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Dyspnoea in acutely ill mechanically ventilated adult patients: an ERS/ESICM statement

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Abstract

This statement outlines a review of the literature and current practice concerning the prevalence, clinical significance, diagnosis and management of dyspnoea in critically ill, mechanically ventilated adult patients. It covers the definition, pathophysiology, epidemiology, short- and middle-term impact, detection and quantification, and prevention and treatment of dyspnoea. It represents a collaboration of the European Respiratory Society (ERS) and the European Society of Intensive Care Medicine (ESICM). Dyspnoea ranks among the most distressing experiences that human beings can endure. Approximately 40% of patients undergoing invasive mechanical ventilation in the intensive care unit (ICU) report dyspnoea, with an average intensity of 45 mm on a visual analogue scale from 0 to 100 mm. Although it shares many similarities with pain, dyspnoea can be far worse than pain in that it summons a primal fear response. As such, it merits universal and specific consideration. Dyspnoea must be identified, prevented and relieved in every patient. In the ICU, mechanically ventilated patients are at high risk of experiencing breathing difficulties because of their physiological status and, in some instances, because of mechanical ventilation itself. At the same time, mechanically ventilated patients have barriers to signalling their distress. Addressing this major clinical challenge mandates teaching and training, and involves ICU caregivers and patients. This is even more important because, as opposed to pain which has become a universal healthcare concern, very little attention has been paid to the identification and management of respiratory suffering in mechanically ventilated ICU patients.

Keywords: Dyspnoea, Critically ill, Management, Mechanical ventilation

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Introduction

Lacking air, having to breathe forcefully, experiencing chest constriction or, more generally, the feeling that breathing is abnormal constitute experiences that are among the worst suffering that a human being can experience (Fig. 1, Table 1) [1]. Although it shares many similarities with pain, dyspnoea can be far worse than pain [1], in that it is consistently associated with the fear of dying. As such, it merits universal and specific consideration as an ethical, moral and humanitarian concern [2,

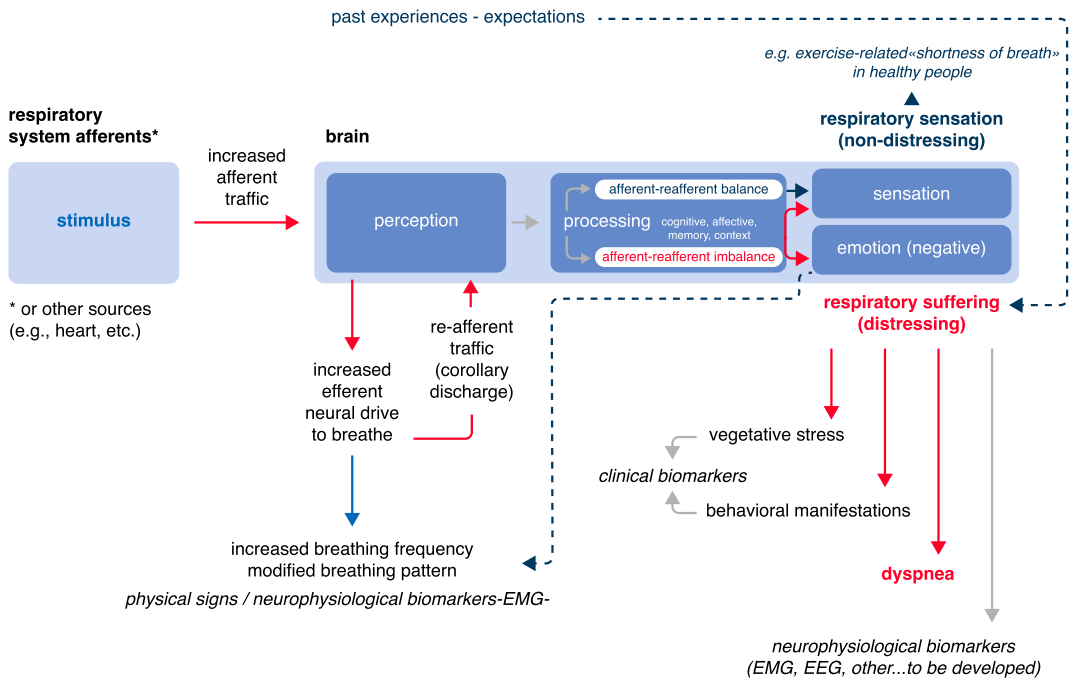

Fig. 1 Schematic representation of the respiratory-related brain suffering concept, its determinants and its consequences. *EMG* electromyography, *EEG* electroencephalography

Table 1 Dyspnoea in acutely ill mechanically ventilated patients: a semantic framework

Dyspnoea
Official definition: [the symptom that conveys] a subjective experience of respiratory discomfort made of various sensations that can vary in intensity
Proposed operational definition: [the symptom that conveys] an upsetting or distressing experience of breathing awareness
Dyspnoea is often dissociated from clinical, radiological or physiological abnormalities; as a result, dyspnoea should be the primary guide of clinical management when it can be evaluated
Dyspnoea is a symptom, hence its identification and assessment rely on self-report; yet, the inability for a patient to self-report does not negate the possibility that the patient can experience respiratory distress
Dyspnoea is the symptom of respiratory-related brain suffering (see below)
Respiratory-related brain suffering
Definition: an ensemble of brain responses to abnormal or abnormally interpreted respiratory-related messages
The respiratory-related messages can be actual or imaginary (memory/anticipation)
A clinical appearance of unconsciousness cannot exclude respiratory-related brain suffering
Respiratory-related brain suffering can be identified through self-reporting of the corresponding experience (dyspnoea), but also through clinical, physiological and behavioural indicators, or through neurophysiological biomarkers
Persistent dyspnoea/persistent respiratory-related brain suffering
Definition: the dyspnoea or respiratory-related brain suffering that persists despite the implementation of available corrective measures for identified pathogenic abnormalities
The persistence of dyspnoea (or of respiratory-related brain suffering) requires a paradigm shift in clinical management, which must then address dyspnoea (or respiratory-related brain suffering) as an autonomous entity
Persistent dyspnoea (or persistent respiratory-related brain suffering) requires brain-oriented management in addition to measures to improve respiratory, cardiovascular or metabolic status

3], and must be identified systematically, prevented and relieved when recognised in patients.

30–50% of mechanically ventilated patients experience breathing difficulties (because of their physiological status or because of the constraints imposed by mechanical ventilation) [4, 5], while at the same time they may be unable to signal their distress, thereby delaying treatment or interventions to alleviate the discomfort. Addressing

this major clinical challenge mandates involving intensive care unit (ICU) stakeholders in discussions of the problem, and subsequent teaching and training. Over the past decades, attention has increasingly been paid to the detection and management of pain in ICU patients [6, 7]. In contrast, during the same period, very little attention has been paid to dyspnoea. For instance, clinical trials devoted to the improvement of the comfort of mechanically ventilated patients did not include the relief of dyspnoea in their protocols [8, 9], while they often included pain relief [6].

For this reason, and with the aim of delineating the magnitude of the problem, the European Respiratory Society (ERS) and the European Society of Intensive Care Medicine (ESICM) decided that publication of a statement was required.

Methods

A multidisciplinary task force, with members from the ERS and the ESICM, including specialists in intensive care, respiratory intensive care, pulmonology, respiratory physiology, neurophysiology, palliative care and psychiatry, together with a patient representative of the European Lung Foundation, defined and answered key issues related to the clinical problem of dyspnoea in critically ill mechanically ventilated patients. In this specific population, task force members compiled a list of six objectives that they considered important and relevant: (1) propose an operational definition of dyspnoea and clarify the underlying concepts; (2) provide insights into the pathophysiology of dyspnoea; (3) estimate the prevalence and severity of dyspnoea; (4) gather the perspectives of patients experiencing dyspnoea while mechanically ventilated and summarise data on the short- and middle-term consequences of dyspnoea; (5) describe approaches for the detection of dyspnoea in mechanically ventilated patients who may or may not be able to communicate with caregivers and (6) identify current and available strategies for dyspnoea relief, as well as areas for future investigation. The task force decided to focus on adult patients and on the acute setting, and hence to exclude chronic home ventilation.

The six topics related to these objectives were discussed in a face-to-face meeting during the ERS International Congress in Madrid (September 2019) followed by a virtual meeting (October 2020). Task force members (19 experts) were divided into subgroups targeting the six topics. Each working group prepared a report, which was integrated into a final report by the task force chairs. The final manuscript was discussed within groups (November 2022) and subsequently revised until consensus among all co-authors was reached (December 2022). All co-authors critically revised and approved the final statement (January 2023). The manuscript was finalised and submitted to the European Respiratory Journal and Intensive Care Medicine.

The present ERS/ESICM statement combines an evidence-based approach with the clinical expertise of the task force members, based on both literature review and discussions during meetings. A systematic database search of medical literature (PubMed) was performed by the members of each working group (supplementary Figure E1 shows the PRISMA diagram for the literature search for the topic related to "estimation of the prevalence and intensity of dyspnoea").

