Dyspnoea and respiratory muscle ultrasound to predict extubation failure

Martin Dres[1,2,3,4], Thomas Similowski[1,2], Ewan C. Goligher[4,5], Tai Pham[3,6,7], Liliya Sergenyuk[1], Irene Telias[3,4,5], Domenico Luca Grieco[3,8,9], Wissale Ouechani[1], Detajin Junhasavasdikul[3,10], Michael C. Sklar[3,4], L. Felipe Damiani[3,11], Luana Melo[3], Cesar Santis[3,12,13], Lauriane Degravi[1], Maxens Decavèle[1,2], Laurent Brochard[3,4] and Alexandre Demoule[1,2]

[1]AP-HP, Groupe Hospitalier Universitaire, AP-HP, Sorbonne Université, Site Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive Réanimation (Département R3S), Paris, France. [2]Sorbonne Université, INSERM, UMRS_1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France. [3]Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada. [4]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada. [5]Division of Respirology, Dept of Medicine, University Health Network, Toronto, ON, Canada. [6]Hôpital Bicêtre, Service de Médecine Intensive – Réanimation, Hôpitaux Universitaires Paris-Saclay, Le Kremlin-Bicêtre, France. [7]Équipe d'Épidémiologie Respiratoire Intégrative, Centre for Epidemiology and Population Health (CESP), Université Paris-Saclay, UVSQ, Université Paris-Sud, INSERM, Villejuif, France. [8]Dept of Emergency, Intensive Care Medicine and Anaesthesia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. [9]Dept of Anaesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, Rome, Italy. [10]Dept of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. [11]Carrera de Kinesiología, Departamento Ciencias de la Salud, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. [12]Departamento de Medicina Interna, Universidad de Chile, Campus Sur, San Miguel, Chile. [13]Unidad de Pacientes Críticos, Hospital Barros Luco Trudeau, Santiago, Chile.

Corresponding author: Martin Dres (martin.dres@aphp.fr)

Shareable abstract (@ERSpublications)
Respiratory muscle ultrasound and dyspnoea intensity early after extubation predict extubation failure https://bit.ly/39Uqo9o

Cite this article as: Dres M, Similowski T, Goligher EC, *et al*. Dyspnoea and respiratory muscle ultrasound to predict extubation failure. *Eur Respir J* 2021; 58: 2100002 [DOI: 10.1183/13993003.00002-2021].

This article has supplementary material available from erj.ersjournals.com

Received: 3 Jan 2021
Accepted: 30 March 2021

Abstract

Background This study investigated dyspnoea intensity and respiratory muscle ultrasound early after extubation to predict extubation failure.

Methods The study was conducted prospectively in two intensive care units in France and Canada. Patients intubated for at least 48 h were studied within 2 h after an extubation following a successful spontaneous breathing trial. Dyspnoea was evaluated by a dyspnoea visual analogue scale (Dyspnoea-VAS) ranging from 0 to 10 and the Intensive Care Respiratory Distress Observational Scale (IC-RDOS). The ultrasound thickening fraction of the parasternal intercostal and the diaphragm was measured; limb muscle strength was evaluated using the Medical Research Council (MRC) score (range 0–60).

Results Extubation failure occurred in 21 out of 122 enrolled patients (17%). The median (interquartile range (IQR)) Dyspnoea-VAS and IC-RDOS were higher in patients with extubation failure *versus* success: 7 (4–9) *versus* 3 (1–5) ($p<0.001$) and 3.7 (1.8–5.8) *versus* 1.7 (1.5–2.1) ($p<0.001$), respectively. The median (IQR) ratio of parasternal intercostal muscle to diaphragm thickening fraction was significantly higher and MRC was lower in patients with extubation failure compared with extubation success: 0.9 (0.4–2.1) *versus* 0.3 (0.2–0.5) ($p<0.001$) and 45 (36–50) *versus* 52 (44–60) ($p=0.012$), respectively. The thickening fraction of the parasternal intercostal and its ratio to diaphragm thickening showed the highest area under the receiver operating characteristic curve (AUC) for an early prediction of extubation failure (0.81). AUCs of Dyspnoea-VAS and IC-RDOS reached 0.78 and 0.74, respectively.

Conclusions Respiratory muscle ultrasound and dyspnoea measured within 2 h after extubation predict subsequent extubation failure.

Introduction

Extubation failure occurs in 10–15% of patients [1], and is associated with prolonged duration of mechanical ventilation and increased mortality [2]. The timing of re-intubation is likely to influence the

outcome: delayed re-intubation is associated with a higher mortality rate [3]. Therefore, early identification of patients at high risk of re-intubation is of great importance. In clinical practice, after extubation, recognition of clinical worsening can be delayed because key elements of respiratory monitoring (*e.g.* tidal volume) are no longer available and respiratory rate alone is not a good indicator of inspiratory effort [4].

Dyspnoea, a key feature of acute respiratory failure, could be a warning sign of extubation failure. For instance, in patients admitted to the intensive care unit (ICU) for acute respiratory failure, moderate-to-severe dyspnoea is independently associated with noninvasive ventilation failure [5]. Therefore, assessing for dyspnoea after extubation could help predict the risk of extubation failure. The intensity of dyspnoea is strongly correlated with the activity of extra-diaphragmatic inspiratory muscles such as the parasternal intercostal and scalene muscles [6–8]. These muscles are commonly activated together with the diaphragm in acute respiratory failure and weaning failure [9, 10]. Accordingly, the activity of the inspiratory muscles relative to the diaphragm could provide another early predictor of extubation failure. The activity of the parasternal intercostal [11] and the diaphragm [12, 13] can be easily quantified by ultrasound, which could be useful during the weaning process. A recent study failed to identify differences in terms of diaphragm activity between patients who succeed and those who fail extubation in patients at high risk of extubation failure when ultrasound was performed during a spontaneous breathing trial [14]. Here, we tested the hypothesis that, early after extubation, dyspnoea and parasternal intercostal muscle/diaphragm ultrasound can predict subsequent extubation failure in nonselected patients separated from the ventilator after a successful spontaneous breathing trial.

