ERS statement on respiratory muscle testing at rest and during exercise

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Diverse methods are available for assessment of the respiratory muscles; the technique used should be tailored to the question posed http://ow.ly/poE830o8y58

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ABSTRACT Assessing respiratory mechanics and muscle function is critical for both clinical practice and research purposes. Several methodological developments over the past two decades have enhanced our understanding of respiratory muscle function and responses to interventions across the spectrum of health and disease. They are especially useful in diagnosing, phenotyping and assessing treatment efficacy in patients with respiratory symptoms and neuromuscular diseases. Considerable research has been undertaken over the past 17 years, since the publication of the previous American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on respiratory muscle testing in 2002. Key advances have been made in the field of mechanics of breathing, respiratory muscle neurophysiology (electromyography, electroencephalography and transcranial magnetic stimulation) and on respiratory muscle imaging (ultrasound, optoelectronic plethysmography and structured light plethysmography). Accordingly, this ERS task force reviewed the field of respiratory muscle testing in health and disease, with particular reference to data obtained since the previous ATS/ERS statement. It summarises the most recent scientific and methodological developments regarding respiratory mechanics and respiratory muscle assessment by addressing the validity, precision, reproducibility, prognostic value and responsiveness to interventions of various methods. A particular emphasis is placed on assessment during exercise, which is a useful condition to stress the respiratory system.

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Introduction

Assessing respiratory mechanics and respiratory muscle structure and function is an essential component of both clinical practice and research. It is especially useful in patients with respiratory symptoms and neuromuscular diseases (NMDs), contributing to diagnosis, patient phenotyping, assessment of treatment efficiency and patient follow-up. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) published a statement on respiratory muscle testing in 2002, reviewing the rationale and technical characteristics of the main methods available [1]. Nearly two decades later, given the large amount of novel research in the field, the chairs of the present task force felt a need to summarise the latest knowledge on respiratory mechanics and muscle assessment both for clinicians and researchers. Since 2002, key advances have been made in the field of mechanics of breathing, respiratory muscle neurophysiology, and respiratory muscle imaging in health and disease, including in paediatrics and critically ill patients in the intensive care unit (ICU). A specific focus of the task force has been the assessment of respirator muscles and mechanics during exercise, a situation stressing the respiratory system and thus allowing the evaluation of respiratory muscle response to increased ventilatory demand.

Methods

The task force was formed in June 2016, composed of experts from the ERS Clinical Respiratory Physiology, Exercise and Functional Imaging Group (04.01), the ERS Rehabilitation and Chronic Care Group (01.02), the Physiotherapists Group (09.02), and representatives from the European Lung Foundation and the ERS Science Council. The task force received support from ERS methodologists throughout the project. Three meetings of the task force were held; two during the annual congress of the ERS (September 2016 and 2017) and one in Lausanne in March 2017. All task force members signed conflict of interest disclosures at the beginning of the project and updated them at project finalisation or when any new relevant conflict of interest appeared. Conflicts of interest were managed according to ERS rules.

Studies that reported the evaluation of respiratory muscles (inspiratory and expiratory) and upper airway muscles at rest or during exercise in adults and children with cardiorespiratory diseases were reviewed, without restrictions on study design. MEDLINE and Cochrane Library records from 1970 to 2017 were searched. Selected references considered to be of particular relevance were included up to June 2018. Reference lists of all primary studies and review articles were examined for additional citations. Only studies written in English, or for which an English translation was available, were consulted. Studies were included that refer (singly or in combination) to reported validity (*i.e.* the extent to which a test or variable is related to the function of a physiological system or to patient-meaningful variables, such as symptoms or exercise), precision or reproducibility, prognostic information (*i.e.* relationship with the natural history of the disease), discrimination (*i.e.* whether a variable can differentiate the severity of the disease as conventionally measured), clinical meaningful difference (*i.e.* the minimal difference in a tested variable that is considered to be functionally worthwhile or clinically important), or test response to interventions. Studies that did not meet the inclusion criteria based on title or abstract were excluded.

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Studies that met the inclusion criteria were retrieved in full text to determine whether they were suitable for inclusion. For each section, the articles selected by the primary task force author had to be approved by a second author with expertise in the field. Disagreements, if any arose, were resolved by consensus. The reader is advised and encouraged throughout the text to refer to the 2002 statement for the scientific basis and classical methodological approach of respiratory muscle function.

Of note, this statement contains additional information on respiratory muscle evaluation in two particular settings, of paediatrics and the ICU; due to manuscript constraints, these two settings are confined quasi-exclusively to the supplementary material, along with more technical and methodological details concerning each section of the article.

Section 1. Respiratory muscle function

1.1. Airway opening, oesophageal and gastric pressures: technical considerations

1.1.1. Pressure measurement

Respiratory muscles have two distinct functions: force development (pressure changes) and shortening (lung volume changes). Several key points must be considered [1]:

1) Pressures reflect barometric pressure difference.
2) In unaltered physiology/anatomy, specific pressures represent entire corresponding spaces. Gravity/shear-stress affects pressure readings [2]. Figure 1 indicates pressure recording sites.
3) Pressure differences are assessed across corresponding structures. Table 1 lists thoracic pressure readings.
4) Pressure differences between two points reflect difference across at least two (group of) structures (*e.g.* chest wall/pleural cavity).
5) Pressure measurement reflects global muscle "output" (rather than contractile property *per se*).
6) Assessment occurs *via* voluntary manoeuvres or *via* evoked contractions (see below).

1.1.2. Pressure assessment devices

1.1.2.1. Pressure transducers

Frequency response flat up to 10–15 Hz assesses dynamic/static pressures [1]. Transducers should be calibrated in specific settings, since attached systems (*e.g.* catheters) alter frequency responses [3]. One should ensure identical frequency responses on both sides (differential transducers) [1]. Digital calibration is acceptable; however, a check *via* water manometer should be done regularly [1]. Pressure range should be ±300 cmH_2O and resolution ⩽0.5 cmH_2O [1].

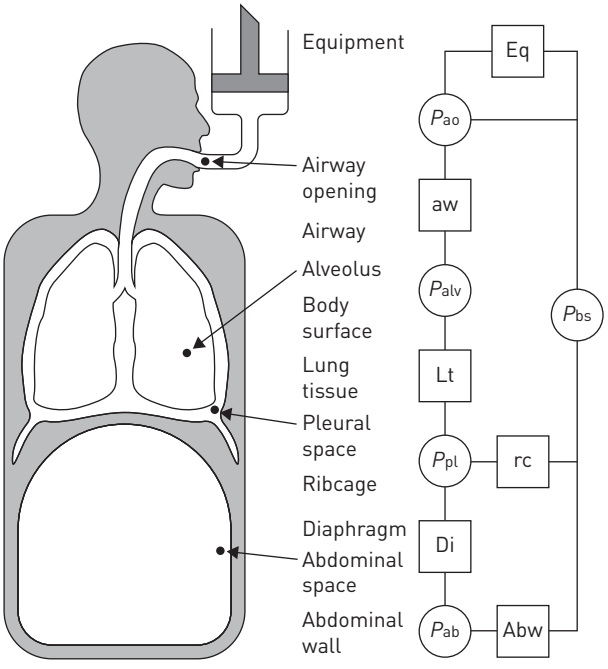

FIGURE 1 Pressure recording sites. Abw: abdominal wall; aw: airway; Di: diaphragm; Eq: equipment; Lt: lung tissue; P_{ab}: abdominal pressure; P_{alv}: alveolar pressure; P_{ao}: pressure at airway opening; P_{bs}: body surface pressure; P_{pl}: pleural pressure; rc: ribcage. Reproduced with permission of the publisher [1].

TABLE 1 Thoracic pressure readings

Pressures at a location

P_{ao} (airway opening pressure)
P_{alv} (alveolar pressure)
P_{pl} (pleural pressure)
P_{ab} (abdominal pressure)
P_{bs} (body surface pressure)

Pressure differences across structures

$P_{el(L)}$ (elastic recoil pressure of the lung (pressure across lung tissue))
P_L (transpulmonary pressure)
P_{rc} (pressure across the rib cage)
P_{aw} (flow-resistive pressure in airways)
P_{cw} (pressure across the chest wall)
P_{di} (transdiaphragmatic pressure)
P_{rs} (transrespiratory system pressure)
P_{abw} (transabdominal wall pressure)
P_{eq} (pressure across the equipment)

Relationship among pressures

$$\left.\begin{array}{l} P_{aw} = P_{ao} - P_{alv} \\ P_{el(L)} = P_{alv} - P_{pl} \end{array}\right\} = P_L = P_{ao} - P_{pl}$$

$$\left.\begin{array}{l} P_{rc} = P_{pl} - P_{bs} \\ P_{di} = P_{pl} - P_{ab} \\ P_{abw} = P_{ab} - P_{bs} \end{array}\right\} = P_{cw} = P_{pl} - P_{bs}$$

$$P_{rs} = P_{ao} - P_{bs} = -P_{eq}$$

1.1.2.2. Probes for invasive pressure assessment

Air-filled balloon catheters are used to record oesophageal (P_{oes}, ∼pleural pressure) and gastric pressure (P_{ga}, ∼abdominal pressure) [4]. Specific characteristics need to be considered and standardised preparation is required [1, 5]. Certain catheters additionally allow diaphragmatic electromyography (EMG) [1].

Repeated checking of air filling volumes and entire system volume displacement coefficient guarantees adequate balloon inflation [1, 5].

Appropriate system frequency responses (*e.g.* catheter diameter) are crucial for dynamic manoeuvres with high pressure changing rates (*e.g.* sniffs/twitches) [1]. Important characteristics include reasonable stiffness and several spirally arranged catheter holes at balloon portion, to avoid dampened signals [1, 5].

Liquid-filled catheters and catheter-mounted microtransducers have drawbacks (*e.g.* damped pressure signal in oesophagus/stomach or wide limits of agreement) and are not used in this setting [1, 6].

1.1.2.3. Devices for measurement of airway opening pressure

Airway opening pressure (P_{ao}) is usually sampled from side taps ("lateral pressure") located in the mouthpiece/tracheal tube/facemask/nostril plug [1, 7]. Nasal pressure reflects airway pressure only during undisturbed communication between nostrils/mouth with nasal flows [1]. The device to which the side tap is connected must have a cross-sectional area large enough to minimise the Bernoulli effect [8].

For P_{ao} to estimate alveolar pressure during dynamic respiratory efforts against an occluded airway, alveolar–oral pressure transmission must be fast [1]. The transmission time constant depends on airway resistance and compliance of extrathoracic airways (*i.e.* mouth/cheeks/equipment) [1]. This is especially important when airway resistance increases (*e.g.* asthma, chronic obstructive pulmonary disease (COPD)) [1].