In addition, we performed a patient-centred literature review of the experiences of patients who had suffered dyspnoea while being mechanically ventilated for an acute illness. This was performed in the published and grey literature (patients and caregivers discussing their experiences of dyspnoea while receiving mechanical ventilation). Supplementary Figure E2 shows the PRISMA diagram for the patient-centred literature search.

Dyspnoea in acutely ill, mechanically ventilated patients: conceptual, semantic and operational challenges

The task force proposes the following framework and semantics (Table 1).

Definition of "dyspnoea" and operational issues in the ICU

The American Thoracic Society defines dyspnoea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [2], noting that dyspnoea is actually not an experience in itself, but the symptom that conveys an experience (Table 1). This definition is clear but sophisticated. In the ICU context, the word "discomfort" may not be sufficiently emotionally charged to convey the reality of the ordeal experienced by concerned patients and to create adequate commitment and empathetic concern from healthcare professionals. A simpler and stronger wording could help raise engagement from ICU professionals. A literature search was conducted to find simpler dyspnoea definitions identified the terminology "awareness of respiratory distress" [10]. This definition was adapted to current knowledge by the group leader (T. Similowski, to introduce the notions of "multidimensionality" and "lived experience") and discussed among group members (D. Adler, M.J. Johnson and L. Naccache). The opinions of the task force members and external personalities were gathered, and the definition was disseminated to the ensemble of the task force. Ultimately, the task force proposes that dyspnoea be described as "the symptom that conveys an upsetting or distressing experience of breathing awareness" (Table 1). This proposition

is open to discussion among the concerned communities. Of note, "breathlessness" can be used interchangeably with "dyspnoea" in clinical contexts, namely when there is no ambiguity regarding the "healthy breathlessness" that normal people can experience during exercise or other activities.

The definition of dyspnoea is that of a symptom (as opposed to a physical sign), which places a very strong emphasis on self-reporting [2] to ensure that patients are not denied adequate care if their lived experience does not match measurable physiological abnormalities [3]. The observation of signs of "respiratory distress" (e.g. use of accessory muscles of ventilation, nasal flaring, facial expressions) may indicate the presence of dyspnoea; these physical signs may, however, be attenuated by many factors, including therapeutic interventions otherwise unlikely to relieve respiratory discomfort (e.g. paralytic agents). The inability to verbally or physically report a symptom does not mean that its source is not present and does not cause suffering, as clearly acknowledged about pain [11]. The nature and the very existence of dyspnoea as a symptom depend on a complex series of processes linking its expression to the underlying phenomena, including past experiences and the associated expectations (Fig. 1) [12]. Any abnormality at any stage of these processes can modify the relationship between the symptom and its source. Symptoms also depend on complex interactions between multiple physiological, psychological, social, cultural and environmental factors.

Mechanically ventilated patients frequently have a compromised ability to convey their existential experience to others (*e.g.* speech impeded by ventilator interface, fluctuating vigilance impairing non-verbal communication, ICU-acquired muscle weakness, etc.), and the multiple assaults to the brain that are associated with critical illness are bound to interfere, in a time-varying manner, with the very neural process from which the symptom derives.

Consequently, self-reporting may not be a viable means for the identification of breathing difficulties in mechanically ventilated patients, thereby exposing patients to being left helpless and unacceptably unattended, which typically represents a risk factor for post-traumatic psychological consequences [5]. This justifies broadening the reflections of the clinician to extend beyond "dyspnoea" per se and towards "what is dyspnoea the symptom of", to ensure the adequate management of critically ill, mechanically ventilated patients with troubled breathing.

What is dyspnoea the symptom of?

By definition, a symptom is the self-reported reflection of an abnormal physiological process. While dyspnoea is generally (but not necessarily) triggered by respiratory, cardiovascular, muscular or metabolic abnormalities, it stems from the perception, cognitive processing and emotional treatment of these "peripheral" signals by the brain.

Consistent evidence shows that dyspnoea occurs concomitantly with the activation of brain networks involving motor, sensory and interoceptive regions [2]. This has been shown using functional magnetic resonance imaging and electroenceophalography during experimental dyspnoea of various types in healthy humans [13–16], during clinical dyspnoea in patients with chronic respiratory diseases [17–19] or under mechanical ventilation [20, 21]. This has also been shown during the anticipation of dyspnoea in normal subjects [22, 23] and in patients with chronic obstructive pulmonary disease (COPD) [18, 24]. This phenomenon, which can be summarised as "an ensemble of brain responses to abnormal respiratory-related messages" could tentatively be termed "respiratory-related brain suffering". Respiratory-related brain suffering (or whatever term will be retained to designate it) represents the source event, of which dyspnoea is "only" the symptom (Fig. 1). Respiratory-related brain suffering, with its sensory and emotional consequences, can therefore occur, for example, in patients apparently unconscious but who are actually "minimally conscious" (as defined in [25]), keeping in mind that distinguishing "minimal consciousness" from "vegetative state" can be difficult in routine care at the bedside. Any doubt about a patient's consciousness status raises the hypothesis that respiratory-related respiratory suffering is a possibility, as in the case of nociception/pain. Indeed, data from brain imaging suggest that adverse experiences are processed by the brain even when the patient is unconscious from sedation [26]. Furthermore, respiratory-related brain suffering can occur as a result of experience/expectation phenomena, *i.e.* in the absence of an actual respiratory stimulus [12, 27], in the same way that pain can occur in the absence of nociception [11].

Of note, the concept of respiratory-related brain suffering as the source of dyspnoea and as a legitimate diagnostic and therapeutic target is only now emerging. As a result, the word "dyspnoea" is mainly used in the present document, but in many instances replacing it with "respiratory-related brain suffering" would be appropriate.

Operational consequences: identifying dyspnoea when possible, respiratory-related brain suffering when not

Since the inability to report dyspnoea does not negate the possibility of respiratory-related brain suffering (by analogy with pain [11]), most task force members actively and systematically enquire about dyspnoea but also try to identify respiratory-related brain suffering, particularly

when interactive communication with the patient is unreliable (Fig. 2).

Certain clinical, behavioural and physiological manifestations scored together (known as "respiratory distress observation scales") correlate with dyspnoea in patients who can communicate, and might serve as markers of respiratory-related brain suffering in patients who cannot convey their experience [28, 29]. Since the bedside presence of ICU healthcare professionals is inherently intermittent, development of physiological markers of respiratory-related brain suffering that could be continuously monitored is a relevant research priority. Meanwhile, because of the high risk of respiratory-related brain suffering in mechanically ventilated patients, most task force members look for dyspnoea systematically (as for pain) in perilous situations (*e.g.* weaning from mechanical ventilation, changing ventilator settings), to evaluate corrective interventions.

From symptom to existential experience: occult and persistent dyspnoea

Unidentified or under-addressed respiratory-related brain suffering generates helplessness, frustration and fear, a recipe for post-traumatic psychological consequences [5, 30]. This is also the case when the treatment of identified causes fails to fully solve the problem (the "chronic breathlessness" concept [31]). The adjective "persistent" can be used to designate dyspnoea or respiratory-related brain suffering still present after the implementation of the measures available to correct their sources [32]. Persistent dyspnoea or persistent respiratory-related brain suffering then become autonomous entities, irrespective of the underlying disorders [31]. This requires a paradigmatic change in therapeutic strategies, and interventions targeting brain mechanisms need to be considered in addition to measures to improve respiratory, cardiovascular or metabolic status [33].