Methods

This study complies with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. It was conducted between August 2016 and May 2018 in two sites: the Medical and Surgical ICU, St Michael's Hospital, Toronto, ON, Canada (August 2016–November 2017) and the Pulmonology and Intensive Care Dept, Hôpital Pitié-Salpêtrière, Paris, France (August 2017–May 2018). All patients or their next of kin provided informed consent. The study was approved by the Institutional Review Boards at both participating institutions (Comité de Protection des Personnes Ouest 17/048-3; St Michael's Hospital REB 16-161) and was performed in accordance with the ethical standards laid down in the 2008 Declaration of Helsinki.

Patients

Consecutive adult patients who were mechanically ventilated for at least 48 h and who were extubated after a successful spontaneous breathing trial were eligible. Exclusion criteria were related to "do not re-intubate" orders, unplanned extubation, current use of extracorporeal membrane oxygenation, inability to perform ultrasound of the diaphragm and parasternal intercostal muscle (morbid obesity and thoracic dressings), tracheostomy, and pre-existing neuromuscular diseases or known diaphragm paralysis.

Patients were eligible for a spontaneous breathing trial as soon as they met predefined readiness-to-wean criteria: arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) $\geqslant$90% on inspiratory oxygen fraction $\leqslant$0.4 and positive end-expiratory pressure $\leqslant$8 cmH_2O, and low/no doses of vasopressors [15]. The spontaneous breathing trial was performed while patients were connected to the ventilator with no pressure assist of any kind (zero positive end-expiratory pressure and a pressure support level of zero) for 30 min. Success or failure of the spontaneous breathing trial and the decision to extubate were determined by the physician in charge who had no role in the study (usual criteria for spontaneous breathing trial success and for extubation are listed in the supplementary material). Prophylactic noninvasive ventilation or high-flow nasal cannula could be applied in patients with pre-identified risk factors for extubation failure (chronic respiratory disease, chronic cardiac disease and age >65 years) [16]. The decision to use noninvasive ventilation or high-flow nasal cannula was taken before the extubation by the physician in charge who had no role in the study.

Measurements

Dyspnoea evaluation

Presence and severity of dyspnoea were evaluated by using self-evaluation of dyspnoea and dyspnoea observation scales [17], depending on whether patients were communicative or noncommunicative. Patients were considered as communicative when the Richmond Agitation–Sedation Scale was between −1 and +1 and if they were able to consistently self-report dyspnoea, attested by a dyspnoea visual analogue scale (Dyspnoea-VAS) variation not exceeding 1 cm for three consecutive measures [18, 19]. In communicative patients only, self-evaluation was performed by means of the Dyspnoea-VAS that consisted of a 10-cm scale ranging from "no respiratory discomfort" to "intolerable respiratory discomfort". Hetero-evaluation was performed in communicative and noncommunicative patients, by means of the

Intensive Care Respiratory Distress Observational Scale (IC-RDOS) [17], which is based on respiratory, neurovegetative and behavioural signs, and includes five observable items (heart rate, use of neck muscles during inspiration, abdominal paradox during inspiration, facial expression of fear and supplemental oxygen). IC-RDOS correlates strongly with Dyspnoea-VAS [20] and has been previously validated in noncommunicating ICU patients [21]. Clinically significant dyspnoea was defined as Dyspnoea-VAS ⩾4 [17] and IC-RDOS ⩾2.4, since this latter predicts Dyspnoea-VAS ⩾4 with equal sensitivity and specificity (72%) [20].

Respiratory muscle ultrasound

All investigators involved in ultrasound measurements received a training programme with a minimum of 15 ultrasounds supervised by an investigator experienced in respiratory muscle ultrasound imaging. Respiratory muscle measurements were performed by investigators who were independent of the clinical team. At the time of ultrasound, patients were breathing spontaneously without noninvasive ventilation or high-flow oxygen therapy. When indicated, noninvasive ventilation or high-flow oxygen therapy was applied after ultrasound measurements. Ultrasound was performed by using two machines: Sparq (Philips Healthcare, Bothell, WA, USA) and Sonosite (Fujifilm Sonosite, Bothell, WA, USA). The methods used to evaluate diaphragm and parasternal intercostal thickness and thickening have been extensively detailed and validated elsewhere (supplementary material) [11, 22]. Briefly, the parasternal intercostal muscle was evaluated by using a 10–15 MHz linear array transducer positioned at the level of the second right intercostal space. The second right parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes running, respectively, from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echotexture. Using M-mode, the thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration and at peak inspiration. Change in thickness determined the thickening fraction of the parasternal intercostal muscle (TFic) as: TFic=(peak inspiration thickness–end-expiratory thickness)/end-expiratory thickness. Only the right parasternal intercostal muscle was evaluated for simplicity.

Diaphragm ultrasound was conducted using a 10–15 MHz linear array transducer. As for the parasternal intercostal muscle, diaphragm thickness (including pleural and peritoneal membranes) was measured at end-expiration and at peak inspiration, and the thickening fraction (TFdi) was calculated offline as: TFdi=(peak inspiration thickness–end-expiratory thickness)/end-expiratory thickness.

All ultrasound recordings were analysed offline by one single investigator (M. Dres) who was blinded to the clinical outcomes. All ultrasound measurements were repeated on at least three separate breaths and their average was reported. Reproducibility of diaphragm and parasternal intercostal muscle ultrasound has been reported elsewhere and was not tested in the present study [11, 22].

Clinical data collection

Demographic data were collected from the electronic medical charts of the patients: age, gender, comorbidities (chronic hypertension, chronic pulmonary disease, diabetes, chronic renal failure and left heart dysfunction), Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation III scores, date of ICU admission, date of intubation, main reason for intubation, weight and height at admission, number of spontaneous breathing trials before extubation, and ventilation mode before extubation. At the time of dyspnoea evaluation and respiratory muscle ultrasound, the following variables were collected: arterial blood pressure, heart rate, S_{pO_2} and respiratory rate. We also evaluated limb muscle strength by the Medical Research Council (MRC) score in communicative patients [23]. ICU-acquired weakness was defined by an MRC score <48 [24]. Finally, cough strength was assessed by using a semiquantitative categorical scale that classified cough strength as “weak”, “moderate” or “strong” [14].

Study protocol

Patients were enrolled in the study following extubation, and ultrasound of the diaphragm and the parasternal intercostal muscle was performed on the right side within 2 h after extubation. Immediately before ultrasound measurements, dyspnoea was assessed with Dyspnoea-VAS in communicative patients and the items of IC-RDOS were collected in all patients and the sum was computed offline.

The primary end-point was extubation failure defined as re-intubation or death within the 7 days following planned extubation.