1.2. Voluntary tests of respiratory muscle strength

1.2.1. Maximal static inspiratory and expiratory mouth pressure

Measurements of maximum static inspiratory (P_{Imax}) or expiratory (P_{Emax}) pressures at the mouth allow a simple assessment of global respiratory muscle strength in a clinical setting [1]. Tests are volitional and require full subject cooperation. P_{Imax} is usually measured at residual volume and P_{Emax} at total lung capacity (TLC) to record the maximum value of three manoeuvres that vary by less than 10% (more details can be found in the supplementary material). Measuring P_{Imax} at functional residual capacity (FRC) has the advantage of representing the maximal static inspiratory pressure measured at the lung volume at which patients breathe tidally; however, it is greatly influenced by the level of lung hyperinflation or the severity of restriction, so careful attention should be paid under these conditions.

P_{Imax} is strongly related to exertional dyspnoea (figure S4) [9]. The test might also serve as a screening instrument to identify patients with respiratory muscle weakness (figure 2, and supplementary material) [10]. Results should not be interpreted in isolation but together with the overall clinical picture (pathology, symptoms, and load/capacity balance during daily activities). The test is responsive to evaluate changes within subjects. Characteristics of studies that provide reference values for P_{Imax} and P_{Emax} measurements are summarised in the supplementary tables S2–S8 [11]. Measurements of mouth pressures are also used in cooperative children older than 6–8 years of age (table S14), and to evaluate muscle strength in the ICU (supplementary material).

1.2.2. Maximal sniff nasal inspiratory pressure

During measurement of maximal sniff nasal inspiratory pressure (SNIP), inspiratory pressure is recorded by a pressure transducer connected to a catheter placed in the nostril [12]. The test is performed at FRC. The subject is instructed to sniff quickly and deeply. SNIP has been validated in healthy individuals [12] and patients with COPD [13], and is also very useful for children >2 years of age [14]. Precision is good in healthy subjects without severe nasal congestion. Even in COPD there is good repeatability [13]. More information including normative values is presented in supplementary table S9.

1.2.3. Peak cough flow

Peak cough flow (PCF) estimates the effectiveness of mucus clearance and expiratory muscle function in neuromuscular disorders [15, 16]. The measurement is performed with subjects seated. An oronasal mask/mouthpiece is connected to a pneumotachograph or peak flow meter. Subjects are instructed to perform a maximal cough after complete inhalation [17]. They should perform 3–6 manoeuvres (<5% variability) and the maximum PCF ($L{\cdot}min^{-1}$) should be reported [17]. In NMDs, (manually) assisted PCF might be appropriate [18]. Hand-held peak flow meter devices might overestimate PCF if spirometer recordings of PCF are <270 $L{\cdot}min^{-1}$ [17].

PCF informs the need to start manual/mechanical exsufflator/insufflator therapy because PCF <270 $L{\cdot}min^{-1}$ is associated with higher likelihood of pulmonary complications in neuromuscular disorders [17]. Healthy (children) adults achieve PCF measurements of approximately (150) 470–600 $L{\cdot}min^{-1}$; PCF

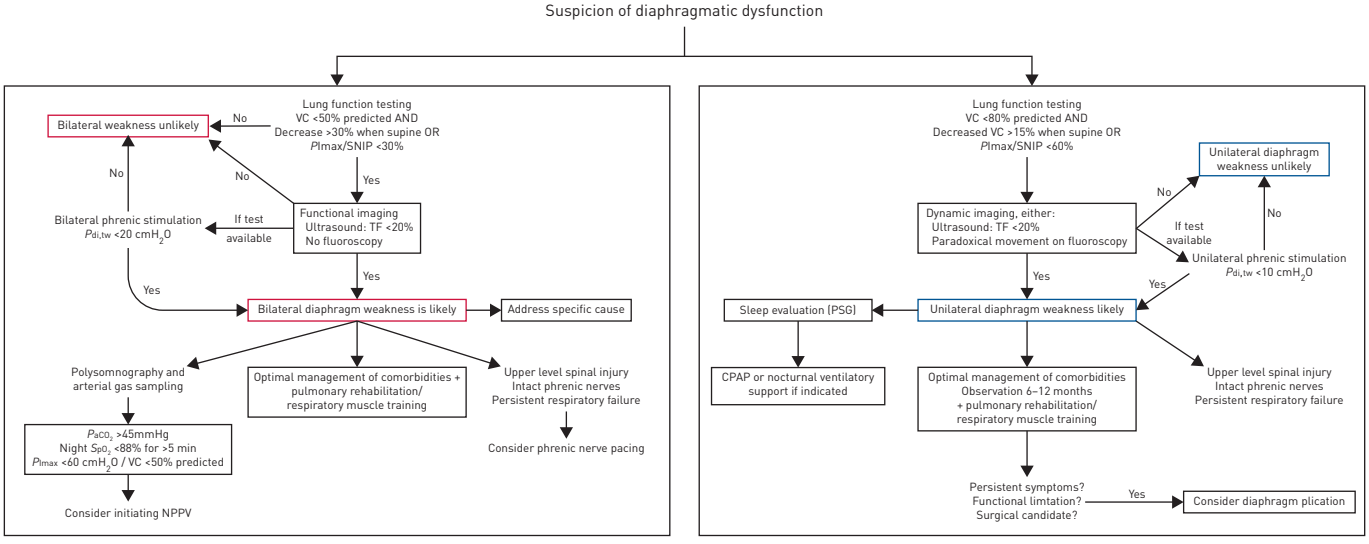

FIGURE 2 Expert opinion on the suspicion of diaphragmatic dysfunction. The figure describes the current practice of how the members of the task force suspect and treat respiratory muscle dysfunction (especially for unilateral and bilateral diaphragm weakness), outside of the intensive care setting (this is, however, not intended as a recommendation for clinical practice). In the absence of clearly defined lower limits of normal, it has long been accepted that a P_{Imax} or sniff-P_{di} or P_{dimax} ⩾80 cmH_2O in men and ⩾70 cmH_2O in women, and/or SNIP ⩾70 cmH_2O in men and ⩾60 cmH_2O in women are generally thought to exclude clinically significant inspiratory muscle weakness [1], and unilateral and bilateral diaphragm paralysis can be expected to decrease P_{Imax} or SNIP in the ranges of 60% [41] and <30% [42] of the predicted values, respectively. However, these values may be greatly impacted by the presence of underlying obstructive or restrictive lung disease [40]. A $P_{di,tw}$ >10 cmH_2O with unilateral phrenic nerve stimulation or >20 cmH_2O with bilateral phrenic nerve stimulation also rules out clinically significant weakness [1]. Please refer to the text for more details. SNIP: sniff nasal inspiratory pressure; VC: vital capacity; P_{Imax}: maximal inspiratory pressure; TF: thickening fraction of the diaphragm; PSG: polysomnography; CPAP: continuous positive airway pressure; P_{di}: transdiaphragmatic pressure; $P_{di,tw}$: twitch transdiaphragmatic pressure; NPPV: noninvasive positive pressure ventilation; P_{aCO_2}: arterial partial pressure of carbon dioxide; S_{pO_2}: peripheral oxygen saturation.

<160 $L \cdot min^{-1}$ is associated with higher likelihood of extubation/weaning failure in neuromuscular disorders (more details can be found in the supplementary material) [17, 19].

1.3. Voluntary manoeuvres with oesophageal and gastric pressures

Measurements of P_{oes}, P_{ga} and transdiaphragmatic pressure ($P_{di}=P_{ga}-P_{oes}$) while sniffing and coughing are useful when noninvasive measures of in- and expiratory muscle function (*e.g.* SNIP or PCF) provide equivocal information. Assessments during sniff are particularly useful when SNIP yields suspiciously low values, *e.g.* in patients with upper airway obstruction (hypertrophy of the adenoids, rhinitis, polyps) or lower airway obstruction. Assessments during cough are needed to assess the expiratory muscles when glottis function is compromised, for example in patients with bulbar amyotrophic lateral sclerosis (ALS). These measurements may also be used to refine clinical diagnosis [20, 21]. Maximal muscle relaxation rate (MRR) can provide additional information on respiratory muscle function [22, 23] but its clinical application is limited. Measurements of P_{oes} and P_{ga} during voluntary manoeuvres can also be obtained in the ICU and in children (supplementary material).

In adults, the average within-subject, between-occasion coefficient of variation (CV) is 11% for sniff-P_{di} [24] and 6.9% for cough-P_{ga} (table 2) [21]. No such values are available for children. For sniff-MRR, within-subject and between-occasion CVs range from 6 to 26% [25].

Reference values are given in table 2 where available.

In many diseases, pressures produced during sniff and cough are less than normal, both in adult patients (*e.g.* heart failure [26], stroke [27], COPD [25], pulmonary fibrosis [25], cystic fibrosis [28] and NMDs [20, 21, 29]) and in children with NMDs [30, 31]. In a cohort of patients with mixed diagnoses [20], adding SNIP to P_{Imax} reduced the false-positive diagnosis of inspiratory muscle weakness by 20% (with sniff-P_{di} not adding more diagnosis accuracy). Adding cough-P_{ga} to P_{Emax} decreased false-positive diagnosis of expiratory muscle weakness by 30% [20].

The use of sniff-P_{di} and cough-P_{ga} has not been widely explored for prognosis. In ALS patients, sniff-P_{di} correlated with SNIP [32] and SNIP <40 cmH_2O was associated with desaturation during sleep; hazard ratio for death was 9.1. Sniff-P_{di}, sniff-P_{oes} and twitch P_{di} ($P_{di,tw}$, see below) were significant predictors of ventilation-free survival in ALS patients [33], while P_{Emax} and transdiaphragmatic pressure elicited by phrenic nerve stimulation ($P_{di,tw}$) were predictors of absolute survival.

After lung volume reduction surgery [34], sniff-P_{di}, SNIP and P_{Imax} increased significantly, while 8 weeks of rehabilitation did not add any further improvement [34].

In COPD, after exhaustive treadmill walking, sniff-P_{oes} did not change significantly; sniff-P_{oes}-MRR decreased by 42%, and recovered within 5 min of rest [35].

1.4. Respiratory muscle-related mechanics of breathing

1.4.1. Lung function testing

Pulmonary function tests, especially measurements of upright and supine vital capacity (VC), which depends on activation of both inspiratory and expiratory muscles [36], are noninvasive and readily available measurements contributing to the evaluation of respiratory muscle function, especially the diaphragm [36–39]. Unilateral diaphragm weakness is usually associated with a modest decrease in VC, to approximately 75% of predicted [40, 41], with a further 10–20% decrease in the supine position (15% which represents twice the CV of the measure could be considered the lower limit of normal) (figure 2) [41], while FRC and TLC are usually preserved [40, 41]. In severe bilateral diaphragm weakness, VC is usually 50% of predicted and can further decrease by 30% or more when supine [42]. A normal supine VC makes the presence of clinically significant diaphragmatic weakness unlikely.