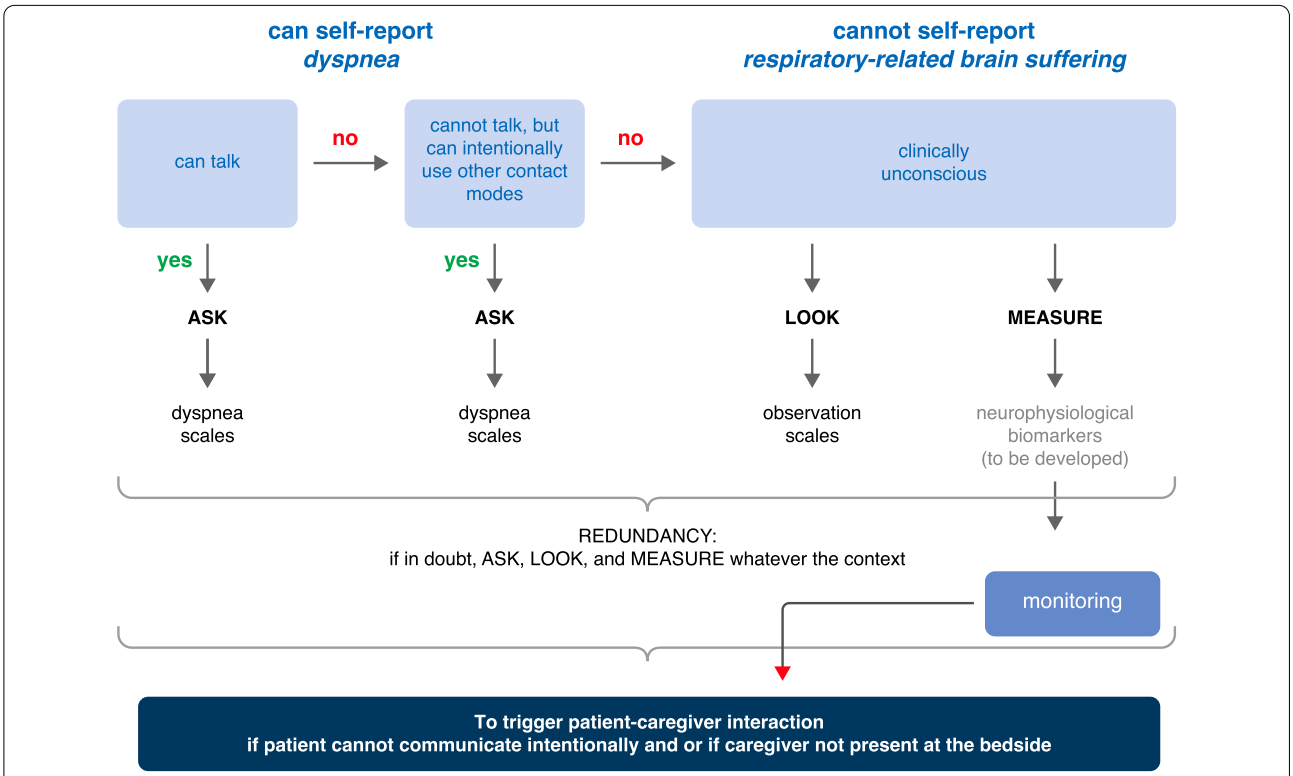

Fig. 2 Approach to identify respiratory-related brain suffering in mechanically ventilated patients in the intensive care unit (ICU), depending on their communication capabilities ("Ask, Look, Measure"). This figure describes the approach used by task force members and is not intended as a general recommendation. Whatever these capabilities, redundancies and the monitoring of biomarkers are likely to improve diagnosis and, by way of consequence, access to care (e.g. an ICU patient able to communicate at a given point in time may not be able to do so, or less reliably, very shortly afterwards). "Clinically unconscious" can correspond to "minimal consciousness", namely to states in which behaviour can only be explained by the participation of cortical networks (consciously or not). It can also correspond to states in which behaviour can be fully accounted for by subcortical mechanisms (vegetative) [6]. Distinguishing these situations at the bedside can be challenging

Pathophysiology of dyspnoea and factors associated with mechanical ventilation that may affect dyspnoea

In contrast to pain, which is typically a very easily localised discomfort, dyspnoea is an interoceptive experience that integrates signals from multiple sources throughout the body [34].

The pathophysiology of dyspnoea is complex and includes increased resistive and elastic loads on the ventilatory pump, as well as input from a range of receptors, such as chemoreceptors, pulmonary stretch receptors and C-fibres, trigeminal nerve sensory branches, and muscle spindles, which provide information contributing to the central drive to breathe and inform the brain of the mechanical response of the respiratory system for any given neurological output to the respiratory muscles [35]. It has been proposed that efferent neural drive to breathe, which contains a sensory consequence (the corollary discharge), is continuously compared within the cortex with the incoming flux of respiratory-related afferents [36]. Dyspnoea arises in the event of a mismatch between the expected (corollary discharge) outcomes and real (afferent) sensory information associated with the achieved ventilation [36]. According to this uncoupling theory, dyspnoea can be seen as an imbalance between the "demand for breathing" (i.e. the respiratory drive) and the capacity of the respiratory system to "satisfy this demand", which depends in part on the level of assistance delivered by the ventilator (Fig. 3).

The quality and intensity of the breathing discomfort largely reflect the origins and nature of the stimuli and the ventilatory response. Based on the nature of the cardiorespiratory abnormalities responsible for "respiratory-related brain suffering", the institution of mechanical ventilation may either relieve, leave unaffected or, paradoxically, worsen dyspnoea. There are three main distinct uncomfortable breathing sensations: air hunger, excessive effort and chest constriction. These different forms of dyspnoea are caused by different afferent mechanisms and are evoked by different physiological stimuli [37]. However, they are commonly associated with each other in a given patient.

Excessive breathing effort, also described as increased sense of work, is perceived when the physical work of breathing is increased by an augmentation of respiratory muscle loading, or when cortical motor drive is increased because of respiratory muscle weakness [37]. Increased respiratory muscle loading can be due either to decreased lung compliance or increased airway resistance.

In theory, the ventilated patient should not have to perform excessive respiratory work since the ventilator is supposed to assume a large part of the work of breathing. However, if the level of assistance provided by the ventilator does not compensate the load excess, there is an imbalance between the patient's demand and the level of assistance, a typical cause of the perception of excessive inspiratory effort. Although common and sometimes intense, the sense of excessive breathing effort may not evoke an emotional response (e.g. fear and anxiety) as strong as that associated with air hunger [38].

Air hunger is the conscious perception of the need for more air and is typically described by subjects as "not getting enough air" [39]. This is one of the strongest and most unpleasant forms of dyspnoea [39, 40]. This sensation typically arises when there is a strong stimulus to breathe, as dictated by the respiratory control centres, and is exacerbated when the movement of the lungs and chest wall is restricted (neuromechanical uncoupling) [41, 42]. For instance, during volume control ventilation in both healthy subjects and in alert patients ventilated for respiratory muscle paralysis, an acute rise in arterial carbon dioxide tension ($PaCO_2$) evokes severely uncomfortable air hunger [39]. When ventilatory modes that diminish patient control in establishing parameters such as inspiratory flow, duty cycle and inspiratory volume are employed, dyspnoea may be worsened. In this respect, lung protective ventilation with low tidal volume may cause air hunger [43]. Air hunger is not necessarily caused by contraction of respiratory muscles. However, mechanoreceptor input arising from the respiratory system can dramatically reduce air hunger; increasing tidal volume under constant minute ventilation is known to decrease dyspnoea [44]. When the neural drive to breathe results in lower-than-expected consequences of the mechanical work, *i.e.* the patient's work of breathing does not result in the expected ventilatory output due to high respiratory impedance, irrespective of the ventilatory mode, the patient experiences a sense of air hunger and respiratory discomfort ensues [38].

Finally, it is important to keep in mind that dyspnoea does not depend solely on perceptual mechanisms (comparison of the efferent neural drive to breathe with the respiratory-related afferent influx) but also on cognitive and emotional mechanisms. A given respiratory sensation can result in different emotions depending on a large variety of factors, including prior dyspnoeic experiences. As a result, interventions that interfere with "respiratory cognition" can relieve dyspnoea independently of any change in respiratory mechanics or the neural drive to breathe [45, 46]. Recent data indicate that brain-targeted interventions can be effective in mechanically ventilated patients [47]. This means that dyspnoea relief is possible without increasing lung volume, a major finding in situations where lung protective ventilation is of the essence.