Statistical analyses

Variables are presented as median (interquartile range (IQR)) or number (percentage). As, to the best of our knowledge, no previous publications have evaluated the level of dyspnoea or respiratory muscle

ultrasound after extubation, a formal sample size calculation was deemed not possible, and we estimated that a sample of 15–20 patients with extubation failure would be appropriate to make a relevant comparison between groups regarding their dyspnoea scales and ultrasound respiratory muscle indices. Based on an estimate rate of extubation failure of 15% [25], we planned to enrol 120 patients.

Differences between patients with and without extubation failure were assessed using the Mann–Whitney or Chi-squared test, where appropriate. Potential risk factors for extubation failure were assessed by univariate analysis and their predictive performances were computed with receiver operating characteristic (ROC) curves. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios, and areas under the ROC curves (AUCs) were calculated. AUCs were determined to identify optimal cut-off values in predicting failure and these estimates were obtained using bootstrapping with 1000 replications. The best threshold value for each index was determined as the value associated with the best Youden index for the prediction of failure.

The Spearman correlation was used to evaluate the relationship between ultrasound indices (TFic, TFdi and TFic/TFdi) and dyspnoea scales (Dyspnoea-VAS and IC-RDOS). In all cases, a p-value <0.05 was considered statistically significant and two-tailed testing was used to test hypotheses. All analyses were performed using Prism version 8 (GraphPad, San Diego, CA, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

Results

Population

Among the 470 patients eligible during the study period, 122 patients were enrolled in the study (figure 1). The main characteristics of the patients are shown in table 1. There were significant differences between both centres regarding some characteristics of the patients (supplementary table S1). The main reasons for intubation were hypoxaemic acute respiratory failure and coma, and the median (IQR) duration of mechanical ventilation at the time of enrolment was 5 (3–8) days. Extubation failure occurred in 21 (17%) of the 122 patients. The median (IQR) duration between extubation and extubation failure was 1 (0–3) days (supplementary table S2). Of these 21 patients, one patient was not re-intubated because of a decision of "do not re-intubate" taken after extubation (see supplementary table S2 for the detailed causes of extubation failure). Respiratory distress was the reason for extubation failure in 18 patients; three patients

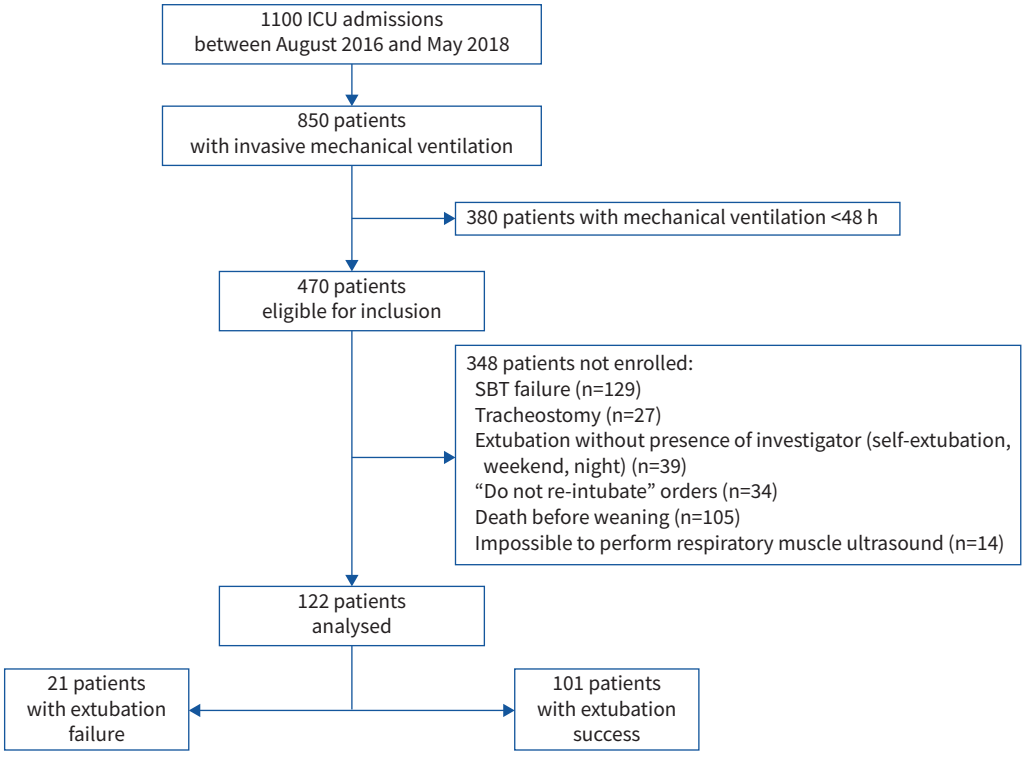

FIGURE 1 Flowchart of the study. ICU: intensive care unit; SBT: spontaneous breathing trial.

TABLE 1 Characteristics of the patients

	Extubation success	Extubation failure	p-value
Patients	101	21	
Age years	59 (46–66)	55 (48–72)	0.617
Male	63 (62)	14 (67)	0.903
Body mass index kg·m^{-2}	25 (22–31)	25 (23–29)	0.884
Comorbidities			
Hypertension	39 (39)	8 (40)	1.000
Chronic pulmonary disease	17 (17)	1 (5)	0.310
Diabetes	21 (21)	4 (20)	1.000
Chronic renal failure	9 (9)	2 (10)	0.190
Left heart dysfunction	11 (11)	1 (5)	0.150
Severity upon admission			
SOFA score	7 (5–10)	6 (5–9)	0.611
APACHE III score	26 (20–43)	46 (20–81)	0.104
Main cause of intubation			
Hypoxaemic ARF	38 (38)	8 (40)	1.000
Hypercapnic ARF	6 (6)	1 (5)	1.000
Coma	21 (21)	7 (35)	0.255
Shock	10 (10)	0 (0)	0.208
Cardiac arrest	4 (4)	1 (5)	1.000
Gastric bleeding	6 (6)	0 (0)	0.588
Post-surgery	16 (16)	4 (20)	0.898
Weaning			
Time since intubation days	5 (3–7)	6 (4–11)	0.059
Spontaneous breathing trials n	2 (1–3)	1 (1–2)	0.491
Ventilation mode			
Pressure support	96 (95)	20 (95)	0.688
Assist control ventilation	2 (2)	1 (5)	1.000
NAVA	1 (1)	0	1.000
Pressure control ventilation	1 (1)	0	1.000
Proportional assist ventilation	1 (1)	0	1.000

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; ARF: acute respiratory failure; NAVA: neurally adjusted ventilatory assist.

failed extubation for other reasons (one for coma, one for seizure and one for sepsis). No stridor occurred after extubation.