TLC can also be reduced (70–79% of the predicted value with mild weakness, up to 30–50% of the predicted value in moderate-to-severe weakness), while residual volume can be elevated [43]. Of note, in patients with diaphragm weakness, the magnitude of fall in VC in the supine position correlates with the reduction in sniff-P_{di} [43].

In many NMDs [44–50], such as ALS, a significant reduction of VC at diagnosis, as well as its rate of decline over time, are recognised as criteria for initiating noninvasive ventilation [51, 52]. Reduction in VC is also predictive of sleep disordered breathing, respiratory failure, worse prognosis and response to treatment, to a lesser extent, with good sensitivity (80–95%) but quite variable specificity (50–90%) [53].

1.4.2. Indices of respiratory muscle effort

The pressure output of the respiratory muscles can be assessed by calculating 1) the work of breathing (WOB), 2) the pressure–time product (PTP) of either the oesophageal pressure (PTP_{oes}; reflecting

TABLE 2 Characteristics of the main voluntary and evoked manoeuvres to assess respiratory muscle strength

Tests	Main variables	Reference values and discriminative values	Repeatability/reliability/validity	Cautions	Setting (expert centres, general clinical use, research, *etc.*)	Remarks
Voluntary manoeuvres with mouth pressure	P_{Imax}	Yes (tables S2–S4)	Sufficiently repeatable and reliable measurements in untrained subjects (<10% variability between efforts) can usually be obtained within 5 efforts [297]. Peak values are typically reached after 9 attempts [298].	Standardisation of lung volumes, mouthpiece and recorded pressure (peak *versus* plateau) required.	SNIP and mouth pressures can be used in clinical practice after thorough training of the procedures.	Always to be interpreted in clinical context of symptoms and diagnosis.
	P_{Emax}	Yes (tables S5 and S6)	Reliable peak values usually achieved after 5–6 efforts. Within subject between occasion coefficient of variation around 10% [21].	Standardisation of lung volumes, mouthpiece and recorded pressure (peak *versus* plateau) required.		Always to be interpreted in clinical context of symptoms and diagnosis.
	SNIP	Yes (table S9)	Yes. Possibly fewer efforts needed for acceptably reliable measurements in comparison to P_{Imax} in untrained subjects [12, 13, 20, 299, 300].	Cautions in subjects with severe nasal congestion. Although SNIP and P_{Imax} has a good correlation, the agreement between these two methods is variable. Thus, they are complementary and not interchangeable in the evaluation of inspiratory weakness	SNIP in association with P_{Imax} reduces the false-positive diagnosis of inspiratory weakness by nearly 20% [5].	Should be used as a complementary variable (*i.e.* in addition to a first screening with mouth pressures) to investigate inspiratory weakness. Always use the reference values of your population when available.
	PCF	Healthy subjects: 468–588 $L \cdot min^{-1}$ [301] Increased extubation/weaning failure <160 $L \cdot min^{-1}$ in NMD patients [302]	No sufficient data available.	At least 3–6 PCF with <5% variability need to be assessed [17]	Simple to assess. Especially useful in NMD patients.	No direct link between "cut-off" values and clinical consequences (*e.g.* cough assist).
Voluntary manoeuvres with oesophageal and gastric pressures			Be careful with dose of local anaesthesia.			
	Sniff	No normal values exist; mean±SD (range) achieved by healthy subjects: P_{di} (37 M): 148±24 (111–124, 126–204) cmH_2O [303] P_{di} (27 F): 122±25 (82–182) cmH_2O [303] P_{di} (64): 136±37 (82–204) cmH_2O [303] P_{di} (32): 134±24 (86–195) cmH_2O [24] P_{oes} (37 M): 105±26 (52–150) cmH_2O [303] P_{oes} (27 F): 92±22 (52–140) cmH_2O [303]	CV-P_{di} (healthy adults): 11% [24]	NA	Expert centre research	SNIP/sniff-P_{oes} (children): CF 0.72±0.13 [28] NMD patients 0.83±0.17 [28] Thoracic scoliosis 0.86±0.10 [28] 3-year ventilator-free survival in ALS patients: sniff-P_{di} cut-off 108.5 cmH_2O (sensitivity 0.85, specificity 0.98) [33]

Continued

TABLE 2 Continued

Tests	Main variables	Reference values and discriminative values	Repeatability/reliability/validity	Cautions	Setting (expert centres, general clinical use, research, *etc.*)	Remarks
		P_{oes} (64): 100±25 (52–150) cmH_2O [303] P_{oes} (12) 93±27 cmH_2O [28] P_{ga} (37 M): 43±32 (0–134) cmH_2O [303] P_{ga} (27 F): 29±29 (0–108) cmH_2O [303] P_{ga} (64): 37±31 (0–134) cmH_2O [303]				
	Cough	Normal values [21]: P_{ga} (62 M): 214±42 cmH_2O P_{ga} (37 F): 165±35 cmH_2O Lower limits of normal [21]: 132 cmH_2O (62 M), 97 cmH_2O (37 F)	CV-P_{ga} (healthy adults): 6.9% [21]	NA	Expert centre research	Cough-P_{ga} assessment is helpful for patients with low P_{Emax} to avoid false-positive diagnosis of expiratory muscle weakness.
Evoked manoeuvres	$P_{mo,tw}$	Possible diaphragm weakness $P_{mo,tw}$ <−11 cmH_2O (cervical magnetic stimulation) $P_{mo,tw}$ <−8 cmH_2O (bilateral electrical stimulation)				
	$P_{di,tw}$	Possible diaphragm weakness $P_{di,tw}$ <15 cmH_2O				

P_{Imax}: maximal inspiratory pressure; P_{Emax}: maximal expiratory pressure; SNIP: maximal sniff nasal inspiratory pressure; PCF: peak cough flow; NMD: neuromuscular disease; P_{oes}: oesophageal pressure; P_{ga}: gastric pressure; P_{di}: transdiaphragmatic pressure; P_{mo}: mouth pressure; $P_{di,tw}$: twitch transdiaphragmatic pressure; $P_{mo,tw}$: twitch mouth pressure; ALS: amyotrophic lateral sclerosis; CF: cystic fibrosis; M: male; F: female; CV: coefficient of variation; NA: not applicable.

the effort done by all of the respiratory muscles), the transdiaphragmatic pressure (PTP_{di}; reflecting mostly the effort done by the diaphragm) [54], 3) the tension-time index ($TTI=Pl/P_{Imax}\times tl/t_{tot}$) or 4) the P_{oes} swing. Details on how these indices are calculated, their physiological underpinning, advantages and disadvantages are described in the supplementary material. PTP analyses have been used as an alternative to WOB to quantify respiratory muscle effort in both healthy subjects [55, 56] and patients with COPD [57–59]. PTP is more closely related to respiratory muscle oxygen consumption than WOB [60]. The average value for PTP in healthy subjects is around 100 $cmH_2O{\cdot}s{\cdot}min^{-1}$ while in acute respiratory failure, the average PTP has been reported to be about four-fold greater [61]. During trials of weaning from mechanical ventilation, PTP_{oes} can predict weaning failure [61]. PTP is greater in COPD patients during exercise compared with age- and sex-matched healthy controls [62].

In the clinical setting, inspiratory effort can be simply monitored by measuring tidal swings in P_{oes} ($P_{oes,tid}$) (figure 3) [63]. $P_{oes,tid}$ can serve as an index of global respiratory muscle effort during exercise in patients with chronic respiratory diseases [64]. $P_{oes,tid}$ can identify differences in disease severity between patients with COPD (*i.e.* by Global Initiative for Chronic Obstructive Lung Disease stages) [65] and it is sensitive to changes over time and to interventions [65]. Increases in $P_{oes,tid}$ relative to stable tidal volume responses are related to the perception of dyspnoea during exercise [64, 66]. $P_{oes,tid}$ has been successfully applied as a bedside monitoring tool in sleep studies [67], and during weaning trials [68]. $P_{oes,tid}$ (in analogy with the PTP_{oes}) showed larger changes over the course of a failed weaning trial than breathing pattern parameters (rapid shallow breathing index) [61, 68].

Reduction of resistive and elastic load by continuous positive airway pressure or inspiratory pressure support can reduce inspiratory effort. During exercise, these reductions in inspiratory effort decrease exercise-associated dyspnoea and improve exercise tolerance in patients with COPD [57, 69]. Similar results can be obtained using helium hyperoxia and bronchodilators [70]. It is difficult to establish a minimal clinically important difference of indices of respiratory muscle effort, given the paucity and heterogeneity of the studies. Nonetheless, a clinically meaningful difference of 14–16% from baseline condition has been shown to correlate with a clinically meaningful reduction of exertional dyspnoea after pharmacological intervention such as bronchodilators for both PTP and $P_{oes,tid}$ [71–73]. Finally, exercises that promote slow and deep breathing have the potential to reduce the elastic component of WOB and thereby reduce inspiratory effort [74–76]. In addition, changes in inspiratory duty cycle (decreased tl/t_{tot}) induced by these breathing techniques can further reduce PTP by reducing inspiratory time per minute [77]. Measurements of pressure during brief inspiratory occlusions (typically 0.1 s) applied without warning before the individual recognises the occlusion and reacts (*i.e.* $P_{0.1}$) can be a useful index of respiratory centre motor output (supplementary material).

1.5. Evoked manoeuvres

Non-volitional evaluation of diaphragm (dys)function and fatigue (*i.e.* a reduction in the ability to produce force/pressure following contractile activity) can be performed by phrenic nerve stimulation; diaphragm

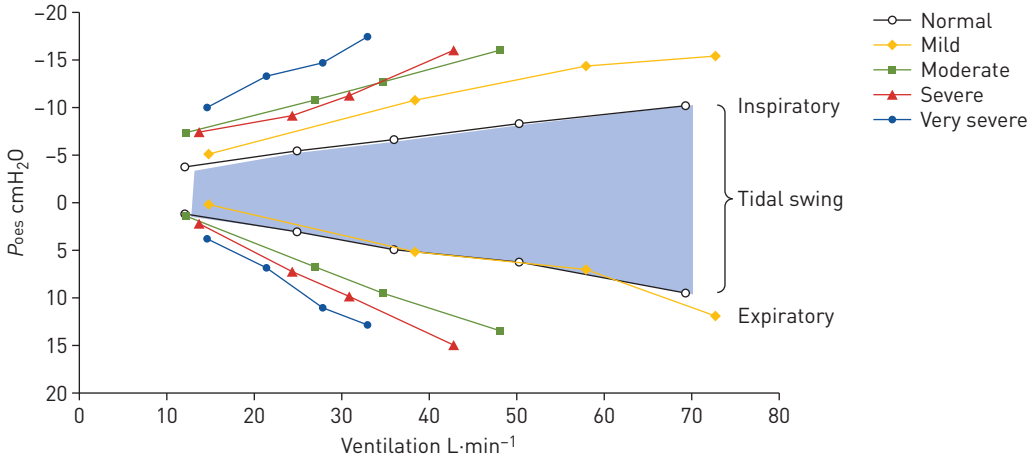

FIGURE 3 Tidal oesophageal pressure (P_{oes}) swings are shown with varying severity of chronic obstructive pulmonary disease and in age-matched healthy control subjects. As disease severity worsens, the amplitude of inspiratory and expiratory P_{oes} increases for a given ventilation during exercise. The shaded area represents the tidal P_{oes} swing in the healthy control subjects. Original data from the authors' laboratory. Values are means.

contraction causes a sudden and short-lasting fall in P_{oes} and a rise in P_{ga}, the difference providing $P_{di,tw}$. Abdominal muscles can be evaluated by stimulation of thoracic nerve roots with measurement of gastric pressure ($P_{ga,tw}$).