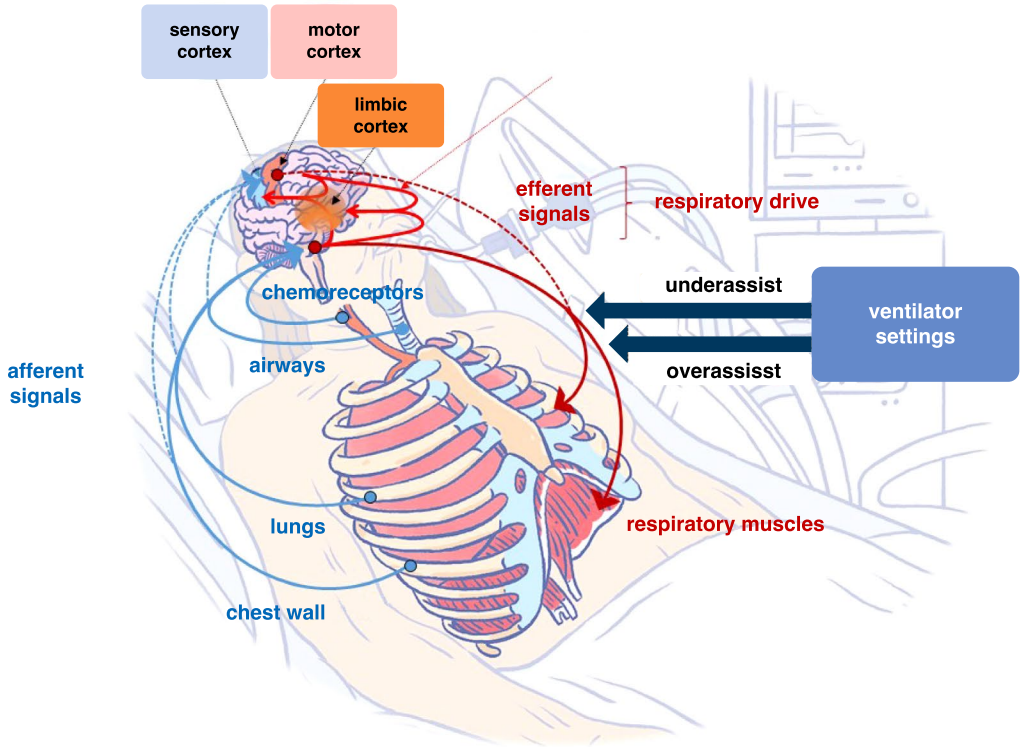

Fig. 3 Mechanisms of dyspnoea. Several regions of the brain (including the brainstem, limbic and sensory cortex areas) are permanently bombarded by multiple respiratory-related afferent messages arising from an array of receptors (e.g. chemoreceptors, lung stretch receptors and C-fibres, trigeminal nerve sensory branches, etc.). It has been proposed that this incoming flux of information is continuously compared with the outgoing flux of commands that leaves the central nervous system to control the respiratory muscles (the respiratory drive to breathe), through "central copies" of the efferent information (corollary discharge theory). If the expected and real sensory information (corollary discharge and afferent traffic, respectively) are matched, the cognitive processing does not give rise to any negative emotion, and the corresponding respiratory sensation can be filtered out. On the contrary, a mismatch between the corollary discharge and the actual sensory information triggers abnormal brain responses in interoceptive and emotional brain networks (including the insula, the cingulate gyrus, the amygdala, etc.) that define respiratory-related brain suffering, of which dyspnoea is the symptom. The sensory "coloration" of dyspnoea varies with the source of the afferent–efferent uncoupling, with "excessive effort" more related to mechanical loading, "air hunger" more related to inadequate alveolar ventilation and "chest tightness" more related to bronchoconstriction. Even though of mixed sensory description, clinal dyspnoea is dominated by "air hunger". It is always associated with anxiety and fear. Patients placed under mechanical ventilation typically lose control of the respiratory mechanical output (e.g. duty cycle, inspiratory flow, tidal volume, minute ventilation). The settings of ventilatory assistance may fail to correct the load–capacity imbalance that is characteristic of respiratory failure (underassist) or create inadequate constraints (overassist). Mechanically ventilated patients are therefore particularly prone to respiratory-related brain suffering due to afferent–efferent discrepancies. This can go unnoticed when the patients are unable to self-report the corresponding dyspnoea, hence the risk of enduring and traumatising suffering

Prevalence and underestimation of dyspnoea

Dyspnoea is listed among the main research topics of about 50 studies conducted in invasively mechanically ventilated patients [4, 5, 20, 29, 35, 48–94]. The conditions and main results of these studies are summarised in supplementary Tables E1–E3.

Prevalence and intensity of dyspnoea

Studies fall into three categories: (1) retrospective recall studies, in which ICU survivors were asked to recount their breathing experiences after ICU discharge (12 studies reported across 14 publications, 1249 patients) (supplementary Table E1) [48, 52–64]; (2) prospective observational studies, in which the prevalence and/or intensity of dyspnoea was assessed without any planned interventions (21 studies, 2356 patients) (supplementary Table E2) [5, 29, 35, 50, 51, 65–80] and (3) prospective interventional studies, in which dyspnoea was assessed during planned interventions, mostly changes in ventilator settings or initiation of a spontaneous breathing trial (17 studies, 430 patients) (supplementary Table E3) [4, 20, 49, 81–94].

The median prevalence of dyspnoea is 45% (from 9% to 100%) in retrospective studies, 49% (from 11% to

100%) in observational studies and 47% [4] and 66% [93] in the two interventional studies in which it was quantified (Fig. 4). On a dyspnoea rating scale from 0 mm (no dyspnoea or respiratory discomfort) to 100 mm (worst imaginable dyspnoea or respiratory discomfort), median is 62 mm (from 48 mm to 92 mm) in retrospective studies, 44 mm in observational studies and 36 mm in interventional studies (Fig. 4).

These studies are extremely heterogeneous in terms of their design. A large variety of terms were used to assess dyspnoea in patients, such as breathlessness, shortness of breath, suffocation, air hunger, choking, endotracheal tube discomfort, respiratory distress, not enough air, etc. Sample size, condition (post-operative, medical, difficult to wean, etc.), scale used to assess dyspnoea (visual analogue, numerical, modified Borg, categorical or Likert), and time point of assessment are very different between studies. For instance, on the day of ICU admission, 57% of patients report dyspnoea, with a median rating of 45 mm [29]. On the first day that intubated patients can reliably self-report dyspnoea, 42% do so, with a median rating of 50 mm [4, 5]. On the day of the first spontaneous breathing trial, before its initiation, 25% of patients report dyspnoea, with a 20 mm median rating [49, 51, 68, 76, 81].

Altogether, these data show that dyspnoea in critically ill patients is frequent and, importantly, also severe. Similar levels of pain would certainly be judged unacceptable by caregivers.

Underestimation of dyspnoea in mechanically ventilated patients

Data from many studies suggest that the prevalence, the intensity and the impact of dyspnoea are all underestimated by caregivers when assessing mechanically ventilated patients. Again, the same applies, to a greater extent, to respiratory-related brain suffering.

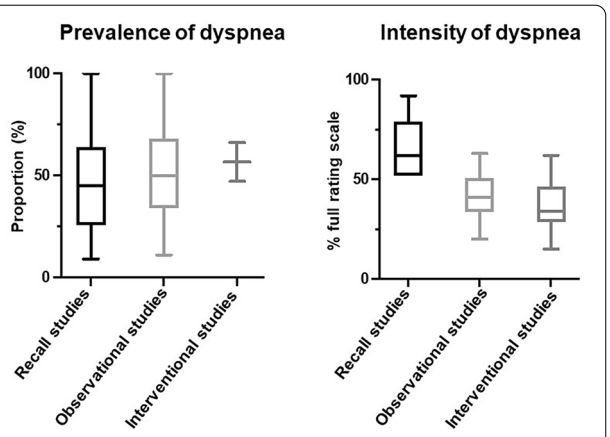

Fig. 4 Prevalence and intensity of dyspnoea in mechanically ventilated patients. Box plots represent median and interquartile range, whiskers represent ranges (maximum and minimum)

Patients are not asked

First, in comparison with pain, the absence of guidelines on dyspnoea in mechanically ventilated patients may suggest a low level of awareness of this symptom within the ICU community. Second, the systematic assessment of dyspnoea at the time of admission is not a routine procedure (in contrast with pain) and must be actively implemented for dyspnoea to become an object of study or of care [95–97]. Third, dyspnoea presents a greater challenge to symptom management than pain, potentially due to the absence of clinical guidelines for the management of dyspnoea in critically ill patients [35].

Patients are unable to self-report dyspnoea

In addition to the limitations imposed by endotracheal intubation and mechanical ventilation with respect to vocal self-report of dyspnoea, many invasively mechanically ventilated patients cannot reliably use other means of communication due to other factors, e.g. because of sedation or a low level of consciousness, delirium, psychiatric disease, deafness or poor language skills. However, being noncommunicative does not mean that a patient is not suffering from breathing difficulties. It only means that the patient cannot report it. In other terms, the inability to communicate intentionally does not negate the possibility of experiencing respiratory-related brain suffering (Fig. 2).

Clinicians underestimate dyspnoea

At least three studies have reported a major discrepancy between patients' perception of their dyspnoea and the estimation of this dyspnoea by healthcare professionals [35, 75, 77]. For this reason, dyspnoea in mechanically ventilated patients may be characterised as "invisible" [98]. Of note, informal personal caregivers (i.e. family members) had good agreement with patient reports of moderate-to-severe dyspnoea [35].

Short- and middle-term impact of dyspnoea

In mechanically ventilated patients, the consequences of dyspnoea may occur either immediately, during the ICU stay, or be delayed.

Short-term impact

Immediate suffering

A patient-centred literature review shows clearly that dyspnoea is an awful feeling, responsible for immediate psychological distress. Patients describe dyspnoea as a very difficult experience [99], labelled in one

study as "the tough time" [100], tiring, frightening and overwhelming: "I can't say anything except that it was tough" [100], "I couldn't stop breathing, my energy was consumed by breathing effort" [48], "It's hell. Not getting air" [101]. Some patients recalled that the dyspnoea they experienced while being ventilated made them feel as though they were dying [48, 102, 103]: "I felt like I was dying and didn't get any air" [103], "I often thought about death while I was attacked by dyspnoea" [48]. The fact of being intubated intensifies this difficulty, especially when patients were unable to communicate their dyspnoea to healthcare staff [104]: "Then, I was trying to point out that everything was stuck in my throat … to get some air into the lungs. They [the nurses] didn't understand that … which was very bad. And then it was so terribly heavy, that I was just … [silence] … I felt that I was crying out, but no one could hear anything" [104]. Patients experiencing dyspnoea also found it hard to think of anything else other than their breathing, and the need to keep breathing to stay alive became all-consuming [48]: "At that time, to me, my breathing was the only thing that mattered in life, like a person is drowning … something to cling to no matter what" [48]. "As one doctor put it, when you can't breathe nothing else matters. So Mum just spends her days in ICU trying to breathe. She can't read, watch television, or even send a text message" [105]. Some patients described the ventilator as a "life saver" and knew it was necessary for their survival [106–109]: "I've decided in my brain that it doesn't matter how uncomfortable it is, it's still a relief and a comfort. I will put up with that sooner than not have the mask" [108].