The 101 (83%) remaining patients were classified as extubation success. Of these 101 patients, two received rescue noninvasive ventilation not followed by a re-intubation. Post-extubation management and outcomes of the patients are reported in supplementary table S3.

Post-extubation assessment

Post-extubation assessment was performed 23 (0–60) min after extubation; there was no difference in timing assessment between patients with extubation success and those with extubation failure (30 (5–59) *versus* 22 (0–61) min, respectively; p=0.45). Median (IQR) Dyspnoea-VAS was 4 (2–5) and was ⩾4 (*i.e.* clinically important dyspnoea) in 49 (52%) of the 95 patients with Dyspnoea-VAS measurements. Median IC-RDOS was 1.9 (1.6–3.5) and was ⩾2.4 (*i.e.* clinically important) in 68 out of 122 (56%) patients. 34 patients (36%) had ICU-acquired weakness, defined by MRC <48. Cough strength was estimated as weak in 14 patients (13%), moderate in 72 patients (65%) and strong in 24 patients (22%).

Factors associated with extubation failure

Clinical features and arterial blood gases before and after the spontaneous breathing trial were not different in patients depending of the extubation outcome (supplementary table S4). Except for the respiratory rate that was higher in patients with extubation failure, the rest of the clinical examination was not different between groups at the time of ultrasound and dyspnoea evaluation (table 2). The proportion of patients with weak, moderate and strong cough was not different between groups (table 2). The MRC score was higher in patients with extubation success compared with patients with extubation failure (table 2).

Clinically relevant dyspnoea (Dyspnoea-VAS ⩾4) was more frequent and dyspnoea was more intense in patients who failed extubation (table 2 and figure 2). TFdi was significantly higher in patients who succeeded extubation, whereas TFic was significantly higher in patients who failed extubation (figure 2 and table 2). TFic/TFdi was higher in patients with extubation failure (table 2). There was a moderate but significant correlation between TFic and IC-RDOS and between TFic and Dyspnoea-VAS, but there was no correlation between TFdi and IC-RDOS or between TFdi and Dyspnoea-VAS (supplementary table S5).

The performance of IC-RDOS, Dyspnoea-VAS, MRC score, TFic, TFdi and TFic/TFdi to predict extubation failure was evaluated by computing their AUCs (figure 3 and supplementary table S6). The best thresholds to predict extubation failure were IC-RDOS >3.3, Dyspnoea-VAS >4.0, MRC score <50, TFic >8.6%, TFdi <15.6% and TFic/TFdi >0.44 (supplementary table S5). IC-RDOS was <3.3 in eight out of 21 patients who failed extubation. Among these eight patients, five had TFic/TFdi >0.44. Therefore, combining IC-RDOS and TFic/TFdi predicted extubation failure in 18 out of 21 patients. A sensitivity analysis comparing patients with extubation failure (re-intubation and rescue noninvasive ventilation) and extubation success reached similar findings (supplementary table S7).

Discussion

This study investigated the performance of dyspnoea scales and respiratory muscle ultrasound following extubation after a successful spontaneous breathing trial to predict the risk of extubation failure. The main findings are: 1) patients who eventually failed extubation experienced higher self-reported dyspnoea intensity and had a higher observational dyspnoea scale after extubation, 2) there was a moderate but significant correlation between dyspnoea and TFic and TFic/TFdi as evaluated by ultrasound, and 3) TFic/

TABLE 2 Clinical evaluation and respiratory muscle ultrasound indices on enrolment

	Extubation success	Extubation failure	p-value
Patients	101	21	
Clinical evaluation			
Systolic blood pressure mmHg	133 (120–147)	125 (110–151)	0.429
Diastolic blood pressure mmHg	69 (61–76)	64 (57–80)	0.334
Heart rate beats·min^{-1}	91 (76–103)	93 (84–117)	0.318
S_{pO_2} %	98 (95–100)	98 (94–99)	0.358
Respiratory rate cycles·min^{-1}	21 (17–24)	24 (21–28)	0.022
Dyspnoea evaluation			
IC-RDOS			
Patients with measurements	101	21	
IC-RDOS	1.7 (1.5–2.1)	3.7 (1.8–5.8)	<0.001
IC-RDOS ⩾2.4	50 (49)	18 (86)	0.002
Dyspnoea-VAS			
Patients with measurements	79	16	
Dyspnoea-VAS	3 (1–5)	7 (4–9)	<0.001
Dyspnoea-VAS ⩾4	35 (44)	14 (88)	0.002
Cough strength			
Patients with measurements	91	19	
Weak	10 (11)	4 (21)	
Moderate	60 (66)	12 (63)	
Strong	21 (23)	3 (16)	
Limb muscles strength			
Patients with measurements	79	16	
MRC score	52 (44–60)	45 (36–50)	0.012
MRC score <48	24 (30)	10 (63)	0.031
Respiratory muscle ultrasound indices			
Patients with measurements	88	19	
TFic %	7 (4–9)	13 (9–22)	<0.001
TFdi %	21 (15–27)	11 (9–19)	0.002
TFic/TFdi	0.3 (0.2–0.5)	0.9 (0.4–2.1)	<0.001

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; Dyspnoea-VAS: dyspnoea visual analogue scale; IC-RDOS: Intensive Care Respiratory Distress Observation Scale; MRC: Medical Research Council; TFic: thickening fraction of the parasternal intercostal muscle; TFdi: thickening fraction of the diaphragm.