Magnetic phrenic nerve stimulation has superseded electrical stimulation, except where patients have pacemakers or other implanted electronic devices where magnetic stimulation is contraindicated. Technical considerations during phrenic nerve stimulation include: 1) stimulation must be supramaximal, 2) potentiation resulting from prior contraction must be avoided or standardised, 3) lung volume must be standardised, and 4) different magnetic stimulation techniques (*e.g.* cervical, bilateral anterior) yield different results and should be used consistently. A noninvasive estimate of $P_{di,tw}$ can be obtained by measuring pressure changes in the upper airway or the mouth ($P_{mo,tw}$) [78] although oesophageal twitch pressure ($P_{oes,tw}$) and thus $P_{mo,tw}$ are more influenced by lung volume than $P_{di,tw}$.

Resting values of $P_{ga,tw}$ have a slightly higher variability (CV 9–10%) than $P_{di,tw}$ (6%).

Age- and sex-specific normal values for adults are lacking, but a cut-off for $P_{di,tw}$ of 18 cmH_2O has been suggested for diagnosis of diaphragm weakness [20]. In healthy subjects, the mean between-occasion variability in $P_{di,tw}$ is 20±11% and CV 11% [79]. The limit of agreement of the difference of $P_{di,tw}$ recordings is ±6 cmH_2O [79]. Variations in $P_{di,tw}$ with disease are shown in table 3.

Exhaustive exercise in healthy subjects can elicit a fall in $P_{di,tw}$ (showing diaphragm fatigue), while in a variety of disease states exercise-induced diaphragm fatigue has been reported by some but not all investigators (please refer to supplementary material for more details). Of note, diaphragm fatigue is not necessarily related to exercise performance and development of fatigue may not predict clinical outcomes [80].

Normal $P_{di,tw}$ values are available for neonates [81], infants [82] and children [83], in whom stimulation is acceptable with local anaesthesia. In critically ill patients, measurement of $P_{ao,tw}$ and $P_{di,tw}$ can be particularly useful and several large case series yielded $P_{ao,tw}$ or $P_{di,tw}$ values [84, 85] that are lower than those recorded in healthy individuals (please refer to supplementary material for further details).

1.6. Respiratory muscle endurance testing

Different approaches can be used to assess respiratory muscle endurance: 1) incremental load testing, 2) constant load testing and 3) time trials. Different tests were developed within these categories: 1) a stepwise load increase by increasing resistance/threshold load or minute ventilation, 2) sustaining a given resistance/threshold load or hyperpnoea level to task failure and 3) time trial, where a maximum ventilation (with/without additional resistance) must be achieved within a given duration. While resistive/threshold loading tests mostly apply inspiratory loads [86], hyperpnoea tests load both inspiratory and expiratory muscles [87].

Since test performance is influenced by breathing pattern, breathing frequency and tidal volume should be controlled (feedback) and/or reported [88–90]. When testing pre/post-interventions, starting load/ventilation and increments (if present) need to be identical.

TABLE 3 Summary of the main causes of perturbation in twitch transdiaphragmatic pressure ($P_{di,tw}$)

$P_{di,tw}$ observation	Partitioning	Interpretation	Consider
$P_{di,tw}$ ↑	$P_{oes,tw}$ ↑, $P_{ga,tw}$ ↑	• Strong patient • Potentiated muscles	
$P_{di,tw}$ ↓	$P_{oes,tw}$ ↓ $P_{ga,tw}$ ↓	• True weakness • Submaximal stimulation (*e.g.* obesity) • Medical comorbidities	• Neurological exam • Is P_{Imax}/SNIP strong? (supports if so) • Age [304], heart failure [305], pulmonary hypertension [306]
$P_{di,tw}$ ↓	$P_{oes,tw}$ ↓ $P_{ga,tw}$ ↔	• Hyperinflation	• Review technique • Investigate for COPD • What is end-expiratory oesophageal pressure? (may reveal intrinsic PEEP) • Check air (in balloon catheter systems)

$P_{oes,tw}$: oesophageal twitch pressure; $P_{ga,tw}$: gastric twitch pressure; P_{Imax}: maximal inspiratory pressure; SNIP: sniff nasal inspiratory pressure; COPD: chronic obstructive pulmonary diseases; PEEP: positive end-expiratory pressure.

1.6.1. Maximal incremental load testing

Resistive/threshold testing requires subjects to breathe against a resistive/threshold [1, 89] or tapered flow-resistive [86] load that is increased at regular intervals (minutes or number of breaths), *e.g.* by 10% of baseline P_{Imax} until task failure. Inspiratory muscle endurance can be defined as the pressure of the last completed step.

Hyperpnoea testing uses stepwise increasing minute ventilation (*e.g.* +8% of maximal voluntary ventilation (MVV) every 3 min) [1]. It needs special equipment to assure normocapnia and has been increasingly applied in recent years [90]. Ventilatory levels achieved in this test were found to be similar to levels reached in the traditional maximal sustainable ventilation test [91, 92]. Normal values have been established for healthy subjects [90].

1.6.2. Constant load testing

During resistive/threshold testing, subjects are instructed to breathe against a submaximal load [86, 88, 89] until task failure. It has been proposed that the selected load should result in a time to task failure (t_{lim}) of 5–10 min, such that post-intervention test durations can be limited to about 15–20 min without important ceiling effects [86, 89]. Main outcomes are t_{lim} and/or total external work performed during the test [86]. The pattern of breathing during such a test is important and must be taken into account when analysing the data.

During hyperpnoea testing, subjects breathe at a constant ventilation (40–70% MVV) to achieve task failure within 8–12 min.

1.6.3. Time trial

The 10–15 s MVV manoeuvre is too short-lasting for assessment of respiratory muscle endurance. Different protocols exist for testing maximal sustainable ventilation, *i.e.* the ventilation that can be sustained for a given, extended period of time (*e.g.* 12–15 min). However, there is no consensus on which protocol to use for this kind of test [1].

The attraction of these different respiratory muscle endurance tests is that they provide a method for evaluating global respiratory muscle endurance in a single test session. The tests are noninvasive and relatively well-tolerated. Several studies showed large improvements in respiratory muscle endurance after respiratory muscle training by using these tests (supplementary material).

Section 2. Respiratory muscle neurophysiology

Respiratory muscle neurophysiological testing includes 1) EMG to measure the output of the respiratory motor neurons, 2) electroencephalography (EEG), which tests the involvement of motor and premotor areas, and 3) transcranial magnetic stimulation (TMS) which assesses the neural pathways to the respiratory muscles (figure 4).

2.1. Electromyography

EMG is the technique that quantifies the electrical activity of muscles and is used in research and clinical practice to assess respiratory muscle control at rest and during exercise, including estimation of respiratory motor output (as previously reviewed [93, 94]), neuromechanical coupling during loaded breathing [95] and the efficacy of muscle contraction when coupled with measurements of ventilation [96, 97]. Finally, EMG can also be used in the diagnosis of myopathic and neuropathic diseases [1]. A thorough review of the theoretical background and methodology of respiratory EMG recordings is available [1].

Respiratory EMG can be recorded with surface electrodes, an oesophageal electrode inserted *via* the nose, and intramuscular wire or needle electrodes. Appropriate selection of electrodes depends on the EMG technique (*e.g.* physiological recordings *versus* evoked responses), the target muscle, signal reliability and safety (table 4).

Respiratory EMG measurement is usually contaminated with ECG readings, which should be eliminated [98, 99] or excluded from EMG measures. Moreover, respiratory EMG recordings, especially with surface electrodes, are subject to electromagnetic interference [1, 94, 100], contamination from adjacent muscles and changes in lung volume or posture [1, 101]. Diaphragm EMG can be quantified with a multi-pair oesophageal electrode [102, 103], usually standardised to a maximal value (table 4). Given its noninvasive nature, surface parasternal intercostal EMG has been proposed as an alternative measure of respiratory motor output, respiratory load-capacity balance and, potentially, lung disease severity [104–107], but may not be useful during exercise testing [108]. The single motor unit technique can accurately assess respiratory motor output [93] and avoids many of the caveats related to contamination of EMG signals

and normalisation. For evoked responses, normal values of phrenic nerve conduction time are available using either electrical or magnetic stimulation (table 4) [1, 94, 109, 110].

The reliability of these respiratory EMG techniques is reported in table 4.

Respiratory EMG has been used to assess respiratory muscle control in cardiorespiratory disease at rest (table S10) and during exercise (table S11). Briefly, diaphragm EMG is a surrogate of respiratory effort [102, 111–113], it can be used to distinguish between central and obstructive sleep apnoea events [111, 112, 114], to assess exertional breathlessness during exercise [64, 97, 115, 116] and, when combined with V_T recordings, it can be used to assess upper airway resistance [112, 117]. Given increased respiratory motor output to the respiratory muscles in COPD [118, 119] and the relationship between EMG and lung function, respiratory EMG has been taken as a marker for disease severity in stable COPD [103] and to predict COPD exacerbations [105], early hospital admission [107] and the effect of medical interventions [120–122].

In the ICU, recordings of the electrical activity of the crural diaphragm (EA_{di}) using a dedicated nasogastric tube with EMG electrodes has greatly facilitated bedside monitoring of diaphragm activity in both paediatric [123] and adult patients [124]. The EA_{di} signal can be used to trigger and determine the level of assistance during mechanical ventilation, *i.e.* "neutrally adjusted ventilatory assistance" [125]. The ratio of actual EA_{di} to maximum EA_{di} can be used to estimate the patient's effort to breathe [126]. EA_{di} is a promising tool for diaphragm activity monitoring, especially during the weaning phase [127].