Association with anxiety

Mechanically ventilated patients with dyspnoea are more likely to present with anxiety than non-dyspnoeic patients (71% versus 24% [4]), and dyspnoea is independently associated with anxiety in intubated patients [4, 29, 49] and in those who receive non-invasive ventilation (NIV) [34]. Dyspnoea relief, e.g. as obtained through modified ventilator settings, is associated with dramatic anxiety relief, which suggests causality [4]. In the patient-centred literature, patients recounted how the sensation of dyspnoea made them feel anxious, fearful and panicked. This would then worsen their dyspnoea, which would in turn increase their panic, leaving them trapped in a cycle of breathlessness and fear [48, 101, 102, 104, 110]: "During the acute dyspnoea, I was panicked, I felt I will die and this thought had made my breathing harder" [48]. The interplay between anxiety and dyspnoea is well-established and complex; causal relationships can exist in both directions [111].

Association with poor sleep

In mechanically ventilated patients, dyspnoea is associated with poor sleep, at least in patients receiving NIV [112]. Patients reported that the sensation of fatigue could be exacerbated by the panic and anxiety caused by dyspnoea, together with difficulty sleeping because of it [101, 103].

Weaning from mechanical ventilation

A higher level of dyspnoea during the ICU stay or prior to the initiation of the spontaneous breathing trial seems to be associated with a higher risk of weaning failure [49, 50, 113]. The intensity of dyspnoea at the end of a spontaneous breathing trial is higher in patients who fail the spontaneous breathing trial [51, 114]. In intubated patients, persistent dyspnoea despite an optimisation of ventilator settings is associated with delayed extubation [4].

Risk for intubation

Dyspnoea, being a marker of the respiratory system load–capacity imbalance, has been proposed as a predictor of intubation in patients admitted to the ICU for acute respiratory failure. In patients receiving NIV, the level of dyspnoea 1 h after NIV initiation was independently associated with NIV failure [34]. A similar observation was made in patients affected by coronavirus disease 2019 (COVID-19) treated with either high-flow nasal cannula oxygen or helmet NIV [115].

Mortality and length of stay

Whether dyspnoea is independently associated with a higher mortality or length of stay in intubated patients is uncertain [4, 5]. In patients receiving NIV for acute respiratory failure, moderate-to-severe dyspnoea after the first NIV session is associated with higher ICU and hospital mortality, and with longer ICU and hospital length of stay [34].

Delayed impact of dyspnoea on dark recollections of ICU stay and on post-traumatic stress disorders

Survivors of an ICU stay often carry extremely dark "respiratory" recollections of the experience, which may persist for several weeks. About 55% of COPD patients remember being suffocated while they were mechanically ventilated [52]. Almost 29% of patients mechanically ventilated for more than 48 h recalled after their stay in the ICU that they had been distressed by not getting enough air from the endotracheal tube [53].

The combination of a distressing threat to life and a feeling of helplessness may generate trauma and

subsequent post-traumatic stress disorder (PTSD) [30], which concerns approximately 20% of patients [116]. The inherently traumatic nature of breathlessness arises from its uncontrollability. Unpredictable and uncontrollable stressors have more severe psychological impact than predictable and controllable events [117]. The uncontrollable nature of breathlessness and its association with PTSD were evidenced by studies of torture survivors. In a study that examined the relative psychological impact of 45 torture methods, asphyxiation was the most important predictor of more PTSD symptoms [118]. In another study, asphyxiation was rated as the most uncontrollable and the second most distressing stressor event after rape [119].

Having been mechanically ventilated seems to play an important role in the genesis of PTSD [120, 121]. In mechanically ventilated patients, those who experience repeatedly a traumatic experience, including respiratory distress, have maximal impairment in psychosocial functioning [54]. In a cohort of intubated patients interviewed 90 days after ICU admission, a significantly higher proportion of individuals with probable PTSD was observed among patients who were dyspnoeic on the first day they were able to communicate (29% versus 13%) [5]. The density of dyspnoea (number of dyspnoeic episodes divided by time from enrolment to extubation) was independently associated with probable PTSD. Multiple exposures to dyspnoea during mechanical ventilation therefore appears to be an independent predictor of probable PTSD. This is in line with research in the field of human rights. Indeed, with suffocation torture, there is a linear dose–response relationship between the frequency of episodes of suffocation torture and PTSD symptoms that does not exist with other forms of torture [122, 123].

Tools to detect dyspnoea in communicative and in noncommunicative patients

Like pain, the assessment of dyspnoea is based on self-report, which requires the patient to be communicative. In noncommunicative patients, observation scales or physiological markers can be used as dyspnoea surrogates.

Self-report of dyspnoea in communicative patients

Unidimensional tools: measurement of dyspnoea presence and intensity

As is the case with pain [7], to self-report dyspnoea, the patient must be able to interpret sensory stimuli, pay attention to the clinician's instructions, concentrate on formulating a dyspnoea self-report, be able to communicate in some way, and be able to recall the previous report, when trending is requested [124]. Clinical studies show that two-thirds of critically ill patients who are not deeply sedated are generally able to reliably answer simple questions about their symptoms or experiences when questioned during their care [29, 73, 80]. This proportion significantly decreases (less than 50%) in patients receiving invasive mechanical ventilation [73]. There are no clearly defined criteria to determine whether a patient is communicative or able to reliably self-report a symptom. A reasonable level of awareness, defined by a Richmond Agitation and Sedation Scale score (RASS) [125] between -2 and $+2$, combined with the absence of delirium/confusion according to the Confusion Assessment Method for the ICU (CAM-ICU) [126], seems reasonable, but there is significant clinical variability in patient capabilities within these parameters.

The following approach is usually used to detect the presence of dyspnoea: the caregiver may employ dichotomous trigger questions, such as "is your breathing comfortable?", "do you feel breathless?", "do you feel short of breath?", "are you getting enough air?" while ensuring that the patient's answers are consistent between at least two formulations [2]. Consistency between the answers to these dyspnoea trigger questions will reinforce the conviction that self-report can be reliably elicited in a patient. The last step is then to evaluate the intensity of dyspnoea. Of note, this approach may underestimate the prevalence of dyspnoea, since almost 40% of patients who declare that they do not feel dyspnoea actually rate a dyspnoea that is more than zero on numerical rating scale [127].

Although more than 40 tools are available to quantify the intensity of dyspnoea [128], none of them is ideal for critically ill patients. If the patient can point to a line, it is possible to use the 100-mm dyspnoea visual analogue scale (VAS) [2]. An alternative is to use a 0–10 numerical rating scale (NRS), which consists of determining, either verbally (asking between 0 and 10) [129] or visually (pointing a finger/mark on the 0–10 scale), which value corresponds to the patient's dyspnoea intensity [130]. In the modified Borg category ratio (0–10) scale, which consists of verbal descriptors linked to specific numbers, the spacing of the numbers and corresponding descriptors essentially provides a category scale with ratio properties [131].

Multidimensional tools: measurement of emotions and sensations related to dyspnoea

The Multidimensional Dyspnea Profile [132] is the only multidimensional tool that has been used in the ICU [133]. It quantifies the respective affective (unpleasantness of breathing), sensory (physical breathing effort, air hunger, tightness, mental breathing effort and hyperpnoea) and emotional (depressed, anxious, angry, frustrated and afraid) components of dyspnoea. Its

A. RDOS

Variables	0 points	1 point	2 points
1 - Heart rate (beats/min)	< 90	90-109	≥ 110
2 - Respiratory rate (breaths/min)	≤ 18	19-30	> 30
3 - Restlessness: nonpurposeful movements	None	Occasional, slight movements	Frequent movements
4 - Paradoxical breathing pattern: abdomen moves in on inspiration	None		Present
5 - Use of neck muscles during inspiration: rise of clavicle during inspiration	None	Slight rise	Pronounced rise
6 - Grunting at end inspiration: guttural sound	None		Present
7 - Nasal flaring: involuntary movement of nares on inspiration	None		Present
8 - Facial expression or fear	None		Eyes wide open, facial muscle tense, brow furrowed, mouth open, teeth together

B. IC-RDOS

Variables	Score
0 -	3.3
1 - Heart rate (beats/min)	+ (Heart rate) / 65
2 - Use of neck muscles during inspiration	
if present	+ 1
if absent	- 1
3 - Paradoxical breathing pattern	
if present	+ 1
if absent	- 1
4 - Facial expression of fear	
if present	+ 1
if absent	- 1
5 - Oxygen supplemental	
if present	+ 0.7
if absent	- 0.7

C. MV-RDOS

Variables	Score
0 -	3.3
1 - Heart rate (beats/min)	+ (Heart rate) / 65
2 - Use of neck muscles during inspiration	
if present	+ 1
if absent	- 1
3 - Paradoxical breathing pattern	
if present	+ 1
if absent	- 1
4 - Facial expression of fear	
if present	+ 1
if absent	- 1
5 - Respiratory rate (breaths/min)	+ (Respiratory rate) / 50

Fig. 5 Calculation of the **A** Respiratory Distress Observation Scale (RDOS), **B** intensive care RDOS (IC-RDOS) and **C** the mechanical ventilation RDOS (MV-RDOS)

application to clinical practice is not clearly delineated yet.