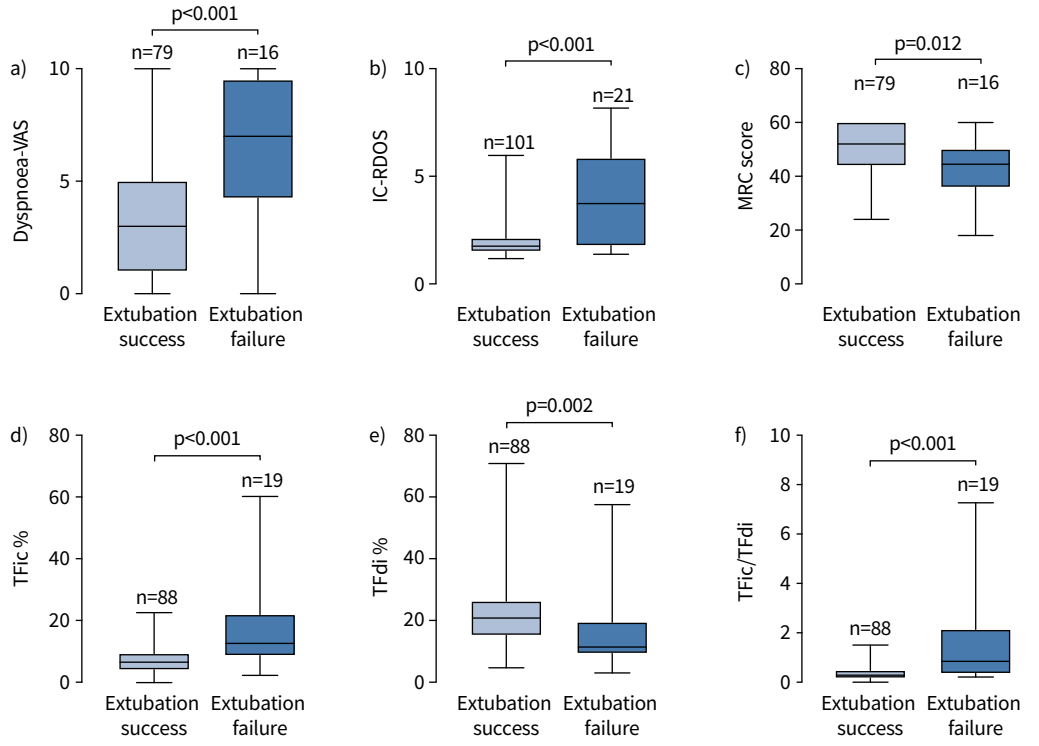

FIGURE 2 a) Dyspnoea visual analogue scale (Dyspnoea-VAS), b) Intensive Care Respiratory Distress Observation Scale (IC-RDOS), c) Medical Research Council (MRC) score, d) thickening fraction of the parasternal intercostal muscle (TFic), e) thickening fraction of the diaphragm (TFdi) and f) TFic/TFdi in patients with extubation success and extubation failure. Box plots represent the median and interquartile range (with minimum–maximum) of the distributions.

TFdi predicted extubation outcome with a good performance (the higher the ratio, the higher the risk of subsequent re-intubation).

Weaning failure occurs when respiratory loading (pulmonary oedema, secretions, atelectasis and hyperinflation) exceeds the compensatory capacity of the respiratory muscles [26]. This load capacity imbalance stimulates the respiratory drive [27], which in turn induces the recruitment of accessory inspiratory muscles [9, 11], both well-established determinants of dyspnoea. Dyspnoea is a frequent but underestimated symptom that is encountered in ∼50% of ICU patients [5, 20, 28, 29]. Dyspnoea is strongly associated with the recruitment of extra-diaphragmatic respiratory muscles [6, 8, 30] and behaves as a reliable surrogate of the increase in respiratory drive that is subsequent to the load capacity imbalance. The correlation between dyspnoea and extra-diaphragmatic respiratory muscle activity has already been established with electromyography [6, 30]. Our study confirms this physiological relationship with ultrasound. In contrast, there was no correlation between dyspnoea and TFdi, a finding already highlighted in a previous study [30]. Therefore, the recruitment of extra-diaphragmatic inspiratory muscles seems to be a better indicator of the respiratory load capacity imbalance than diaphragm activity. This may explain why dyspnoea, which is closely linked to respiratory drive, is better correlated with parasternal intercostal activity than with diaphragm activity alone.

While our patients had successfully passed a spontaneous breathing trial, suggesting a relatively adequate load capacity balance, the prevalence of dyspnoea was as high as 52% after extubation. Since dyspnoea was not evaluated before extubation, it cannot be ruled out that some patients were dyspnoeic while they did not develop classical criteria of spontaneous breathing trial failure. Interestingly, the intensity of dyspnoea predicted extubation outcome. Several studies have already reported on the relationship between dyspnoea (as a warning sign) and clinical outcomes. Dyspnoea seems to be a proxy for the severity of a respiratory or cardiac disease [31]. For instance, there is an association between poor respiratory comfort and hospital mortality in patients with suspected acute myocardial infarction [32, 33], in those admitted for acute chronic obstructive pulmonary disease (COPD) exacerbation [34], and even in patients without

