted for ten minutes with a break of approximately five minutes between conditions. Measurement of EMGpara and respiratory flow were made throughout each ten minute epoch. Data were recorded on a computer running LabChart Version 8.1 (ADInstruments). At the end of each condition, participants completed the two VAS scales.

Analysis: Mean peak RMS EMGpara per breath, respiratory rate, tidal volume, minute ventilation, and raw neural respiratory drive index (rawNRDI, the product of EMGpara and respiratory rate, expressed in µV.BPM) were determined for the final minute of each condition. Data were analysed using Prism (Version 7, GraphPad Software Inc., La Jolla, CA, USA) and SPSS (Version 24, IBM Corp, NY, USA). Non parametric statistics were used throughout due to the sample size and all data are presented as median (interquartile range). Friedman’s tests were used to assess for differences across conditions, with post hoc testing performed using Dunn’s correction for multiple comparisons to compare individual conditions. We classified 'music' as the control condition, as it is common practice for music to be in played in our laboratories during respiratory measurements. Spearman's Rho was used to assess the relationship between subjective measurements from the VAS ratings and EMGpara. Linear mixed effects modelling was used to explore the interaction between condition, respiratory variables, and subjective ratings. A p value of <0.05 was accepted as significant.

Results

Median (IQR) respiratory rate, rawNRDI and minute ventilation were significantly higher in the tense condition compared to the other conditions (*table 1*). Results of post hoc analyses are shown in *Figure 1*.

Although VAS ratings did not differ significantly between conditions based on the Friedman's test, linear mixed model analysis indicated that tense VAS scores were significantly related to stimulus (p=0.036). Furthermore the same model demonstrated a significant inverse interaction between tense and relaxed VAS scores across conditions p=0.045), suggesting that the presented stimuli did effectively manipulate affective state with respect to both perceived tension and calmness. There was a significant positive correlation between tension VAS and EMGpara in the tense condition (Spearman's rho = 0.508, p = 0.016). A significant positive relationship between change in EMGpara from the music (control) to tense condition, and tension

VAS in the tense condition was found (Spearman's rho = 0.429, p = 0.046). Linear mixed model analysis also showed a significant interaction between rawNRDI and both tension and calm VAS ratings with changing stimulus condition (p=0.037).

Discussion

We have shown that relatively modest manipulation of affective state in a group of healthy participants through exposure to extrinsic stimuli is associated with elevations in respiratory rate, total EMGpara activity (as determined by rawNRDI), and minute ventilation. Furthermore, subjective ratings of perceived tension were shown to be related to respiratory muscle activity both on univariate and multivariate analysis. The interaction between tense and relaxed VAS scores highlights the complexity of affective state and may explain why across-condition differences were not observed in tense and relaxed VAS values.

To our knowledge, this is the first study to demonstrate an influence of non-physiological stimuli on parasternal intercostal muscle activity. The responsiveness of EMGpara to altered respiratory load is well documented (Reilly et al., 2011, Suh *et al.*, 2015, MacBean *et al.*, 2017), but consideration has not previously been given to subjects' affective state in interpreting the elevated EMGpara and derived indices observed in previous studies. We attributed our previous finding (MacBean *et al.*, 2016) of a significant reduction in healthy adults' EMGpara between first and second measurements within a single testing session to acclimatisation to the laboratory environment and a reduction in the anxiety associated with entering an unfamiliar environment; the results from the current study lend weight to this hypothesis by demonstrating a relationship between perceived 'tension' and 'relaxation' and measures of EMGpara.

The lack of change observed in EMGpara alone (that is, the muscular activation required to generate an individual breath) across the different stimuli, coupled with the changes seen in respiratory rate and thus rawNRDI, highlight the importance of considering breathing pattern when measuring indices of neural respiratory drive. Any affect-mediated changes in EMGpara would be likely to occur as a result of altered tidal volume rather than changes in airway calibre or respiratory mechanics. Tidal volume did not change in this study, but the increase in respiratory rate (and thus minute ventilation) resulted in elevations in total EMGpara activity (measured as rawNRDI). Our study therefore serves to emphasise both the value of measures such as NRDI, which incorporate respiratory pattern to provide a more complete estimation of respiratory muscle activity, as well as their potential limitations in being influenced by non-respiratory factors.