2.2. Electroencephalography

Respiratory-related cortical networks are not normally activated during resting breathing [128], carbon dioxide stimulation [128], or the ventilatory response to exercise [129]. In contrast, these networks are engaged during voluntary respiratory manoeuvres (apnoea, sniffing or hyperventilation) [128, 130, 131]. They are also engaged when the respiratory system is used for non-respiratory purposes, such as speech [132]. Induction of respiratory neuroplasticity using repetitive TMS have suggested these networks exert a tonic excitatory influence on breathing during wakefulness [133]. The respiratory-related

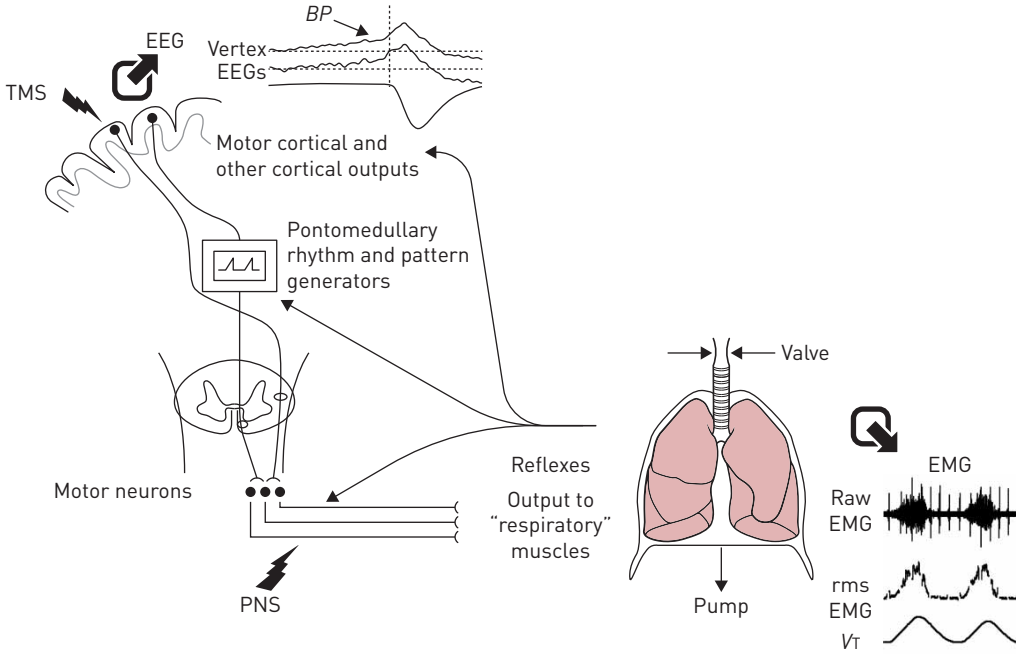

FIGURE 4 Neurophysiological techniques to assess respiratory muscle control. Schematic of the neural control of the human respiratory muscles. Multiple descending pathways integrate at the respiratory motor neurons (with reflex afferent inputs) and determine the functional output of the muscles. Using electromyography (EMG), the output can be measured during resting breathing, exercise and voluntary manoeuvres or as evoked signals in response to transcranial magnetic stimulation (TMS) over the motor areas or phrenic nerve stimulation (PNS) of the peripheral nerve. The output from cortical networks can be measured using electroencephalography (EEG) as the presence of a bereitschaft (readiness) potential (BP) indicates respiratory-related cortical activity. rms: root mean square; V_T: tidal volume.

TABLE 4 Characteristics of electromyography (EMG) techniques at rest

Tests (EMG techniques)	Main variables	Reference values and discriminative values	Repeatability/reliability/validity	Cautions/safety	Setting (clinical, research)	Remarks
EMG during breathing. For surface and oesophageal recordings, raw EMG or integral/root mean square is typically normalised to maximal EMG measured during maximal inspiratory efforts (SNIP, P_{Imax}, inspiration to TLC and MVV). For the single motor unit technique recorded with needle or wire electrodes, the peak discharge rate is typically reported.	sEMGpara, EMGpara%max	Reference values for men and women, with and without a mouthpiece, raw *versus* normalised signal [106].	Negligible bias for raw and normalised EMG between recording sessions. Small bias in raw EMGpara for repeat measures in the same recording session [106].	Considered safe except for small chance of skin abrasion during electrode preparation. However, signal is subject to contamination from other muscle activity and movement of muscle.	Clinical, research	Recordings of sEMGpara show promise as a noninvasive method to measure neural respiratory drive [104].
	sEMGscal	NA	Ensemble average of 80 breaths had comparable timing of inspiratory activity as iEMG recordings for 3 participants [307].		Research	sEMGscal has been proposed as a monitoring tool in the ICU [100].
	sEMGdi	NA for adults. Reference values for children during sleep [308].	Excellent reliability within participants, and excellent agreement between occasions and between observers, but data from children who were snorers [308].		Clinical, research	Surface EMG over the chest wall can be very susceptible to contamination.
	oesEMGdi%max	Reference values for young (<50 years) and old (>50 years) subjects. No difference if signal normalised to max in voluntary manoeuvres or evoked response (*i.e.* oesCMAPdi) [103]	Good repeatability between recording sessions and between observers [103].	Not for use in patients with oesophageal varices.	Clinical, research. Used in neutrally adjusted ventilatory assistance.	The preferred technique for testing respiratory muscle control during exercise given its specificity and safety advantages. Disadvantage of the normalisation procedure is that "maximal efforts" can be, in fact, submaximal [309].
	iEMGdi	No data available for amplitude during quiet breathing. This measure is typically used to compare activity between experimental procedures [310].		Usual considerations with needle insertion (bleeding, pain and infection). Risk of pneumothorax can be minimised with appropriate precautions (*e.g.* ultrasound and online audio/visual feedback), but greater risk during exercise due to increased lung excursion and chest wall movement.	Research	Even intramuscular recordings are susceptible to cross-talk [311], although to a much smaller degree than surface recordings. Can be used for single- or multi-unit recordings.
	SMUdi, SMUia	Multiple studies in small samples of healthy subjects are available (refer to [93] for references).	Excellent validity given recordings do not need to be normalised, are much less susceptible to recordings artefacts.	Safety considerations as above.	Used in research, and occasionally clinically, in expert centres.	Recorded using needle or selective wire electrodes. A needle electrode can be manipulated in the muscle to sample populations of respiratory motor units.

Continued

TABLE 4 Continued

Tests (EMG techniques)	Main variables	Reference values and discriminative values	Repeatability/reliability/validity	Cautions/safety	Setting (clinical, research)	Remarks
Evoked signals Measured as the compound muscle action potential in response to electrical stimulation or magnetic stimulation over the cervical spinal cord (CMS) or anterolaterally on the neck (unilateral; UMS) of the phrenic nerve(s).	sCMAPdi	Typically, latency 6–8 ms, depending on stimulation technique or side [109, 312]. Amplitude of CMAP more variable.	Latency is reproducible for both electrical and cervical magnetic stimulation [109].	For magnetic stimulation, the contraindications are listed in the supplementary table.	Both clinical investigation and research.	Signal free of contamination if phrenic nerve is activated without co-stimulation of other muscles. Usually used to diagnose neuromuscular diseases.
	oesCMAPdi	Using a multi-pair electrode, latency is 6–8 ms [102, 313]. Latency shorter on right *cf.* left side and shorter compared to sCMAPdi from costal diaphragm [313]. Amplitude of CMAP is more variable [313].	Good reproducibility between recording sessions for latency [102, 313]. Good agreement between electrical and unilateral magnetic stimulation for latency and amplitude [102].	Safety considerations for magnetic stimulation as above. Oesophageal catheter not for use in patients with oesophageal varices.	Clinical, research.	

s: surface recordings; ia: intercostal/accessory muscles; oes: oesophageal; para: parasternal intercostal muscle of the second interspace; scal: scalene muscle; di: diaphragm; %max: as a percentage of maximal EMG; SNIP: sniff nasal inspiratory pressure; P_{Imax}: maximal inspiratory pressure; TLC: total lung capacity; MVV: maximal voluntary ventilation; ICU: intensive care unit; SMU: single motor unit; CMS: cervical magnetic stimulation; UMS: unilateral magnetic stimulation; CMAP: compound muscle action potential; NA: not applicable.

cortico-subcortical networks are also engaged in situations where the breathing control system is challenged. Thus, a cortical drive to breathe contributes to the maintenance of ventilatory activity during wakefulness, in spite of profound hypocapnia [134]. Respiratory-related cortico-subcortical networks are also activated when the respiratory system is faced with mechanical constraints [128, 135–138]. This activation is not only sensory, but also motor. A motor respiratory-related cortical activity has been described in various clinical situations. Patients with deficient respiratory automaticity due to Phox 2B mutations (congenital central alveolar hypoventilation) exhibit respiratory-related cortical activity on their electroencephalograms during resting breathing [139]. Detailed observations made in one such patient showed better cognitive performance during mechanical ventilation than during unsupported breathing [140]. This finding lends support of the actual role of the cortical activity in sustaining ventilation ("dual tasking paradigm" [141]). A similar cortical activity has been described in patients with severe forms of the obstructive sleep apnoea syndrome (OSAS) [142] (probably related to the inspiratory load induced by upper airway abnormalities) and in patients with inspiratory muscle weakness due to ALS [143]. Experimental and clinical data are therefore consistent with the notion that the respiratory-related cortical networks provide cortico-medullary co-operation when automatic breathing is compromised. Activation of respiratory-related cortical networks in response to experimental loading is accompanied by respiratory discomfort [137, 138, 143]. In patients with diaphragm dysfunction, alleviating dyspnoea by mechanical ventilatory assistance silences respiratory-related cortical activity [143], suggesting a causative relationship. These observations have led to the hypothesis that respiratory-related EEG activity could constitute a surrogate for self-reported dyspnoea in patients unable to directly communicate with their caregivers, thus forming the basis for a patient–ventilator interface [144]. Of note, the motor cortical activities related to breathing are not synonymous of breathing discomfort (*e.g.* voluntary respiratory manoeuvres), and it must be kept in mind that the brain correlates of breathing discomfort are numerous, very complex and mostly sensory in nature (as exemplified by a host of specific studies that are beyond the scope of this statement).

2.3. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a widely used noninvasive neurophysiological technique to assess the excitability of the cerebral cortex and of the corticospinal tract *in vivo* (table 4) [145].

TMS causes no long-term adverse effects in healthy subjects. High frequency (1–50 Hz), high-intensity repetitive TMS (rTMS), however, has the potential to induce epileptic seizures even in healthy individuals [146]. This can be minimised by careful selection of subjects [147] and stimulus threshold, and strict adherence to the available safety guidelines (table 5, table S12) [55].