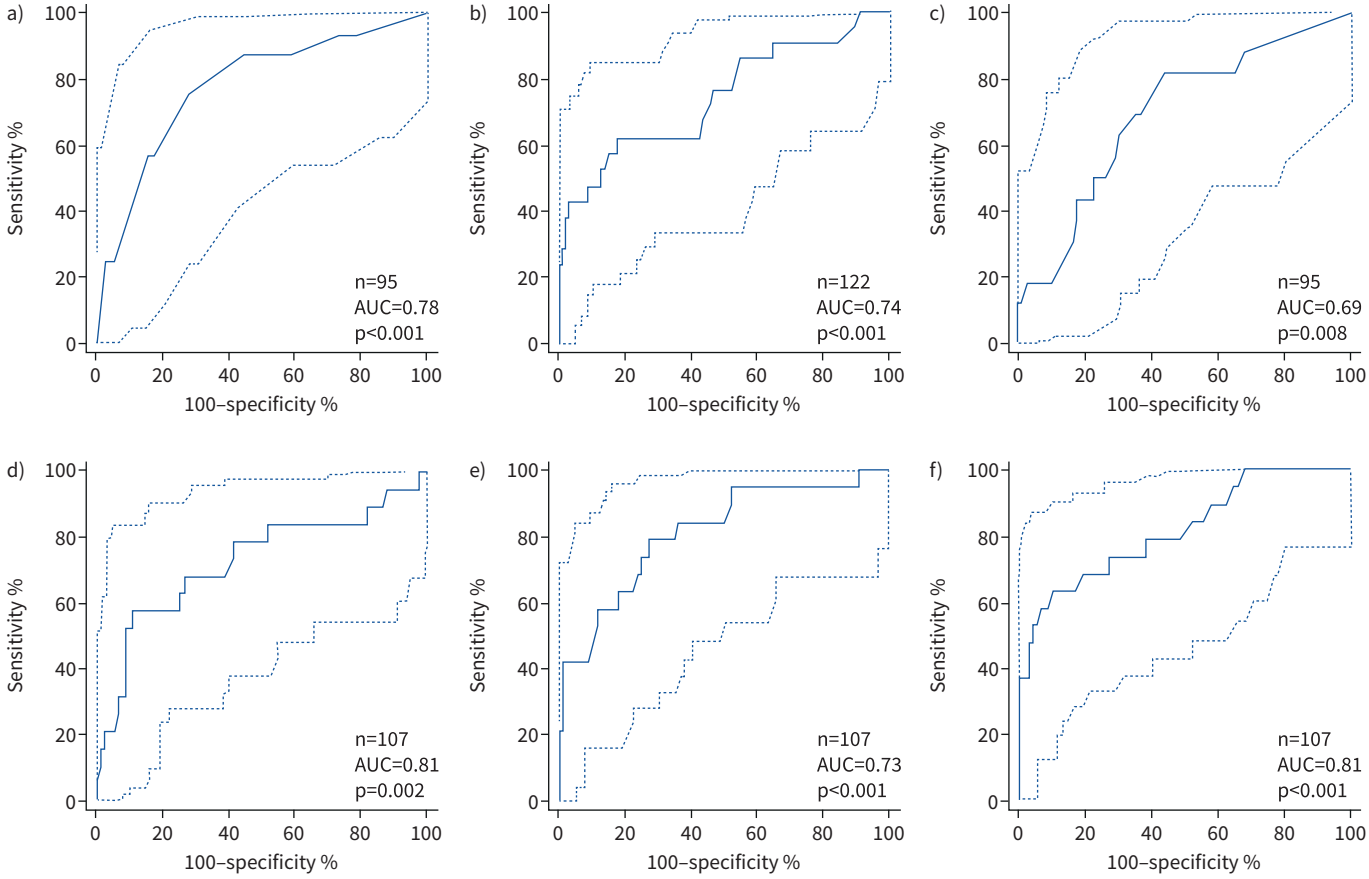

FIGURE 3 Receiver operating characteristic (ROC) curves (with 95% CIs) of a) dyspnoea visual analogue scale (Dyspnoea-VAS), b) Intensive Care Respiratory Distress Observation Scale (IC-RDOS), c) Medical Research Council (MRC) score, d) thickening fraction of the parasternal intercostal muscle (TFic), e) thickening fraction of the diaphragm (TFdi) and f) TFic/TFdi. AUC: area under the ROC curve.

previously diagnosed cardiopulmonary diseases [35]. Regarding the prediction of intubation, a recent study suggested that in patients receiving noninvasive ventilation for acute respiratory failure, moderate-to-severe dyspnoea can predict noninvasive ventilation failure and subsequent intubation [5]. These findings and ours suggest that evaluation of dyspnoea in nonintubated patients (before or after extubation) may be of clinical interest. Eventually, further studies will have to investigate whether preventive strategies for extubation failure could rely on dyspnoea scales and timely application of noninvasive ventilatory supports.

It is notable that IC-RDOS, an observational scale that can evaluate dyspnoea in noncommunicative patients as opposed to Dyspnoea-VAS that requires patient cooperation, performed as well as Dyspnoea-VAS to predict extubation failure. This is of great help since freshly extubated patients may show delirium and be unable to self-report dyspnoea. Finally, it is important to note that, with a median Dyspnoea-VAS of 4, dyspnoea was present in a substantial proportion of patients. Similar pain intensity would have immediately triggered a medical response involving the administration of analgesic medication. The suffering that dyspnoea induces in extubated patients should not be neglected as dyspnoea contributes to the dark recollections following an ICU stay [36]. For some authors, failing to address dyspnoea breaches human rights [37, 38].

The present study shows that ultrasound of respiratory muscles could identify patients who further presented extubation failure. Indeed, patients who developed extubation failure had a lower TFdi and a higher TFic. The association between either increased TFic or decreased TFdi and weaning failure has already been well established [11, 39]. It is noticeable that, at the time of respiratory muscle ultrasound, patients who further developed extubation failure had similar clinical presentation compared with their counterparts. Furthermore, respiratory rate was associated with a poor ROC curve, suggesting that ultrasound was able to detect a subclinical impairment of the respiratory load/capacity balance.

Because diaphragm dysfunction is compensated for by an increase in extra-diaphragmatic inspiratory muscle activity [40–42], the relationship between TFic and TFdi is inverse, *i.e.* the lower the TFdi, the higher the TFic [11]. TFic/TFdi combines the evaluation of the diaphragm and the extra-diaphragmatic inspiratory muscle. When the TFic/TFdi ratio increases, it indicates a recruitment of parasternal intercostal muscles (high TFic) because of a weak diaphragm (low TFdi). This ratio may appropriately reflect the respiratory load/capacity balance. Indeed, in the case of increased respiratory drive, extra-diaphragmatic respiratory muscles are activated more prematurely and more vigorously than the diaphragm [43]. Recruitment of scalene muscles predicts weaning failure in ICU patients [9] and recruitment of the parasternal intercostal muscle predicts poor outcome in patients with COPD exacerbation [44]. These data and ours raise the relevance of monitoring extra-diaphragmatic inspiratory muscles, which seem to be a better indicator of the respiratory load capacity imbalance than diaphragm activity alone. However, combining TFdi with TFic did not offer any predictive advantage for extubation failure, probably because TFdi provides a lower performance than TFic to predict extubation failure, as already reported by Vivier *et al.* [14] who observed similar values of TFdi in patients who succeeded and in those who failed extubation. In Vivier *et al.* [14], diaphragm ultrasound was performed when patients were still under mechanical ventilation while on a T-piece and not after extubation (such as in our study). In addition, patients in Vivier *et al.* [14] were selected as being at high risk of extubation failure, which was not particularly the case of our population. Our approach was to evaluate a strategy aiming to predict extubation outcome after and not before extubation, which could be questionable. We reasoned that despite a successful spontaneous breathing trial, the risk of extubation failure still ranges between 10% and 20% [25, 45]. This is explained by the fact that the spontaneous breathing trial behaves like any other diagnostic test and will never reach a perfect specificity (*i.e.* 100%) [46]. Accordingly, we believe that it is still relevant to evaluate the risk of extubation failure after extubation. The implications (not investigated in the present work) would be to personalise the management of these patients in order to prevent post-extubation acute respiratory failure and subsequent re-intubation (noninvasive ventilation, high-flow nasal oxygen, physiotherapy, mobilisation and delayed ICU discharge).