Inference of dyspnoea in noncommunicative patients

Observation scales

Observation scales are an alternative way to identify respiratory-related brain suffering when dyspnoea cannot be self-reported.

The Respiratory Distress Observation Scale (RDOS) is an eight-item ordinal scale, which infers the presence of dyspnoea based on three dimensions: respiratory (respiratory rate, use of neck muscles, paradoxical motion of the abdomen, nasal flaring, grunting at end expiration), vegetative (heart rate) and emotional (facial expression of fear). It has established inter-rater and scale reliability as well as construct, convergent and discriminant validity [28, 134–136].

The intensive care RDOS (IC-RDOS) is version of this scale that has been adapted to the ICU [29, 137, 138]. This scale is reliable in noncommunicative critically ill patients. It includes five observable items (Fig. 5). Inter-rater reliability, as well as construct and convergent validity, are high. More recently, the mechanical ventilation RDOS (MV-RDOS) has been designed to be more adapted to intubated patients [139]. Calculation of RDOS, IC-RDOS and MV-RDOS is depicted in Fig. 5 and an online calculator has been developed (https://dos-calc.pvsc.fr).

Figure 6 describes the way task force members usually assess respiratory-related brain suffering in critically ill or terminally ill patients.

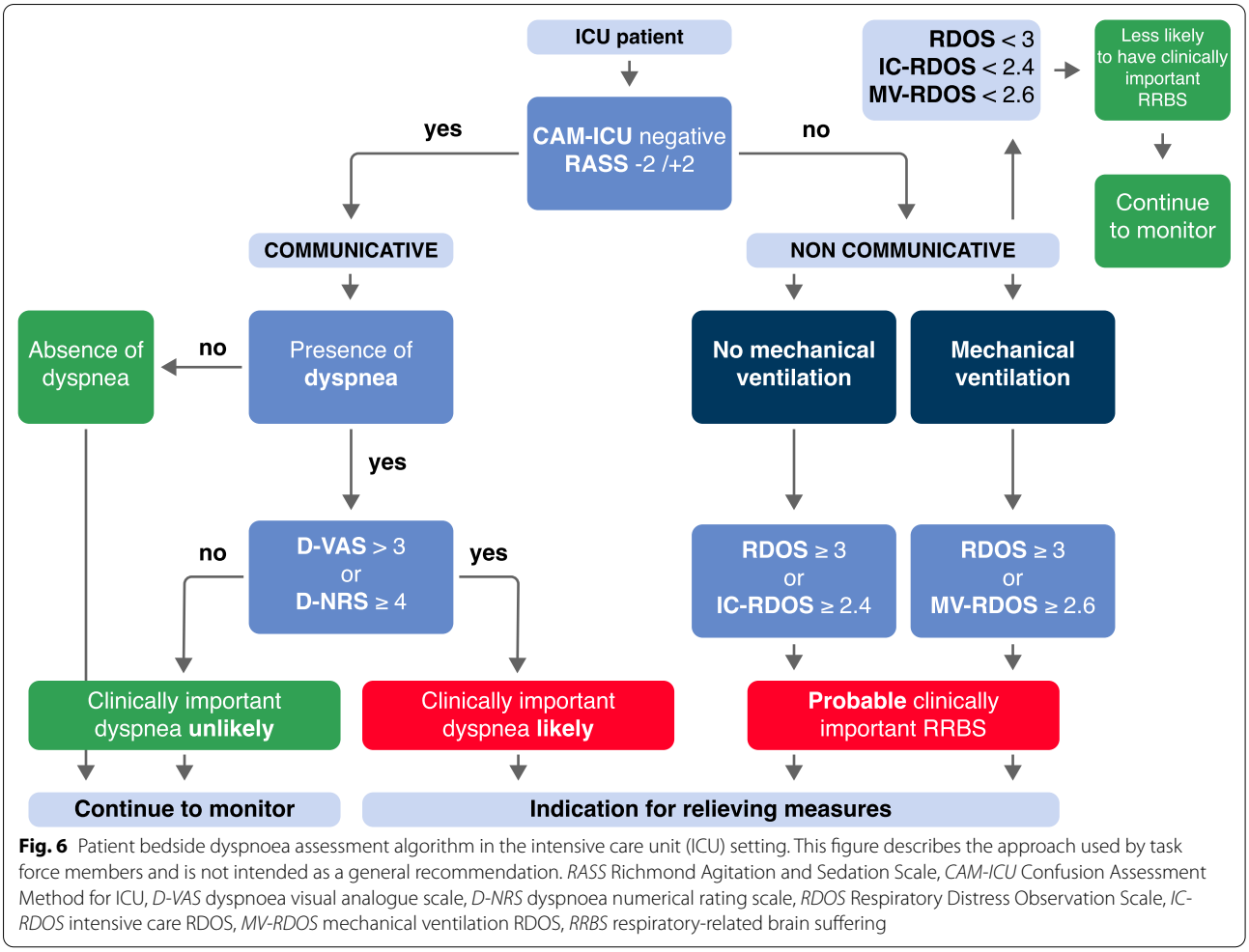

Fig. 6 Patient bedside dyspnoea assessment algorithm in the intensive care unit (ICU) setting. This figure describes the approach used by task force members and is not intended as a general recommendation. *RASS* Richmond Agitation and Sedation Scale, *CAM-ICU* Confusion Assessment Method for ICU, *D-VAS* dyspnoea visual analogue scale, *D-NRS* dyspnoea numerical rating scale, *RDOS* Respiratory Distress Observation Scale, *IC-RDOS* intensive care RDOS, *MV-RDOS* mechanical ventilation RDOS, *RRBS* respiratory-related brain suffering

Electrophysiological indicators of dyspnoea in intubated patients

Two electrophysiological indicators of respiratory-related brain suffering have currently been correlated with dyspnoea in healthy subjects and ICU patients: (1) electromyographic activity of the diaphragm [40] and of extra-diaphragmatic inspiratory muscles [86, 140, 141]; and (2) respiratory-related electroencephalographic signatures as identified in an event-related manner (premotor inspiratory potentials) or through continuous connectivity analyses [20, 142]. These indicators are correlated with dyspnoea, but the clinical value of these tools remains to be established.

What is a clinically important dyspnoea?

Clinically important dyspnoea is often defined as dyspnoea VAS > 3 or dyspnoea NRS ≥ 4, as this cut-off has been used to benchmark the quality of palliative care in academic hospitals [143]. Various elements justify this cut-off. First, it corresponds to the lower quartile of dyspnoea ratings in ICU patients experiencing dyspnoea [86, 128]. Second, a dyspnoea NRS ≥ 4 corresponds to "moderate intensity" when compared to verbal descriptors [144]. Third, by analogy with pain, a pain NRS ≥ 4 is also the cut-off for "moderate-to-severe pain" and constitutes a clear indication for prompt analgesic prescription [7]. Fourth, dyspnoea NRS ≥ 4 is associated with poorer outcomes, such as weaning failure [51, 114], extended time until intubation [75], NIV failure and hospital mortality, in NIV patients [34]. However, in the only study assessing whether a given level of dyspnoea is "acceptable" to patients, a significant proportion (30%) of patients with ratings < 4 considered their discomfort to be "unacceptable" [145].

Interventions to relieve dyspnoea

The relief of dyspnoea is currently considered by some authors to be a basic human right [30, 146]. In mechanically ventilated patients in the ICU, the minimal clinically important difference, which is the minimal change in dyspnoea that any intervention should target, is not defined. In other populations, the minimal clinically

important difference is one point on a scale from 0 to 10 (or 10 points on a scale from 0 to 100) [147, 148] or a 15% decrease in the dyspnoea VAS [149]. Because of the frequent lack of correlation between dyspnoea and physiological abnormalities, the latter may be unreliable to guide dyspnoea-targeted therapeutic interventions (for example, an intervention that improves haematosis may fail to relieve dyspnoea). Therefore, as in the case of pain, dyspnoea itself, when it can be assessed, must be used to guide the corresponding clinical management.

Reassurance of patients regarding their dyspnoea and enhancement of patients' sense of control

Feeling unsupported by healthcare staff or experiencing poor communication from staff also exacerbates an already unpleasant situation for patients [99]. For some, just knowing that staff were in the room or nearby could be comforting, give them a sense of security and make the experience less frightening [48, 99, 104, 107, 110]. Others recounted how staff were able to calm them, give explanations for their dyspnoea, and provide an empathetic and reassuring presence [48, 107, 108]: "She continued, 'I'll watch your breathing, don't worry.' She was like one of my daughters, and my fear was relieved by her" [150]. For others, however, being instructed to relax or control their breathing could be counterproductive, as they found that this could make the situation worse [48]: "A nurse in the ICU repeatedly told me to control my breathing, but I just couldn't do it, and this even made me feel more stressed" [48].

The lack of control over stressor events (or helplessness anxiety) has an important role in traumatic stress [117], which can be reduced by interventions specifically aimed at enhancing sense of control in trauma-exposed individuals [151, 152]. Being able to communicate gives patients a sense of control and allows them to take a more active part in their treatment [150].