The validity of TMS critically depends on the appropriate location of EMG electrodes [148] and control of background muscle activity and noise. In the research laboratory, single- and paired-pulse TMS have been used to document and describe the corticospinal pathway to the diaphragm at rest and during different physiological conditions in healthy subjects (supplementary material) [149–151]. In the clinical field, TMS has been used to document the involvement of the respiratory muscles in patients with neurological conditions, such as stroke and multiple sclerosis [152–154] (table S13).

Test–retest reliability of TMS for respiratory muscles are not available. These data for limb muscles are summarised in table 5.

Results mostly from upper airway and diaphragm muscles in response to TMS are documented. Widespread disease-related alteration of corticomotor excitability (as documented by changes in a hand muscle) could also indirectly influence respiratory muscle control and are summarised in the table S13.

In OSAS patients, genioglossus central motor conduction time (CMCT) closely correlates with severity of disease [155]. An increase in cortical-motoneuronal excitability is observed in the genioglossus and diaphragm muscles of awake OSAS patients [155, 156], but not for submental muscles [157, 158]. No plasticity-related changes in genioglossus cortical activity is observed in response to rTMS trains [159, 160].

In stable patients with COPD, intracortical facilitation (ICF) of the diaphragm correlates with inspiratory muscle strength, whereas intracortical inhibition correlates with arterial partial pressure of CO_2 [161]. In COPD, the corticospinal pathway to the diaphragm is more excitable and intracortical facilitation of the diaphragm is markedly attenuated compared to healthy subjects [162].

In the ICU, diaphragm response to TMS in patients with central ventilatory paralysis (*e.g.* cervical spinal cord lesions) predicts the recovery of spontaneous ventilation within 1 year [163]. In patients with stroke, the respiratory system response to TMS represents a simple bedside technique to assess airway clearance and evaluate aspiration risk [164].

For the use of TMS to evaluate interventions, please refer to table S13.

TABLE 5 Characteristics of transcranial magnetic stimulation (TMS) paradigms and related measures

Tests (TMS paradigms)	Main measures	Definition	Physiological significance	Repeatability/reliability/validity	Safety	Setting (clinical, research)
Single-pulse TMS		Noninvasive and painless neurophysiological technique to evaluate the excitability of motor cortical area and the cortical spinal pathways conductivity through the administration of magnetic stimuli over the scalp.			Carries little risk beyond occasional local discomfort at the site of stimulation or a transient headache in susceptible subjects. No change in blood pressure, heart rate, EEG, serum prolactin level, serum cortisol level, or in a variety of memory, cognitive, learning, sensory and motor tests [314].	
	Motor evoked potential (MEP)	Muscular response obtained after a single TMS pulse applied over the contralateral primary motor cortex at appropriate stimulation intensity.	Integrity of the corticospinal tract and excitability of the corticospinal system.	Moderate to good reliability for MEP amplitude of FDI muscle at rest and under active condition; MEP amplitude is more reliable at 120% intensity of stimulation than those obtained at 100% [315].		Research
	MEP latency	Time interval between the application of the TMS pulse on the motor cortex area and MEP onset from the contralateral target muscle; it reflects the conductivity of both the central and peripheral nervous systems, as well as neuromuscular junctions and muscles.				Research
	MEP amplitude	Amplitude of MEP response measured peak-to peak. It reflects the excitatory state of output cells in the motor cortex, nerve roots and the conduction along the peripheral motor pathway to the muscles.				Research
	Resting motor threshold (RMT)	Lowest TMS intensity able to evoke MEPs in the resting target muscle when single-pulse stimuli are applied to the motor cortex.	Reflects the excitability of a central core of neurons, which arises from the membrane excitability and a balance between inhibitory and excitatory input from local circuits.	Good reliability in FDI for short- and long-term interval [315], also in ADM [316] and APB, EDC, FCR [317].		Research
	Active motor threshold (AMT)	Lowest TMS intensity required to obtain a MEP response during a weak muscle contraction.		Good to excellent short- and long-term reliability in FDI [315].		Research
	Cortical silent period (CSP)	Period of suppression of EMG activity following a twitch suprathreshold TMS stimulus of a target muscle during a sustained voluntary contraction of this muscle.	Cortico (spinal) inhibitory mechanisms, possibly GABAb mediated (but not only).	Moderate to good reliability in ADM [315] and FDI [317].		Research
	Central motor conduction time (CMCT)	Latency difference between the MEPs induced by TMS and by peripheral (motor root) stimulation.	Reflects the integrity of the cortical-spinal tract, from the upper to the lower motor neurons.			Research

Continued

TABLE 5 Continued

Tests (TMS paradigms)	Main measures	Definition	Physiological significance	Repeatability/reliability/validity	Safety	Setting (clinical, research)
Paired-pulse TMS		TMS paradigm to study intracortical inhibitory and excitatory phenomena by means of a conditioning subthreshold stimulus preceding a suprathreshold test stimulus applied at different interstimulus interval.				Research
	Intracortical facilitation (ICF)	Paired-pulse TMS measure obtained with long interstimulus interval where the conditioning stimulus is followed by an enhanced response with respect to the test stimulus; it is modulated by multiple neurotransmission pathways.	Expresses the activity of glutamatergic excitatory circuits	Poor reliability in ADM [315].		Research
	Short latency intracortical inhibition (SICI)	Paired-pulse TMS measure obtained with short interstimulus interval where the conditioning stimulus is followed by an inhibition with respect to the test stimulus; it is attributed to an activation of inhibitory neuronal system transmission.	Reflect the activity of GABAergic inhibitory circuits	Good short-term and long-term reliability under resting, not for active conditions [315].		Research
Repetitive TMS (rTMS)	rTMS	Train of TMS pulses of the same intensity applied at a given frequency to a given brain area, that can transiently influence the function of stimulated and connected brain areas, mainly dependent on stimulation frequency.			Even in normal subjects, prolonged, high intensity, rTMS at 10–25 Hz rates can produce partial seizures with or without secondary generalisation [146]. Short inter-train intervals can cause transient degradation in short term verbal memory immediately following rTMS [318].	Research
	Low-frequency rTMS	Trains of variable duration at $\leqslant$1 Hz stimulation frequency.	Depression of the excitability of the stimulated regions, possibly *via* LTD.			Research
	High-frequency rTMS	Trains of variable duration at $\geqslant$1 Hz stimulation frequency.	Increase of the excitability of the stimulated regions, possibly *via* LTP.			Research
	Theta burst stimulation (TBS)	A form of complex rTMS trains combining different frequencies (*i.e.* 50 Hz pulse-trains repeated at a rate of 5 Hz) with after-effects on cortical-spinal and cortical-cortical excitability that may reflect changes in synaptic plasticity.	Inhibition when higher than 1 Hz.			Research

EEG: electroencephalography; LTD: long-term depression; LTP: long-term potentiation; ADM: abductor digiti minimimuscle; FDI: first dorsal interosseous; APB: abductor pollicis brevis; EDC: extensor digitorum communis; FCR: flexor carpi radialis muscles.

Section 3. Respiratory muscle imaging

3.1. Ultrasound

Since the publication of the previous ATS/ERS statement [1], numerous studies have reported on the use of ultrasound to assess diaphragm dimensions and activity. With the increasing availability of ultrasound at the bedside, this technique allows a simple, rapid and direct evaluation of the diaphragm that is more sensitive than fluoroscopy for the identification of muscle activity [165].

The most frequently assessed variables using diaphragm ultrasound are: 1) static measurement of end-expiratory diaphragm thickness (T_{di}); 2) dynamic evaluation of the ratio of inspiratory to expiratory diaphragm thicknesses, reported as thickening ratio (TR; inspiratory thickness/expiratory thickness) or thickening fraction (TF; (inspiratory thickness − expiratory thickness)/end-expiratory thickness); and 3) diaphragmatic excursion [166]. Measurements of T_{di} and TF are performed by placing a high-frequency linear probe at the level of the zone of apposition, while diaphragm excursion is measured using a curvilinear probe placed in the subcostal region and recording diaphragm movements in M-mode (figure 5).

3.1.1. Diaphragm thickness

In healthy subjects at rest, intra- and inter-observer reliability of T_{di} are high [167–171] and ultrasound estimates of T_{di} are correlated to direct anatomical measurements [168]. The lower limit of normal for T_{di} has been reported to be 0.15 cm in healthy subjects, with a wide baseline range of values [167]. Similar values have been reported for patients with COPD [172]. It is unclear whether a T_{di} value below this threshold can be used to identify diaphragm dysfunction. T_{di} does not seem to change with age [167] but can be influenced by posture [173], stature [171, 174] and body composition [171, 175]. In addition, in studies of patients with diaphragm weakness, a large proportion of subjects had T_{di} values of 0.15 cm [176–178]. However, the temporal evolution of T_{di} in these patients was related to the change in VC in those with recovery of diaphragm function [176]. This observation suggests that T_{di} can be used to monitor the evolution of diaphragm weakness [176]. In mechanically ventilated patients, T_{di} is reproducible [179, 180]. T_{di} is not correlated with $P_{ao,tw}$ when patients are receiving assist control ventilation or pressure support ventilation [181]. T_{di} is a poor predictor of weaning outcome [182–184]. Finally, over the course of mechanical ventilation, T_{di} can decrease, increase or remain unchanged [185, 186].

3.1.2. Diaphragm thickening fraction and ratio

The measurement of TF is reproducible [179], with a reported lower limit of normal of 20% in healthy subjects and patients with COPD [167, 172]. A TF around 20%, however, is possibly more closely associated with near complete paresis rather than partial dysfunction, as the mean values for TF in healthy subjects can frequently exceed 100% [167].