Strengths and limitations of the study

The study was conducted in two centres in two different countries and used a standardised weaning protocol. In addition, the inclusion criteria were broad, which might help generalise our findings. However, this study has limitations. First, the number of patients is limited due the weak occurrence of extubation failure and there were significant differences between both centres regarding some characteristics of the patients; further studies will have to evaluate the extrinsic validity of our calculated cut-offs and to confirm the predictive thresholds identified in the present work in a validation cohort. Second, the reproducibility of Dyspnoea-VAS and IC-RDOS was not evaluated in our study, although previous studies reported good reproducibility [20, 47]. Third, in order to standardise measurements, ultrasound was performed while patients were breathing spontaneously. Accordingly, ultrasound measurements may not reflect the patients' conditions under prophylactic measures (noninvasive ventilation or high-flow oxygen therapy). In addition, the use high-flow oxygen therapy may have influenced the outcome of some patients. At the time of study, no evidence-based guidelines were available on the use of high-flow oxygen therapy, which was driven by the experience of the physician in charge.

Conclusions

In patients who successfully passed a spontaneous breathing trial and were subsequently extubated, dyspnoea as assessed by self-report or observational scales and respiratory muscle activity assessed with ultrasound predicted extubation failure. Although these results need to be confirm by a larger study, they suggest that monitoring dyspnoea in every newly extubated patient may be useful to predict a future re-intubation. Our results pave the way for future studies evaluating whether monitoring dyspnoea following extubation may enable tailoring the oxygenation and ventilation strategy in the post-extubation period.

Author contributions: M. Dres and L. Brochard designed the study. M. Dres coordinated the study. M. Dres, T. Pham, L. Sergenyuk, W. Ouechani, I. Telias, D.L. Grieco, M.C. Sklar, D. Junhasavasdikul, L. Melo, C. Santis, L.F. Damiani, L. Degravi, M. Decavèle and L. Brochard were responsible for patient screening, enrolment and follow-up. M. Dres, T. Similowski, L. Brochard, A. Demoule and E.C. Goligher analysed the data. M. Dres, A. Demoule and T. Similowski wrote the manuscript. All authors had full access to all of the study data, contributed to drafting the manuscript or critically revised it for important intellectual content, approved the final version of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: M. Dres reports personal fees from Lungpacer SA, outside the submitted work. T. Similowski reports personal fees from AstraZeneca France, Boehringer Ingelheim France, GSK France, Teva France, Chiesi France, Lungpacer Inc. and ADEP Assistance, personal fees and nonfinancial support from Novartis France, grants from Air Liquide Medical Systems, outside the submitted work. E.C. Goligher reports personal fees and nonfinancial support (research equipment) from Getinge, nonfinancial support (research equipment) from Timpel, outside the submitted work. T. Pham has nothing to disclose. L. Sergenyuk has nothing to disclose. I. Telias reports grants from CIHR, personal fees for lectures from MBMed SA, Argentina and Covidien, Argentina, outside the submitted work. D.L. Grieco reports grants from GE, nonfinancial support from Dimar, Maquet and Fisher & Paykel, outside the submitted work. W. Ouechani has nothing to disclose. D. Junhasavasdikul has nothing to disclose. M.C. Sklar has nothing to disclose. L.F. Damiani has nothing to disclose. L. Melo has nothing to disclose. C. Santis has nothing to disclose. L. Degravi has nothing to disclose. M. Decavèle has nothing to disclose. L. Brochard reports grants from Medtronic Covidien, grants and nonfinancial support from Fisher & Paykel, nonfinancial support from Sentec and Philips, other (patent) from General Electric, outside the submitted work. A. Demoule reports personal fees from Medtronic, Baxter, Hamilton, Getinge and Lowenstein, grants, personal fees and nonfinancial support from Philips, Respinor and Lungpacer, personal fees and nonfinancial support from Fisher & Paykel, grants from French Ministry of Health, outside the submitted work.

Support Statement: M. Dres was supported by the French Intensive Care Society (SRLF bourse de mobilité 2015), the 2015 Short Term Fellowship programme of the European Respiratory Society, the 2015 Bernhard Dräger Award for Advanced Treatment of ARF of the European Society of Intensive Care Medicine, Assistance Publique Hôpitaux de Paris, Fondation pour la Recherche Médicale (FDM 20150734498) and Mitacs Globalink Sorbonne Universités. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Hernández G, Vaquero C, Colinas L, *et al.* Effect of postextubation high-flow nasal cannula *vs* noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomised clinical trial. *JAMA* 2016; 316: 1565–1574.
2 Béduneau G, Pham T, Schortgen F, *et al.* Epidemiology of weaning outcome according to a new definition. The WIND study. *Am J Respir Crit Care Med* 2017; 195: 772–783.
3 Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998; 158: 489–493.
4 Vaporidi K, Akoumianaki E, Telias I, *et al.* Respiratory drive in critically ill patients. Pathophysiology and clinical implications. *Am J Respir Crit Care Med* 2020; 201: 20–32.
5 Dangers L, Montlahuc C, Kouatchet A, *et al.* Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact: a prospective observational study. *Eur Respir J* 2018; 52: 1702537.
6 Schmidt M, Kindler F, Gottfried SB, *et al.* Dyspnea and surface inspiratory electromyograms in mechanically ventilated patients. *Intensive Care Med* 2013; 39: 1368–1376.
7 Luiso D, Villanueva JA, Belarte-Tornero LC, *et al.* Surface respiratory electromyography and dyspnea in acute heart failure patients. *PLoS One* 2020; 15: e0232225.
8 Chiti L, Biondi G, Morelot-Panzini C, *et al.* Scalene muscle activity during progressive inspiratory loading under pressure support ventilation in normal humans. *Respir Physiol Neurobiol* 2008; 164: 441–448.
9 Parthasarathy S, Jubran A, Laghi F, *et al.* Sternomastoid, rib cage, and expiratory muscle activity during weaning failure. *J Appl Physiol* 2007; 103: 140–147.
10 Dres M, Schmidt M, Ferre A, *et al.* Diaphragm electromyographic activity as a predictor of weaning failure. *Intensive Care Med* 2012; 38: 2017–2025.
11 Dres M, Dubé B-P, Goligher E, *et al.* Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation. *Anesthesiology* 2020; 132: 1114–1125.
12 Rittayamai N, Hemvimon S, Chierakul N. The evolution of diaphragm activity and function determined by ultrasound during spontaneous breathing trials. *J Crit Care* 2019; 51: 133–138.
13 Dres M, Goligher EC, Dubé B-P, *et al.* Diaphragm function and weaning from mechanical ventilation: an ultrasound and phrenic nerve stimulation clinical study. *Ann Intensive Care* 2018; 8: 53.
14 Vivier E, Muller M, Putegnat J-B, *et al.* Inability of diaphragm ultrasound to predict extubation failure: a multicenter study. *Chest* 2019; 155: 1131–1139.
15 Boles J-M, Bion J, Connors A, *et al.* Weaning from mechanical ventilation. *Eur Respir J* 2007; 29: 1033–1056.
16 Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426.
17 Decavèle M, Similowski T, Demoule A. Detection and management of dyspnea in mechanically ventilated patients. *Curr Opin Crit Care* 2019; 25: 86–94.
18 Gentzler ER, Derry H, Ouyang DJ, *et al.* Underdetection and undertreatment of dyspnea in critically ill patients. *Am J Respir Crit Care Med* 2019; 199: 1377–1384.