No qualitative studies have explored the experience of relatives observing their family members suffering from dyspnoea. For the patients, there could be ambivalence about having loved ones present and witnessing their distress. On the one hand they were reassured by their presence [101, 104, 107]; on the other, they wanted to protect them from the experience [102]: "Q: Does their [the family's] presence reassure you?" "A: Hmm… it reassures me if they're there. But it doesn't reassure me when they see me fighting the mask. I have mixed feelings" [102].

Reduction of non-respiratory stimuli of respiratory drive

Various stimuli, such as fever, acidosis, pain or anaemia may stimulate the respiratory drive, and respiratory drive in excess of achieved ventilation causes air hunger [4]. The impact of these stimuli of respiratory drive on dyspnoea is all the more important in the presence of respiratory system mechanics abnormalities, such as high resistance and low compliance.

Attention to dyspnoea associated with care activity

Dyspnoea is frequently associated with normal care activities such as planned turns, transfers, bathing and suctioning [65]. It was found that allowing patients to participate in their own suctioning could ease these feelings [101]. In some procedures generating a high level of dyspnoea, such as bronchoscopy, it is possible to administer a pre-emptive dose of a very short-acting opioid agent before commencing [153].

Being able to change posture (i.e. sitting) could also help [150], even if it increases dyspnoea in the short term [101].

Minimisation of respiratory impedance and alterations of gas exchange

In mechanically ventilated patients, a specific cause of dyspnoea, such as partial endotracheal tube obstruction, major pleural effusion or bronchoconstriction, could be recognised in up to 20% of patients [4].

When increased airway resistance is due to COPD or asthma, bronchodilators are usually used. If increased airway resistance is due to copious secretion or endotracheal tube encrustation, suctioning may be needed.

In the ICU, common causes of low respiratory system compliance are disorders involving the parenchyma (fibrosis and pulmonary oedema), the pleura (pneumothorax and large pleural effusions), or the chest wall (kyphoscoliosis, recent thoracic surgery and obesity). In the case of a reduced compliance due to a pneumothorax or a large pleural effusion, thoracentesis might sometimes be performed. In other cases, such as reduced pulmonary compliance due to pneumonia or pulmonary oedema, there is no other option than waiting for the benefit of the treatment of the causative disease.

Although it seems reasonable to avoid severe hypoxaemia, robust data are lacking concerning the symptomatic response of dyspnoea to supplemental oxygen [154].

Optimisation of ventilator settings

After excluding these causes, the most intuitive step to relieve dyspnoea is adjusting the ventilator settings in an effort to align the patient's respiratory drive and desired output with the mechanical outcomes of the ventilator. In fact, changing ventilator settings can substantially reduce dyspnoea. In an observational study of 96 mechanically ventilated patients, of whom 47% reported dyspnoea, optimising ventilator settings partially alleviated dyspnoea in 35% of cases [4]. This corresponded to a median

reduction of reported dyspnoea by 4.6 on a dyspnoea VAS from 0 to 10.

Patients receiving controlled ventilation

In patients receiving controlled ventilation, the first step is to evaluate the possibility of switching to a mode of partial support such as pressure support [4]. However, a study comparing dyspnoea during graded levels of support in various ventilator modes (assist-control ventilation, intermittent mandatory ventilation, and pressure support ventilation) found that, irrespective of the mode, progressively increasing the amount of work done by the ventilator proportionally reduced dyspnoea [81]. This suggests that rather than the ventilation mode, the level of assistance is the major determinant of dyspnoea.

Patients receiving pressure support ventilation

If the patient is ventilated in pressure support ventilation, since lower pressure support levels are associated with more intense dyspnoea [4], it is reasonable to increase pressure support to alleviate dyspnoea, taking care to avoid hyperinflation and excessive support [4, 81, 91]. The mechanisms accounting for the relief of dyspnoea achieved by increasing support are not fully elucidated. Increasing pressure support increases tidal volume [81], and dyspnoea relief correlates with tidal volume equally well as with the level of inspiratory support [43]. Yet increasing pressure support can also increase alveolar ventilation and improve blood gases, which can in itself contribute to the relief of air hunger.

Proportional modes of ventilation

Proportional modes of ventilation, such as proportional assist ventilation and neurally adjusted ventilator assist, should, in principle, guarantee improved coupling between the patient's neural drive, mechanical effort and ventilatory output. They are associated with lower dyspnoea in ICU patients and in healthy subjects [93, 155]. No difference was found in dyspnoea containment, however, when compared with optimised settings of pressure support ventilation [88, 156].

Positive end-expiratory pressure

Positive end-expiratory pressure (PEEP) level may affect comfort. First, in the presence of intrinsic PEEP (PEEPi), the level of external PEEP might be set in order to counterbalance PEEPi, which is not always easy to detect without invasive measurements. Second, there is some evidence in chronically ventilated patients and in healthy subjects that comfort is improved when end-expiratory lung volume is raised with PEEP, possibly secondary to increased pulmonary mechanoreceptor activity [89, 157].

Patient–ventilator asynchrony

Patient–ventilator asynchrony may occur when the patient demand and the ventilator support are uncoupled. The relationship between dyspnoea and asynchrony, however, is complex. The most common form of asynchrony, ineffective effort, may be secondary to overassistance by the ventilator, which reduces the mechanical output of the respiratory system necessary to trigger the ventilator. Ineffective effort is therefore inversely correlated with dyspnoea [86]. When asynchrony is associated with high respiratory drive (double triggering and short cycle), the patient "fights the ventilator" and may experience dyspnoea.

Role of lung protective ventilation

Over the past several decades, it has become evident that mechanical ventilation may cause lung injury by a variety of mechanisms [158]. To avoid ventilator-induced lung injury, it is essential to limit regional mechanical stress and strain, which defines lung protective ventilation. A cornerstone of lung protective ventilation is the use of low tidal volume, around 6 mL/kg predicted body weight [159]. This low tidal volume is likely to cause strong dyspnoea [43, 90, 160]. This is typically a condition that generates air hunger, a strong stimulus to breathe (high respiratory drive) with a restriction of the movement of the lungs and chest wall (low tidal volume) [41, 42]. There is a correlation between tidal volume, the level of inspiratory support and dyspnoea [43].

Patients receiving non-invasive ventilation

Patients undergoing NIV at times report that it increases rather than reduces dyspnoea [102]. The mask itself may provoke an unpleasant suffocating feeling, which may increase anxiety and, in turn, worsen dyspnoea [99, 103, 109, 150]: "…being acutely breathless and restrained by the mask was just too much for me, I couldn't breathe" [150], "It scares you. […] I couldn't even breathe, I got claustrophobic" [99]. This is sometimes alleviated by giving the patient time to get used to the mask and by starting the ventilator support at a low level and gradually increasing it so patients can get accustomed to the sensation [109].

In patients receiving extracorporeal lung support

Two studies [161, 162] show the relationship between respiratory loading and respiratory drive and effort, and to some extent, the impact on dyspnoea sensation. By facilitating carbon dioxide removal through a membrane lung, the load imposed on the respiratory pump is reduced. Increasing veno-venous extracorporeal membrane oxygenation sweep gas flow (facilitating

extracorporeal carbon dioxide removal) decreases respiratory drive [161], while reducing sweep gas flow is associated with an increase in respiratory drive (diaphragm electromyography) [162].

Pharmacological approach

The effectiveness of opioids on dyspnoea has been clearly demonstrated [163]. Because of the fear of respiratory depression, intensivists may be reluctant to use opioids for the relief of dyspnoea. However, guidelines from the American College of Chest Physicians and the Canadian Thoracic Society recommend the use of opioids for dyspnoea that persists despite optimal treatment of the underlying cause of dyspnoea [164, 165]. In addition, respiratory depression is not a major issue in intubated patients. A core of literature suggests the benefit of morphine on dyspnoea, and also its safety. Indeed, morphine administration does not alter blood pressure, $PaCO_2$ or peripheral oxygen saturation in patients with moderate-to-severe COPD, end-stage onco-haematological disease or advanced heart failure [166–168]. Studies conducted in patients with COPD, terminal cancer, idiopathic fibrosis or heart failure have shown that morphine was associated with a significant decrease in dyspnoea without inducing respiratory depression, as suggested by unchanged respiratory rate, tidal volume, blood gas and end tidal $PaCO_2$ [169–173]. The dose of opioids needed to treat acute and severe dyspnoea and the optimal route, dose and schedule of administration are not well established. An initial intravenous titration by an immediate-release opioid until the patient reports dyspnoea relief followed by a continuous low dose administration is currently under evaluation [174, 175].

Because of the strong relationship between anxiety and dyspnoea, interventions that relieve anxiety reduce dyspnoea [176, 177], and adjustments of the ventilator settings deemed to improve dyspnoea relieve anxiety [4]. Cannabinoids may be of potential interest, although studies are lacking [178]. The benefit of nebulised diuretics for the management of dyspnoea in terminally ill patients remains controversial [179].