Diaphragmatic contractions produce both muscle shortening and thickening. The correlation between diaphragm thickening and diaphragm effort, however, is tenuous: ultrasound measurements of diaphragm

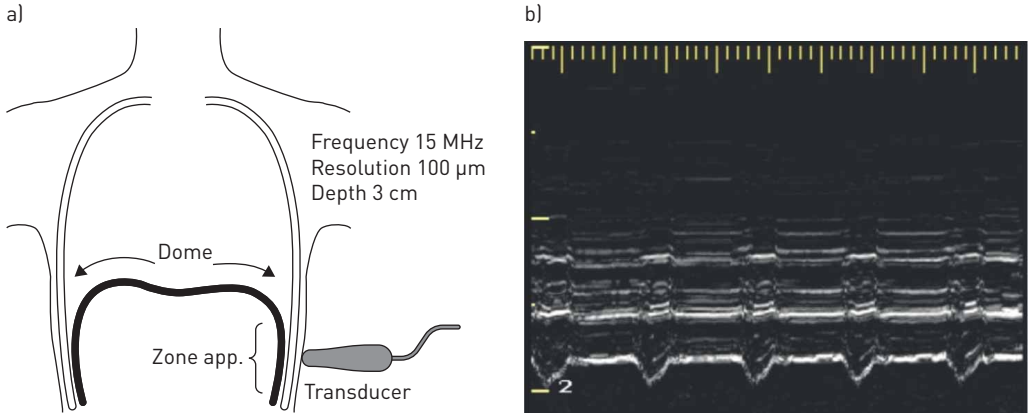

FIGURE 5 Diaphragm ultrasound assessment. a) When measuring diaphragm thickness and thickening fraction, the use of a linear, high-frequency probe is suggested. The probe is positioned in the sagittal-oblique position at the level of the zone of apposition, and image scanning begins at the mid-axillary line. When evaluating diaphragm excursion, use of a curvilinear, low-frequency probe is preferable. The probe is positioned in the sub-hepatic region, with the beam oriented cephalad and posteriorly, aiming at the most cephalad aspect of the diaphragmatic dome. b) M-mode image of diaphragm thickening during inspiration. End-expiratory and end-inspiratory diaphragm thicknesses can be directly measured and thickening fraction can be determined.

thickening explain only one third (or less) of the variability in inspiratory effort [180, 187, 188]. This is not surprising, considering that thickening is a one-dimensional measurement, whereas inspiratory effort results from an active three-dimensional displacement of muscle volume. In addition, the extent of diaphragm thickening for a given level of inspiratory effort varies considerably between subjects and the reproducibility of the measurement is weak (reproducibility coefficients range from 16% to 27%) [187].

In critically ill patients receiving pressure support ventilation, TF <29% has been associated with diaphragm dysfunction, the latter being defined as $P_{ao,tw}$ <11 cmH_2O [181]. In addition, diaphragm TF moderately correlates to indices of neural respiratory drive such as $P_{0.1}$ [188] and has been reported as a possible predictor of weaning outcome [181, 182, 189] and duration of mechanical ventilation [181, 189]. In patients with acute exacerbation of COPD, preliminary data suggests that TF is related to failure of noninvasive ventilation and mortality [190]. Measurements of expiratory and inspiratory diaphragm thickness can be performed using either B- or M-mode ultrasound. The use of M-mode offers the theoretical advantage of making the recording of both variables in a single inspiratory/expiratory cycle easier, and the manual measurement of diaphragm thickness on the same ultrasound frozen image. Whether this translates into a clinically significant difference in measurement compared with B-mode remains to be determined. No studies have yet evaluated TF or TR during exercise.

3.1.3. Diaphragm excursion

Excursion of the right diaphragm has high intra- and inter-observer reliability [191, 192] and its lower limit of normal is 3.6 cm in women and 4.7 cm in men during maximal inspiratory efforts [191]. From a technical point of view, measurement errors may occur when the displacement of the diaphragm is not optimally aligned with the M-mode plane, but angle-independent M-mode sonography may mitigate this effect [193].

Diaphragm excursion is sensitive to changes in respiratory pattern [194], is related to the volume-generating capacity of the diaphragm (measured using VC) following abdominal surgery [195] and has been used to identify diaphragm weakness in the setting of acute exacerbation of COPD [196] and acute stroke [197]. In intubated patients, diaphragm excursion is moderately related to P_{di} [198] and, possibly, to weaning outcome [192, 199]. In children, ultrasound imaging has been used to assess anatomical defects of the diaphragm (lobulated-shaped hemidiaphragms, focal diaphragmatic eventration, diaphragmatic hernia) and to document paradoxical movements of the diaphragm (supplementary material) [200].

3.2. Optoelectronic plethysmography

Optoelectronic plethysmography (OEP) is an established technique that allows tidal changes in the volume of the chest wall and its compartments to be measured (figure 6) [201, 202]. By using this technique, investigators reported that patients with more severe COPD consistently experience dynamic hyperinflation during incremental exercise, while other patients, specifically those with a greater expiratory flow reserve at rest, adopted at least two significantly different patterns of change in end-expiratory volume of the chest wall [203–205]: some showed a progressive significant increase in end-expiratory volume of the chest wall ("early hyperinflators") and others showed an increase only at higher levels of exercise ("late hyperinflators"). Three different, distinct patterns of breathing and chest wall volume displacement were found in patients with severe COPD, interstitial pulmonary fibrosis and cystic fibrosis to cope with chronic respiratory failure [206].

OEP has been used to evaluate a variety of NMDs, such as Duchenne [207–209], limb girdle and Becker muscular dystrophies, facioscapulohumeral dystrophy [210] and ALS [211]. OEP has also been used to assess the effects of different surgical techniques (such as laparoscopic surgery) on chest wall kinematics and inspiratory muscle activity [212], Nuss technique for pectus excavatum [213], diaphragm plication for unilateral diaphragm paralysis [214], and diaphragm repair in congenital diaphragmatic hernia [215]. More recently, OEP has been used to evaluate the effects on chest wall kinematics of several interventions, such as air stacking [216], breath stacking [217], stretching [218], incentive spirometry [219], inspiratory loaded breathing [220] and rehabilitation [221]. OEP can be used to monitor tidal breathing and respiratory muscle function in newborns [222], in children with spinal muscle atrophy type 1 and type 2 [223] and in children and young adults with Duchenne muscular dystrophy [207, 208].

3.3. Other investigations

Chest radiography and computed tomography have been used to assess the position of the diaphragm, particularly to identify diaphragm elevation secondary to weakness or paralysis in patients with myopathies, neuropathies and injured hemidiaphragm [224]. Chest fluoroscopy, although highly ionising, has been used to identify decreased or paradoxical diaphragm motion.

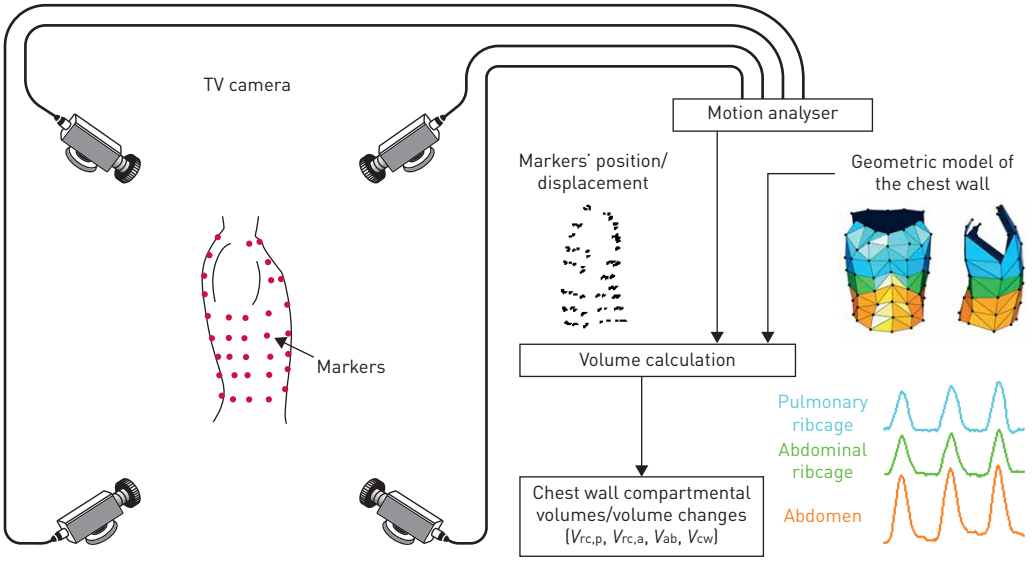

FIGURE 6 Optoelectronic plethysmography. A number of reflective markers are positioned on the trunk of the subject in selected anatomical reference sites of the ribcage and the abdomen. A set of cameras placed nearby the subject under analysis and dedicated stereo-photogrammetric techniques allow measuring the position (three-dimensional coordinates) and motion of the markers. A closed surface is defined by connecting the points and the volume enclosed by the thoraco-abdominal surface and its different parts is computed using Gauss' theorem. The chest wall is typically modelled as being composed of three different compartments: pulmonary ribcage (rc,p), exposed on its inner surface to pleural pressure, abdominal ribcage (rc,a), and the abdomen (ab), the latter both exposed to abdominal pressure. Total chest wall volume (V_{cw}) is the sum of the volume of these three compartments ($V_{rc,p}$, $V_{rc,a}$ and V_{ab}).

Two- and three-dimensional magnetic resonance imaging (MRI) is being increasingly used, particularly in neuromuscular diseases [224], to assess muscle size, structure and altered function by using different tissue-weighting (T1, T2 and proton density). Two-dimensional MRI can assess qualitatively muscular atrophy on axial and coronal images and measure the cranio-caudal diaphragm movement. Dynamic MRI provides information on the motion of the chest wall and the diaphragm on sagittal images [225]. Given the paucity of published studies on this topic, it is difficult to draw conclusions on this imaging tool; further studies are needed to evaluate the validity, precision, reproducibility, prognostic value and responsiveness to interventions of dynamic MRI of the diaphragm.

Structured light plethysmography (SLP) is another emerging imaging tool. SLP is a non-contact, noninvasive method to assess breathing pattern [226]. The technique is based on the stereoscopic analysis of respiratory-related distortions of a black and white chequered pattern projected on the chest wall and abdomen [226–228]. SLP has been validated in healthy subjects and in patients [226–229]. In a recent study, Nierat *et al.* [226] reported that SLP can detect differences in breathing pattern in COPD compared with healthy controls. In the same study, SLP allowed measurement of ventilatory activity while preserving resting tidal breathing variability, reducing instrumental observer effect and avoiding any disruptions in breathing pattern induced by the use of the pneumotachograph-mouthpiece-noseclip combination. SLP allows a detailed compartmentalised analysis of thoraco-abdominal behaviour, which is not the case for wearable devices [226]. In children with asthma, SLP can differentiate those with and without airway obstruction, and may identify responses to bronchodilator [230]. Further research is, however, required to confirm the clinical applications of SLP.

Section 4. Respiratory muscle structure, perfusion and metabolism

Several methodological approaches can provide a comprehensive assessment of the mechanisms regulating respiratory muscle blood flow and oxygen delivery in relation to oxidative metabolic demand and mitochondrial function, as well as the consequences of oxidative stress and inflammation (table 6). These techniques have the potential to be used for monitoring interventions aimed at restoring respiratory muscle function in the ICU and the rehabilitation setting.