Given that extrinsic stimuli were found to be associated with elevated parasternal intercostal muscle activity, we suggest that intrinsic feelings of tension or anxiety would have the same effect. This warrants careful consideration when undertaking studies with populations or individuals known to exhibit higher levels of anxiety, such as individuals with respiratory disease (Katon *et al*., 2004, Mikkelson *et al*., 2004). The relatively innocuous nature of the stimuli used in the current study suggests that even subclinical levels of anxiety may be relevant. Many physiological studies of respiratory muscle function involve detailed, arduous and at times invasive measurement techniques and protocols (Jolley *et al*., 2015, Reilly *et al*., 2011), the anticipation of which may induce anxiety. Patients with respiratory disease have been shown to experience enhanced activation of emotion-related brain areas (amygdala and hippocampus) when anticipating dyspnoea-inducing activity (Esser *et al*., 2017). The data we present here suggest that such alterations in affective state may well be associated with elevated neural respiratory drive, which would negatively influence the accuracy of baseline values and diminish the apparent magnitude of any increases induced by a physiological stressor during an incremental study design. While the magnitude of changes due to external stimuli such as exercise or induced bronchoconstriction are likely to be much greater than those conferred by anxiety, the accuracy of baseline measures is nonetheless of utmost importance in interpreting patterns of change. We suggest therefore that careful consideration should be given to minimising participants' anxiety prior to undertaking any respiratory measurements to optimise the reliability of results. This may be achieved through the use of distraction techniques or longer acclimatization periods to the laboratory environment. More anxious individuals may benefit from a more detailed explanation of the study protocol and ample reassurance prior to commencement of testing.

We had anticipated a reduction in EMGpara and ventilatory parameters during the calming videos condition, but this was not observed. Although we did not record anxiety prior to commencement of testing, the population included in this study can be assumed to have low levels of baseline anxiety – they had no underlying disease nor were they undergoing testing with the anticipation of obtaining an undesirable diagnosis, and were not scheduled to undergo unpleasant or arduous testing procedures. It is therefore reasonable to infer that we encountered a floor effect as reductions in respiratory muscle activity below the level required to maintain ventilation at a level sufficient for blood gas homeostasis are not feasible. Our findings therefore suggest that a standard laboratory environment, with or without a distraction such as music, can be used for undemanding studies involving healthy subjects at ease with the study protocol. In other populations in whom higher levels of anxiety may be seen, calming stimuli may facilitate reduction of EMGpara to levels representative of homeostatic requirement only, eliminating the potential confounding effect of anxiety. Further studies could seek to investigate this.

In summary, our findings of a relationship between indices of parasternal intercostal muscle activity and subjective feelings of tension and relaxation, and the influence of affect-mediated changes in respiratory rate, highlight the importance of considering the influence of affective state when undertaking respiratory measurements. Incorporating strategies to minimise anxiety could improve the robustness of physiological studies.

Acknowledgements

JW was supported by Summer Studentship awards from The Physiological Society and St Anne's College Oxford. The authors are grateful to the participants who committed their time, and would like to thank Burntwood School, JFS School, Graveney School and the Harris Federation of Academies for their support. We also acknowledge the assistance of Mark Porter and Spencer Williams in the conduct of the study.

Conflict of Interest

The authors have no conflicts of interest.

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	No Stimulus	Music	Tense Videos	Calming videos	p value
EMGpara (z-scores)	-0.50 (-0.75 – 0.20)	-0.48 (-0.68 – 0.08)	-0.60 (-0.86 – 0.01)	-0.54 (-0.85 – 0.14)	0.1026
rawNRDI (µV.BPM)	103.20 (70.48 - 119.80)	102.90 (72.00- 136.50)	110.50 (80.64 - 141.60)	95.32 (71.05 - 111.70)	***0.0335***
Respiratory Rate (BPM)	16.76 (14.99 – 19.08)	17.19 (14.57 – 18.99)	18.18 (16.72 – 19.97)	16.43 (15.32 – 18.75)	***0.0080***
Tidal Volume (l)	0.48 (0.44 - 0.52)	0.51 (0.46 - 0.58)	0.48 (0.46 - 0.51)	0.50 (0.46 - 0.55)	0.2690
Minute Ventilation (l/min)	8.05 (7.16 – 9.31)	8.23 (7.45 – 9.01)	8.62 (8.02 – 9.95)	8.27 (7.55 – 8.95)	***0.0034***
Tense VAS rating (mm)	9 (2 -21)	17 (4 – 34)	17 (8 – 40)	13 (4 – 33)	0.0759