Non-pharmacological interventions

Non-pharmacological interventions have no toxicity. A promising approach comprises sensory interventions targeting the brain rather than the respiratory system. The principle of these interventions is to modulate the emotional and affective component of dyspnoea through the use of relaxing music [180], positive pictures [45] or fresh air directed at the cheek [46]. Recent data in mechanically ventilated patients experiencing dyspnoea show that exposure to relaxing music decreased dyspnoea VAS by 40 mm (on a scale from 0 to 100 mm) and exposure to facial air flux delivered by a fan decreased dyspnoea VAS by 30 mm [47].

Interventions to treat dyspnoea such as chest wall vibration, acupuncture/acupressure, relaxation and neuro-electrical muscle stimulation have been recently reviewed and their benefit is unclear [174].

Summary of interventions to relieve dyspnoea

Figure 7 summarises step-by-step management of dyspnoea in ICU patients according to the review undertaken by this task force. The patient-focused literature suggests ways in which healthcare staff could improve the patient experience (Table 2).

Conclusions

Dyspnoea, one of the most distressing experiences, is observed in 35–50% of mechanically ventilated patients, whether they receive invasive mechanical ventilation or NIV. Although its prevalence is unknown, respiratory-related brain suffering, of which dyspnoea is the symptom, is by nature bound to be frequent and often unrecognised in patients who cannot communicate to their healthcare providers. The intensity of dyspnoea as it is reported by mechanically ventilated patients is high: similar pain intensities would prompt immediate therapeutic responses. Dyspnoea has multiple deleterious consequences. Short-term consequences include an immediate suffering with a fear of dying and a strong association with anxiety. In the middle term, dyspnoea is associated with difficult weaning in intubated patients and with an increased risk of weaning failure in those who receive NIV. Long-term consequences of dyspnoea include dark recollections of the ICU stay and a high prevalence of post-traumatic stress disorders, especially in case of multiple exposures to the experience. Like pain, dyspnoea is a self-reported symptom that imperfectly relates with physiological abnormalities. Usually, it may suffice to guide therapeutic interventions. In mechanically ventilated patients able to communicate, the task force members usually elicit dyspnoea self-report as soon as possible during the ICU stay. In patients who are unable to communicate intentionally, an observational scale may usually help to infer respiratory-related brain suffering.

First, it has been proposed that healthcare professionals reassure patients by manifesting empathetic solicitude regarding their dyspnoea: given the intimate and reciprocal interactions between dyspnoea and anxiety, fighting anxiety is of primary concern in dyspnoeic patients. It has been reported that interventions that specifically aim to enhance a sense of control in trauma-exposed individuals may mitigate post-traumatic stress [151, 152]. Second, the task force members usually correct non-respiratory

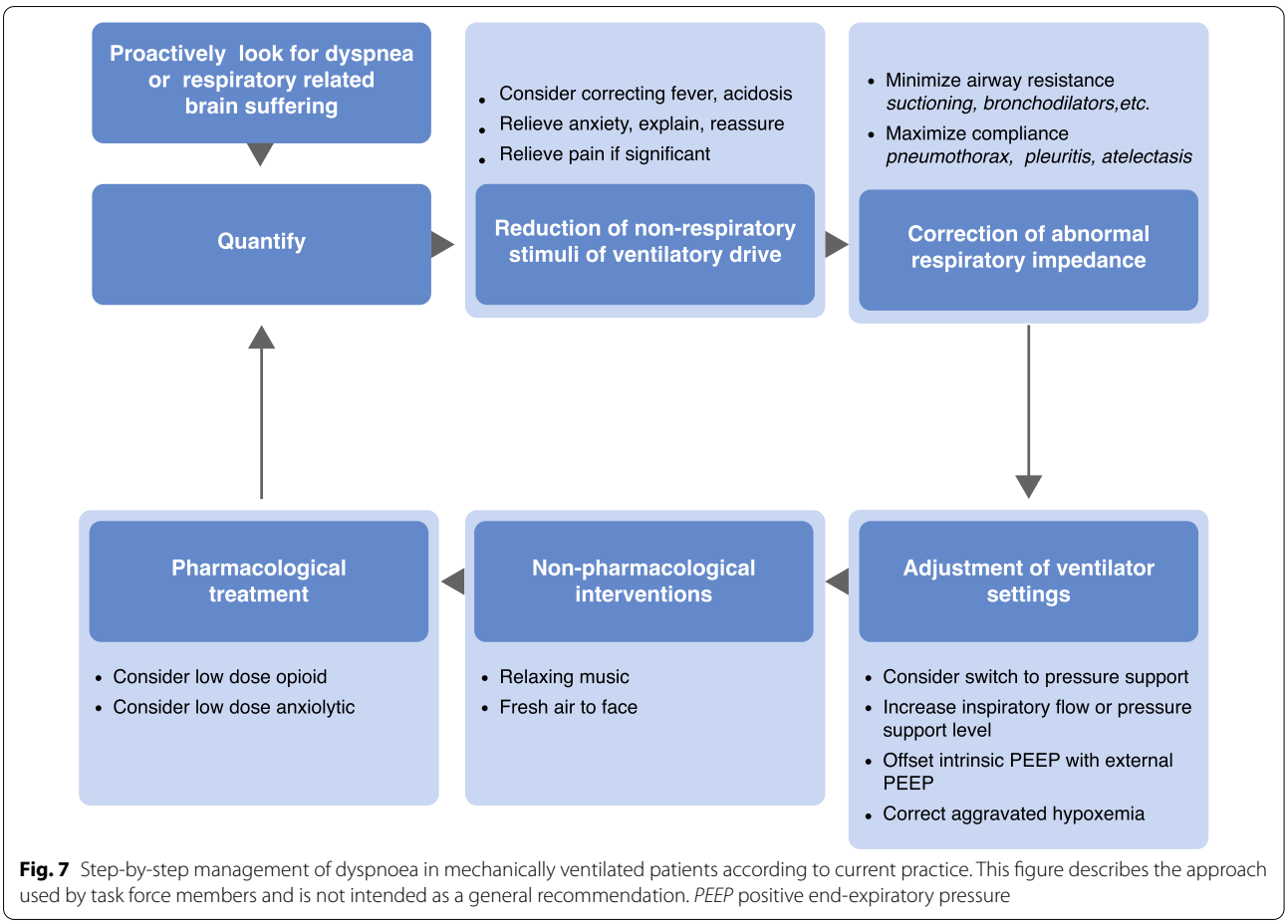

Fig. 7 Step-by-step management of dyspnoea in mechanically ventilated patients according to current practice. This figure describes the approach used by task force members and is not intended as a general recommendation. *PEEP* positive end-expiratory pressure

Table 2 Tips for improving practice according to the patient-focused literature

Explain what is happening to the patients, even if they are unresponsive or apparently unable to communicate
Reassure the patients that we have understood that they are suffering from dyspnoea
Reassure the patients that dyspnoea is an expected consequence of their condition, that their condition is being monitored and that being dyspnoeic does not necessarily mean their condition is worsening or they are going to die
Coach dyspnoeic patients to adopt or try to adopt a slower breathing pattern and remain with them as they practise it
Give time frames, for example: "Tomorrow morning we will turn down the ventilator and see how you manage with your breathing"
Facilitate non-verbal communication methods for patients unable to speak
Help patients adjust to non-invasive ventilation by starting on a low level and gradually titrating up to the required setting
Allow patients some control over the experience where possible, for example allowing them to adjust ventilator settings or participate in suctioning
Explain what is happening to patients' family so they can also be reassured and provide reassurance to the patient

metabolic stimuli of respiratory drive, such as fever and acidosis. They also pay attention to care activity that often generates dyspnoea, such as suctioning. It is common to correct causes of respiratory mechanics abnormalities, such as low compliance and high resistance. In about 35% of patients, optimisation of ventilator settings may dramatically reduce dyspnoea. This optimisation usually involves the choice of mode, the level of inspiratory flow, pressure support, expiratory trigger and external PEEP. Finally, if dyspnoea persists despite these interventions, pharmacological approaches involving opioids and anxiolytics has been reported; sedation alone is not an effective therapeutic intervention. Non-pharmacological interventions modulating emotional and sensorial components of dyspnoea are promising. Further studies should determine the efficacy of strategies designed to minimise dyspnoea on the various consequences of dyspnoea. In mechanically ventilated patients, it appears particularly important to find

ways of solving the contradiction that commonly exists between what should be equivalent concerns, namely lung protection and respiratory comfort.

Given the magnitude and severity of this problem and its long-term sequelae, as demonstrated both in the general medical and ICU literature, we consider respiratory-related brain suffering and its symptom, dyspnoea, as ultimate clinical and research priorities in mechanically ventilated patients [181] and in all patients [30]. Indeed, the identification and management of dyspnoea is currently considered to pertain to the human right of the patient [30, 146]. Future research should aim at improving tools to detect and quantify dyspnoea. It should also propose a systematic therapeutic approach to relieving dyspnoea. Ultimately, the goal would be to provide a medical algorithm for the management (diagnosis and treatment) of dyspnoea in mechanically ventilated patients.

Supplementary Information
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Declarations

Conflicts of interest
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