19 Campbell ML, Templin T, Walch J. A respiratory distress observation scale for patients unable to self-report dyspnea. *J Palliat Med* 2010; 13: 285–290.
20 Persichini R, Gay F, Schmidt M, *et al.* Diagnostic accuracy of respiratory distress observation scales as surrogates of dyspnea self-report in intensive care unit patients. *Anesthesiology* 2015; 123: 830–837.
21 Demoule A, Persichini R, Decavèle M, *et al.* Observation scales to suspect dyspnea in non-communicative intensive care unit patients. *Intensive Care Med* 2018; 44: 118–120.
22 Goligher EC, Laghi F, Detsky ME, *et al.* Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med* 2015; 41: 642–649.
23 Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med* 2014; 371: 287–288.
24 De Jonghe B, Sharshar T, Lefaucheur J-P, *et al.* Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; 288: 2859–2867.
25 Thille AW, Richard J-CM, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013; 187: 1294–1302.
26 Tobin MJ. Monitoring respiratory mechanics in spontaneously breathing patients. *In:* Principles and Practice of Intensive Care Monitoring. New York, McGraw-Hill, 1998; pp. 617–654.
27 Hilbert G, Gruson D, Portel L, *et al.* Airway occlusion pressure at 0.1 s (P0.1) after extubation: an early indicator of postextubation hypercapnic respiratory insufficiency. *Intensive Care Med* 1998; 24: 1277–1282.
28 Schmidt M, Demoule A, Polito A, *et al.* Dyspnea in mechanically ventilated critically ill patients. *Crit Care Med* 2011; 39: 2059–2065.
29 Haugdahl HS, Storli SL, Meland B, *et al.* Underestimation of patient breathlessness by nurses and physicians during a spontaneous breathing trial. *Am J Respir Crit Care Med* 2015; 192: 1440–1448.
30 Ward ME, Eidelman D, Stubbing DG, *et al.* Respiratory sensation and pattern of respiratory muscle activation during diaphragm fatigue. *J Appl Physiol* 1988; 65: 2181–2189.
31 Pesola GR, Ahsan H. Dyspnea as an independent predictor of mortality. *Clin Respir J* 2016; 10: 142–152.
32 Kirchberger I, Heier M, Kuch B, *et al.* Presenting symptoms of myocardial infarction predict short- and long-term mortality: the MONICA/KORA Myocardial Infarction Registry. *Am Heart J* 2012; 164: 856–861.
33 Bøtker MT, Stengaard C, Andersen MS, *et al.* Dyspnea, a high-risk symptom in patients suspected of myocardial infarction in the ambulance? A population-based follow-up study. *Scand J Trauma Resusc Emerg Med* 2016; 24: 15.
34 Steer J, Norman EM, Afolabi OA, *et al.* Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax* 2012; 67: 117–121.
35 Santos M, Kitzman DW, Matsushita K, *et al.* Prognostic importance of dyspnea for cardiovascular outcomes and mortality in persons without prevalent cardiopulmonary disease: the atherosclerosis risk in communities study. *PLoS One* 2016; 11: e0165111.
36 Rotondi AJ, Chelluri L, Sirio C, *et al.* Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. *Crit Care Med* 2002; 30: 746–752.
37 Currow DC, Abernethy AP, Ko DN. The active identification and management of chronic refractory breathlessness is a human right. *Thorax* 2014; 69: 393–394.
38 Başoğlu M. Effective management of breathlessness: a review of potential human rights issues. *Eur Respir J* 2017; 49: 1602099.
39 Dres M, Dubé B-P, Mayaux J, *et al.* Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. *Am J Respir Crit Care Med* 2017; 195: 57–66.
40 Ninane V, Farkas GA, Baer R, *et al.* Mechanism of rib cage inspiratory muscle recruitment in diaphragmatic paralysis. *Am Rev Respir Dis* 1989; 139: 146–149.
41 Brichant JF, De Troyer A. On the intercostal muscle compensation for diaphragmatic paralysis in the dog. *J Physiol* 1997; 500: 245–253.
42 Nochomovitz ML, Goldman M, Mitra J, *et al.* Respiratory responses in reversible diaphragm paralysis. *J Appl Physiol* 1981; 51: 1150–1156
43 De Troyer A, Peche R, Yernault JC, *et al.* Neck muscle activity in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994; 150: 41–47.
44 Murphy PB, Kumar A, Reilly C, *et al.* Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax* 2011; 66: 602–608.
45 Hernández G, Vaquero C, González P, *et al.* Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomised clinical trial. *JAMA* 2016; 315: 1354–1361.
46 Tobin MJ, Jubran A. Variable performance of weaning-predictor tests: role of Bayes' theorem and spectrum and test-referral bias. *Intensive Care Med* 2006; 32: 2002–2012.
47 Bausewein C, Farquhar M, Booth S, *et al.* Measurement of breathlessness in advanced disease: a systematic review. *Respir Med* 2007; 101: 399–410.