Do we "drive" dyspnoea?

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Changes between neural drive and dyspnoea were determined during exercise in severe COPD patients by measuring EMGdi http://ow.ly/FCAs3

Electromyography (EMG) measures neural drive, and is routinely used to investigate movement control and pathophysiology in human subjects. The electrical signals recorded from a muscle indicate the recruitment and discharge of spinal motor neurones by voluntary and reflex activation. EMG recordings are typically made with surface electrodes placed on the skin over the muscle of interest, or intramuscular needle or wire electrodes inserted into the muscle of interest. There are advantages and disadvantages of both techniques [1] but the disadvantages are somewhat amplified for EMG recordings from the respiratory muscles. As many respiratory muscles are small and located close to one other, often in layers of muscle with different functions (*e.g.* the external and internal intercostal muscles), surface recordings are easily contaminated by activity from neighbouring muscles. Intramuscular recordings are more selective but the risks associated with needle use are more serious for the respiratory muscles because of the underlying lung. In saying that, inspiratory muscle surface EMG recordings are possible [2, 3] and electrode position can be optimised for the diaphragm [4] for some protocols. With intramuscular electrodes, the risk of pneumothorax can be minimised by using ultrasound to visualise the muscle and lung and estimate maximal insertion depth prior to recordings [5], and on-line audio and visual feedback of EMG activity during recordings [6]. Intramuscular recordings have been used to assess diaphragm activity with three-fold increases in minute ventilation (V'_E) associated with hypercapnia [7] but have not been used in exercise protocols, potentially due to the high risk of pneumothorax with large changes in lung volume. As surface and intramuscular EMG recordings from the respiratory muscles are complicated by their anatomy, alternative measures, such as V'_E and intrathoracic pressures, have been used as surrogates to assess respiratory neural drive, particularly in clinical populations.

Much of the insight into the pathophysiology of exertional dyspnoea in respiratory disease, including chronic obstructive pulmonary disease (COPD), asthma and pulmonary arterial hypertension, has come from studies using pressure measurements, V'_E and lung volumes to assess respiratory mechanics [8–13]. Neurophysiologically, increased perceived breathing effort is believed to reflect the awareness of increased motor command output to the respiratory muscles ("neural respiratory drive") and increased central corollary discharge from the respiratory motor centres to the somatosensory cortex [8]. It cannot be neglected that when the spontaneous increase in tidal volume (V_T) is constrained (either volitionally or by external imposition) in the face of increased chemostimulation, respiratory discomfort (specifically, air hunger or unsatisfied inspiration) arises [8].

It has long been understood that there is a widening disparity between the drive to breathe and the corresponding mechanical output of the impaired respiratory system during exercise in advanced COPD.

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This increasing dissociation between increased central neural drive (indirectly estimated as measure of effort: the ratio of tidal swings of oesophageal pressure (P_{oes})) relative to maximum inspiratory pressure and a blunted V_T displacement (measured as the V_T response expressed relative to the predicted vital capacity) induced by dynamic hyperinflation has been proposed to reflect, at least in part, the neurophysiological basis of dyspnoea perceived as unsatisfied inspiration [10–12]. In support of this contention, bronchodilator therapy in moderate-to-severe COPD has been associated with a significant reduction in lung hyperinflation, significant increase in V_T expansion and significant improvement in the effort/displacement ratio [8, 14].

These studies have been pivotal to our understanding of exertional dyspnoea and, although intrathoracic pressure provides an estimate of neural drive, this technique has limitations as changes in pressure may not necessarily reflect changes in neural drive especially in the setting of severe respiratory mechanical impairment. Changes in airway resistance will modify pressure signals independent of respiratory EMG and neural drive, and changes in muscle length will affect the pressure development due to an altered muscle length–tension relationship.

The diaphragm is the principle muscle of inspiration [15]. From a central tendon, fibres radiate posteriorly to the first three lumbar vertebrae to form the crural portion of the muscle, and laterally to the upper margins of the lower six ribs and anteriorly to the xiphoid process of the sternum to form the costal portions. Thus, diaphragmatic muscle fibres span the entire inner surface of the ribcage and this unique structure enables an alternative method to record EMG from this muscle to avoid the drawbacks of surface and intramuscular recordings of respiratory muscle activity discussed above. EMG recordings can be made from the inner surface of the diaphragm *via* a catheter, embedded with recording electrodes, that is passed through the nose and oesophagus such that the electrodes are adjacent to the diaphragm. To our knowledge, this is the only skeletal muscle in which such recordings, *i.e.* recordings from the inner surface, are made.

The benefits, drawbacks and changes in electrode design for oesophageal catheter recordings of diaphragm EMG (EMG_{di}) have been summarised by Luo *et al.* [16]. Of note here is that oesophageal catheters record from the crural portion of the diaphragm, an important distinction because activation differences in the crural and costal portions have been reported [16]. These differences are minimal in human subjects for augmented breaths (35% greater than V_T) [17], but it is not known if activation of the two different portions differs for larger lung volume excursions, *i.e.* during exercise. Also important is that changes in oesophageal catheter design have been critical for their application to accurately measure EMG_{di}. Prior to the development of the current multipair design, attempts to minimise artifactual changes in EMG related to diaphragm movement with changes in lung volume (*e.g.* with a stabilisation balloon to anchor the catheter) were somewhat unsuccessful [16]. This was of particular concern for studies assessing EMG_{di} across a wide range of lung volumes, such as exercise studies.