Calm VAS rating (mm)	84 (77 – 96)	81 (69 – 96)	81 (65 – 94)	83 (70 – 94)	0.5129

Table 1: EMGpara and respiratory flow parameters under the four different conditions. All data are shown as median (IQR).

p values from Friedman's test comparing across all four conditions.

FIGURE LEGEND

Figure 1: (A) Minute Ventilation (B) Respiratory Rate (C) RawNRDI under each of the four conditions, showing results of post hoc comparisons.

Figure 2: RawNRDI (closed squares, left y axis), 'tense' VAS scores (closed circles, right y axis) and 'relaxed' VAS scores (open circles, right y axis) across each of the four conditions. Data are shown as median and IQR.

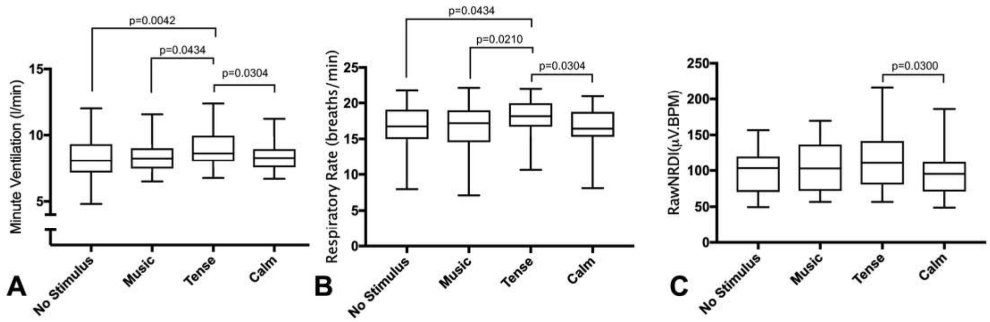

Figure 1: (A) Minute Ventilation (B) Respiratory Rate (C) RawNRDI under each of the four conditions, showing results of post hoc comparisons.

94x35mm (300 x 300 DPI)

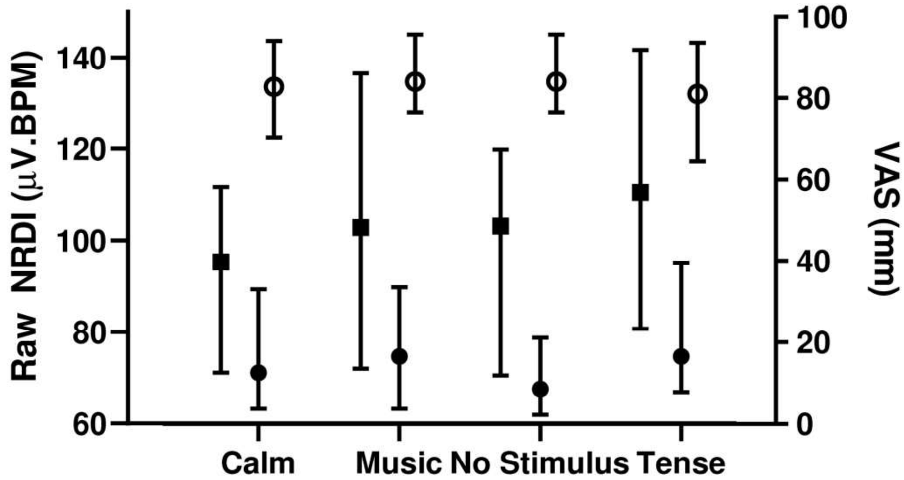

Figure 2: RawNRDI (closed squares, left y axis), 'tense' VAS scores (closed circles, right y axis) and 'relaxed' VAS scores (open circles, right y axis) across each of the four conditions. Data are shown as median and IQR.

210x149mm (300 x 300 DPI)