Morphine to relieve exertional dyspnoea in COPD: myth, dream or reality?

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Dyspnoea, "the subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1], is ever present in patients with chronic obstructive pulmonary disease (COPD) and affects almost all aspects of their daily lives [2]: up 60% of patients have limitations in normal physical activity and more than a third are restricted in family activities [2]. Dyspnoea is usually the earliest and most troublesome complaint for which these patients seek medical attention. As the underlying disease advances, dyspnoea progresses relentlessly, invariably leading to a gradual decrease in activity levels and associated skeletal muscle deconditioning and impoverished quality of life [2]. Dyspnoea also has strong prognostic value for mortality: stronger than the forced expiratory volume in 1 s in patients with COPD or angina in patients with heart disease [3, 4].

The factors that make dyspnoea such a far-reaching symptom are probably what make it so resistant to treatment. Dyspnoea is a complex, multifaceted and highly personalised sensory and affective experience, the basis and mechanisms of which are incompletely understood: there is no unique central or peripheral source for this symptom. It results from the integration of afferent and efferent inputs at the cortical level and is modulated by affective/emotional/behavioural components. The recent statements of the American Thoracic Society [5] and European Respiratory Society [1] have underlined the multidimensional nature of dyspnoea, which comprises three major dimensions: 1) the sensory–perceptual domain; 2) the affective distress; and 3) the symptom impact or burden.

Currently, it is believed that dyspnoea arises when there is a conscious awareness of dissociation between what the brain expects and what it receives through the "corollary discharge": a copy of the descending motor activity sent to sensory to perceptual areas of the brain. This copy is weighted against afferent information from the respiratory system, respiratory muscles, peripheral chemoreceptors and locomotor muscles, and a mismatch will result in dyspnoea [5]. Obviously, breathing is rarely a conscious sensation, because the brain filters (or "gates-out") such routine and inconspicuous information [1]. This prevents us

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from being overloaded by irrelevant sensory information from every nerve ending in the body at the same time. However, with our highly evolved brain, humans have the capacity to bring tidal breathing into conscious awareness at any moment. But even as you suddenly feel yourself breathing while reading these lines, you don't identify the resulting sensation as dyspnoea as sensory input is mandatory, but not sufficient, for dyspnoea to be present. When the sensory stimulus is salient enough to be "gated in" by the mechanisms, we may label it as distressing, thus giving it an affective quality. One could imagine that very similar physiological conditions could be experienced in healthy patients by intense aerobic exercise or a panic attack, but the different affective processing will result in the later begin much more unpleasant than the former.

As such, dyspnoea is not a single sensation, because the brain is able to distinguish different pieces of afferent information and label them with a distinctive "quality". The most frequent subtypes of dyspnoea (and associated descriptors used by patients) are: 1) work/effort ("breathing requires work or effort"); 2) tightness ("chest is constricted, chest feels tight"); and 3) air hunger/unsatisfied inspiration ("starved for air, urge to breathe, like breath holding"). It is generally accepted that these sensations do not share the same physiological mechanisms [1, 5]. Some of these sensations, such as work/effort and air hunger/unsatisfied inspiration may coexist and vary independently in the same subject or experimental condition. Subjectively, each of these sensations may be graded in intensity and unpleasantness. The former relates to the intensity of the sensory experience, and the latter to the degree on discomfort it causes. Revisiting the previous example that compared intense exercise and panics attacks, both could be of similar sensory intensity, with the latter being labelled more unpleasant.

One of the main sources of dyspnoea in patients with COPD is exercise. Exertional dyspnoea can be easily defined as "the perception of respiratory discomfort that occurs for an activity level that does not normally lead to breathing discomfort", and as the disease progresses and patients get worse, exertional dyspnoea will occur with progressively lower exercise intensity. Standardised cardiopulmonary exercise testing, amongst other things, can be used to quantify the intensity of exercise at which dyspnoea becomes limiting. Operationally, the 10-point Borg scale can be used to rate a specific respiratory sensation (*e.g.* inspiratory difficulty, breathing effort, expiratory difficulty or air hunger) or a more general one (*e.g.* breathing difficulty or breathlessness).

Because it is such a prevalent complaint and its measurement is standardised, exertional dyspnoea has become a hallmark in the evaluation of the patients with cardiopulmonary disease that allows both prognostic evaluation and evaluation of response to treatment.

In this issue of the *European Respiratory Journal*, Abdallah *et al.* [6] show that a fast-acting opioid decreased exertional dyspnoea and increased cycle endurance time in patients with COPD. The precise mechanism of the efficacy of opioids on dyspnoea remain obscure, but probably come from the similarities in central processing between some types of dyspnoea and pain [7, 8]. Of note, data from investigations utilising three-dimensional brain-imaging technology have demonstrated that dyspnoea activates cortico-limbic structures that also subserve interoceptive awareness and nociceptive sensations such as pain. Opioids, both endogenous and exogenous, may relieve dyspnoea by altering central processing of efferent and afferent sensory information [1, 5].

It is an emerging concept that the different types of dyspnoea have different underlying mechanisms and may respond to treatment differently. The "air hunger" type dyspnoea appears less related to pain compared with "inspiratory effort" [7, 9]. This is an interesting distinction, because in exercising patients with COPD, there may be a shift from one dyspnoeic sensation to another. Patients will report "work/effort" type dyspnoea early in the exercise, but as tidal volume becomes limited with increasing exercise intensity "unsatisfied inspiration" (which may be similar to "air hunger") becomes the primary dyspnoeic sensation [10].

Inference from the studies showing more similarities between "inspiratory effort" dyspnoea and pain would suggest that opioids may be more effective on this particular type of dyspnoea and that this effect may be more pronounced in the earlier part of exercise, where patients don't experience the sensory consequences of dynamic hyperinflation induced tidal-volume constriction as much. Another mechanism by which opioids may affect individuals differently is through their analgesic effects, potentially affecting the sensation of leg fatigue, an important factor in limiting cycling time in exercising patients with COPD. In a different, but somewhat similar context, narcotics are on the list of World Anti-Doping Agency banned substances for this very reason [11]. These potential individual differences could explain part of why not all patients experienced improvements in exertional dyspnoea in the study by Abdallah *et al.* [6], along with the equivocal results in the literature. Of course some limitations in the study by Abdallah *et al.* [6] should be acknowledged, such as the small study size. In addition, clearly it would have been

helpful to observe the effects of chronic dosing or even a repeat study some time later to see if the *post hoc* classification of responders and nonresponders remained valid.

Nonetheless, opioids remain an interesting source of dyspnoea relief in patients with chronic dyspnoea, and may not be solely for the palliative or refractory cases. Their mechanisms remain to be clearly identified, so as to maximise their efficacy in the clinical setting. Therefore, the study by Abdallah *et al.* [6] is very welcome in the exertional dyspnoea field.

Their widespread use, however, does present a challenge. Even in chronic pain management, long-term opioid use is cautiously recommended and tight surveillance is needed [12]. The risk of abuse and dependence is always looming in the elderly [13], and their respiratory side-effects are particularly noxious to a population with chronic respiratory disease. Other, non-opioid analgesics with fewer side-effects could, in theory, have an effect on dyspnoea, but the few available results have not been encouraging [14]. Recent studies have shown that opioids may increase deleterious outcomes in patients with COPD [15]. So while opioids show promise in the management of exertional dyspnoea, their widespread use has yet to be proven safe in the COPD population.

Opioids are here to stay, but their role and safety in the management of exertional dyspnoea in patients with COPD remains to be determined.

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