A study reported in this issue of the *European Respiratory Journal* by Jolley *et al.* [18] used an oesophageal catheter to measure EMG_{di} during exercise in COPD in order to assess the relationship between neural drive and dyspnoea. Thus, for the first time in severe COPD, changes between neural drive and dyspnoea were determined. The authors found that the intensity of exertional dyspnoea was closely related to EMG_{di} expressed as a percentage of maximal EMG ($EMG_{di\%max}$) as much as it was to $EMG_{di\%max}$ expressed relative to V_T expressed as a percentage of predicted vital capacity, an index of neuroventilatory uncoupling. Data from the study suggest that EMG_{di} is a better biomarker of the sensation of dyspnoea and provides insights into the mechanisms of dyspnoea perception.

Of course, the study by Jolley *et al.* [18] on neural respiratory drive is not strictly comparable with previous mechanistic studies on moderate-to-severe COPD employing only P_{oes}-derived measurements. Nonetheless, the O'Donnell group [19] has recently pointed out that increases in $EMG_{di\%max}$ and P_{oes} expressed as a percentage of maximal pressure were closely correlated throughout exercise in health and mild COPD, thus supporting the contention that P_{oes} measures are reasonable surrogates of respiratory neural drive, at least in mild COPD. Remarkably, even in the setting of mild spirometric abnormalities, V_T expansion and V'_E were significantly reduced for a given EMG_{di} (and respiratory muscle effort) compared with controls [19]. In both groups, dyspnoea increased as a function of increasing EMG_{di}, P_{oes} and V'_E, all relative to maximum. This is in line with the results of Jolley *et al.* [18] in severe COPD patients. Thus, the higher dyspnoea intensity at equivalent work rates in mild COPD compared with controls generally reflects their higher drive to breathe and respiratory muscle effort requirements. This inability to appropriately expand V_T is probably explained by the prevailing mechanical ventilatory constraints. This latter contention is supported by previous findings that bronchodilators, by decreasing lung hyperinflation, allow greater V_T expansion during exercise even in mild COPD [20, 21].

Guenette *et al.* [19] reported that EMG_{di} was markedly higher at rest and throughout cycle exercise in mild COPD compared with healthy controls. The ratio of EMG_{di} to diaphragmatic pressure (P_{di}) was also

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significantly higher relative to controls, indicating some degree of neuromuscular dissociation of the diaphragm. The authors argued that this higher ratio was driven, in part, by the more rapid increase in EMGdi, as the rate of increase in *P*di was similar in both groups and increased linearly with increasing exercise intensity. This is in contrast with the work by SINDERBY *et al.* [22] in moderate-to-severe COPD, where a plateau in *P*di occurred relatively early during exercise despite a continued increase in EMGdi. SINDERBY *et al.* [22] proposed that this was the result of reduced pressure-generating capacity of the diaphragm due to lung hyperinflation. Patients with moderate-to-severe COPD have been shown to present with an EMGdi of 70% of maximum at peak incremental exercise [23], which corresponds to a V'E of around 32±10 L·min^{-1} using the same catheter as used in the study by JOLLEY *et al.* [18]. At a similar absolute V'E, GUENETTE *et al.* [19] found that patients with mild COPD have an EMGdi of 37% of maximum, suggesting that respiratory neural drive increases dramatically with advancing COPD severity. This is supported by data from patients with severe COPD who showed a reduction in the inspiratory discharge rate of single motor units recorded from the costal diaphragm following lung volume reduction surgery [24]. Accordingly, the relatively preserved pressure-generating capacity of the diaphragm in their mild COPD subjects probably reflects the presence of less severe mechanical constraints [19].

A strength of the current study by JOLLEY *et al.* [18] is the use of the oesophageal catheter to measure EMGdi. They report that V'E can perform well as a surrogate for neural respiratory drive in patients with minimal neuroventilatory uncoupling as there are similar increases in both EMGdi and minute V'E with exertional dyspnoea. However, in populations of patients in whom neuroventilatory uncoupling is likely to be prevalent, *i.e.* COPD, EMGdi is a more reliable index of neural respiratory drive. Thus, although the oesophageal catheter is also an invasive technique, the associated risks are less than those of intramuscular EMG recordings with large changes in lung volumes. In light of improvements in oesophageal catheter design and analysis techniques, it is the best method to measure EMGdi to assess neural drive during exercise protocols in patients. Unfortunately, JOLLEY *et al.* [18] did not measure intrathoracic pressure in parallel, which could have provided a comparison between neural drive and intrathoracic pressures, and a greater understanding of the interaction of the mechanisms that contribute to dyspnoea in this population. Versions of the oesophageal catheter do have two balloons for measurement of oesophageal and gastric pressures, and it is unclear why these were not considered in the study design.

The authors argue their data support the hypothesis that diaphragm output should be considered the best indicator of an awareness of breathlessness in COPD, with support from data that demonstrated a decrease in costal diaphragm activity following lung volume reduction surgery in COPD patients [24]. However, GORMAN *et al.*[24] also demonstrated a decrease in the discharge rate of single motor units from the scalene muscle. As acknowledged by JOLLEY *et al.* [18], additional studies have demonstrated scalene and parasternal intercostal EMG changes that mirror dyspnoea sensation. It should also be considered that rather than increasing neural drive to one particular inspiratory muscle, differential changes in neural drive to the obligatory inspiratory muscles, *i.e.* an awareness of a change in the balance of drive to muscles, may correlate with dyspnoea sensation and future studies could determine this.

Despite several limitations, especially the lack of measurements of respiratory mechanics, and of qualitative and affective dimensions of dyspnoea, this study significantly adds to the field, and provides insight regarding the relationship between neural drive and dyspnoea during exercise in severe COPD.

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