4.1. Near-infrared spectroscopy

A decade ago, a technique combining near-infrared spectroscopy (NIRS) with the light absorbing tracer dye indocyanine green (ICG) was employed to measure intercostal muscle blood flow (IMBF) using Fick's

TABLE 6 Laboratory techniques for evaluation of respiratory muscle structure, perfusion and metabolism

Techniques	Invasiveness	Physiology laboratory required	Biology laboratory required	Purpose
Near-infrared spectroscopy	None	Yes	No	Muscle blood flow
Oxygen cost of breathing	None	Yes	No	Ventilation, oxygen uptake
Access to costal diaphragm muscle	Yes, thoracotomy	Yes, always in surgery room	No	Biological and histological analyses
Access to parasternal muscles	Yes, thoracotomy	Yes, always in surgery room	No	Biological and histological analyses
Access to external intercostals	Yes, open biopsy techniques	Yes, possible in surgery room	No	Biological and histological analyses
Immunohistochemical or immunofluorescence analyses		No	Yes	Muscle fibre type and morphometry
Mitochondrial respiratory chain evaluation (respiration procedures)	None	No	Yes	Quantification of mitochondrial respiration (oxygen consumption)
Immunoblotting procedures	None	No	Yes	Quantification of protein levels in muscle specimens
Quantitative real-time PCR	None	No	Yes	Quantification of gene expression levels in muscle specimens
Specific activity assays including mitochondrial enzyme activities	None	No	Yes	Quantification of activity levels of enzymes in muscle specimens

principle. Guenette *et al.* [231] were the first to quantify IMBF in healthy subjects during resting isocapnic hyperpnoea at different fractions of MVV. They reported that as ventilation rose, IMBF significantly correlated with the increase in cardiac output, WOB and P_{di}, suggesting that the NIRS-ICG technique is a sensitive indicator of IMBF in healthy humans. Similar results have been reported by Vogiatzis and co-workers, employing the same NIRS-ICG technique to measure IMBF in healthy subjects [232] and COPD patients [233].

Absolute IMBF measurements *via* the NIRS-ICG technique require arterial cannulation. For this reason, an alternative method was proposed to measure relative changes in muscle perfusion from rest, namely the blood flow index (BFI), requiring only venous catheterisation for the injection of ICG (figure 7) [234].

Habazettl *et al.* [234] compared BFI values obtained from the seventh intercostal space against absolute muscle blood flow determined using the NIRS-ICG technique during cycling in healthy subjects. The investigators reported a very good agreement between BFI and NIRS-ICG techniques in healthy subjects during cycling [234], and also (by retrospective data analysis) in patients with COPD (figure 7) [233]. Guenette *et al.* [235] showed that BFI of intercostal and sternocleidomastoid muscles during isocapnic hyperpnoea was strongly correlated with WOB and surface EMG, thus confirming that the BFI technique provides a minimally invasive and technically less demanding alternative to NIRS-ICG for measuring respiratory muscle perfusion in humans at rest and during exercise.

4.2. Oxygen cost of breathing

The oxygen cost of breathing is an index of the energy required for ventilation. For more detailed information on methods of assessment please refer to the supplementary material. Oxygen cost of breathing was shown to be increased in women [236, 237] and in obesity [238, 239], post-operative patients [240], COPD [240, 241], cystic fibrosis [242, 243], children with asthma [244], sarcoidosis [245] and chronic heart failure [246, 247]. In these conditions, the increased oxygen cost of breathing may contribute to increased energy cost during activities of daily living adding, particularly in diseases imposing a ventilator or cardiac constraint, an extra contribution to the reduced exercise capacity. Several interventions have been used in different patient populations to reduce WOB, which has a potential impact on reducing the oxygen cost of breathing, namely, invasive and noninvasive ventilation [248–250], high flow nasal oxygen [248, 251], ventilation with heliox [252], respiratory muscle training [253, 254] and exercise training [255].

4.3. Biopsy (specificities for respiratory muscles)

In recent years, respiratory muscles have been studied through the analyses of the costal diaphragm, with very restricted access, and only *via* thoracotomy performed for clinical reasons (mainly lung cancer and lung volume reduction surgeries). During thoracotomy, parasternal and diaphragm biopsy specimens have been obtained from the third interspace and the anterior costal diaphragm lateral to the insertion of the phrenic nerve, respectively [256–260]. Additionally, other studies have been based on the analysis of the

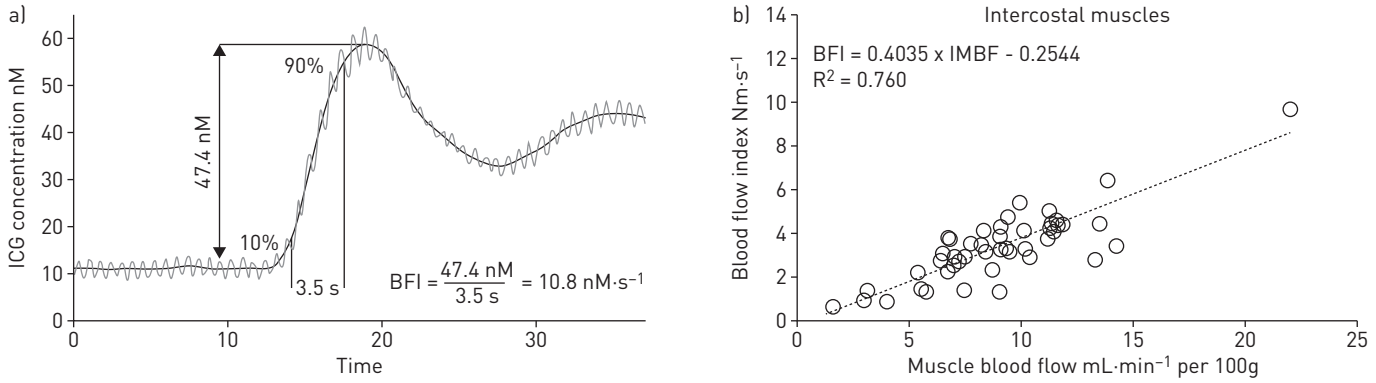

FIGURE 7 Near-infrared spectroscopy (NIRS). a) Typical example of muscle indocyanine green (ICG) concentration curve recorded by NIRS during exercise. The original tracing (grey line) appears with marked oscillations (at a frequency of 84 min^{-1}; 1.4 Hz) due to muscle contraction and relaxation during cycling. Low-pass filtering with a cut-off frequency of 0.5 Hz produced the smoothed curve (black line) that was used for blood flow index (BFI) calculation. Data points at 10 and 90% of ICG concentration peak are indicated, and an example of BFI calculation is given. Reproduced with permission from the publisher [234]. b) Regression analysis of individual BFI assessed by the NIRS-ICG method *versus* actually measured muscle blood flow assessed by Fick's principle at different levels of minute ventilation recorded during isocapnic hyperpnoea trials for the intercostal muscles in chronic obstructive pulmonary disease. IMBF: intercostal muscle blood flow. Data calculated from [233].

external intercostal muscle following procedures involving an open biopsy technique [257, 258, 261–265]. Biopsies from the external intercostals have usually been taken along the anterior axillary line at the sixth intercostal space, as detailed in previous studies [257, 258, 261–265]. In patients with chronic respiratory conditions, limb muscles are more severely affected than respiratory muscles, which need to overcome the increased inspiratory loads and may exhibit adaptive features [266].

4.4. Typology

Respiratory muscles undergo a series of structural changes in lung diseases. These changes have been extensively studied in patients with COPD, in which the diaphragm shows increased type I fibres [267], favouring aerobic metabolism [268]. Structural changes in the respiratory muscles (injury and regeneration cycles) depend mainly on the effect derived from increased ventilatory loads [269, 270]. Increases in capillary and mitochondria numbers and sarcomere length have also been demonstrated [271], along with sarcomere and sarcomeric damage and greater friability of diaphragm [272]. Diaphragm atrophy in patients with COPD has been reported by some, but not all, investigators [256, 259, 273, 274]. Changes in the proportions of fibre types have also been observed in the parasternal and external intercostal muscles of COPD patients [257, 275]. In the latter muscles, an increase in capillary numbers was also described [276], together with fibre atrophy [277]. Respiratory muscle training increased fibre sizes and proportions of type I fibres [278]. In OSAS patients, increased proportions of type I fibres have been reported in the intercostal muscles [262], while no data is available for the diaphragm. Prolonged mechanical ventilation induces sarcomere damage and fibre atrophy in the diaphragm, with no relevant changes in fibre type proportions [279, 280].

4.5. Mitochondrial function

In rats, mitochondrial respiratory rates are lower in the diaphragm than in peripheral muscles [281]. In mice, hypoxia differentially affected peripheral and respiratory muscles with decreased mitochondrial content due to reduced mitochondrial biogenesis and increased mitophagy [282].

Mitochondrial function is altered in patients with COPD [260, 283, 284]. In these patients, mitochondria isolated from intercostal muscles demonstrate electron transport blockade and excessive production of reactive oxygen species, similar to effects found in the vastus lateralis [259, 284]. In the diaphragm, overall mitochondrial respiratory chain capacity was increased and had a higher efficiency in patients with moderate [285] and severe [286] COPD than in healthy controls. In patients with COPD the oxidative capacity of the diaphragm is greater than that of the peripheral muscles [258].

Mitochondrial function and content are impaired in patients with sepsis [287]. In turn, animal models of prolonged mechanical ventilation demonstrate only minor changes in oxidative phosphorylation coupling in diaphragmatic mitochondria [288]. Attempts to improve mitochondrial function using anabolic steroids failed in a hamster model of emphysema [289]. Increased mitochondrial enzyme activity was shown in rodent diaphragm in response to endurance training [290].

4.6. Oxidative stress

Increased oxidant production has been reported in mitochondria and membrane compartments of diaphragm fibres in patients with severe COPD [256, 259]. In several studies [256, 259, 291, 292], the diaphragm of these patients exhibited increased levels of oxidative stress. Such levels inversely correlated with global respiratory and diaphragm muscle function among patients with more severe disease [256, 259]. Contractile actin and myosin, creatine kinase, and carbonic anhydrase-3 are oxidatively modified in the diaphragm of patients with severe COPD, while protein content of myosin [259, 291, 292] and creatine kinase and its activity are reduced [259]. Nonetheless, in saponin-skinned diaphragm and intercostal muscle fibres [265, 286], creatine kinase activity levels do not differ between severe COPD and healthy controls. In external intercostals of COPD patients [264] and in those with OSAS, oxidative stress levels are increased and treatment with continuous positive airway pressure for 6 months does not reduce those levels [262]. In external intercostal muscles of patients with severe sepsis, oxidative stress levels do not differ from those in controls [264]. Oxidative stress in the diaphragm of critically ill patients receiving mechanical ventilation is increased compared to controls [280, 293, 294]. In elderly subjects, markers of oxidative stress are increased in the external intercostals compared to young controls [261].

4.7. Inflammation

Systemic inflammation is a contributor of muscle dysfunction in COPD [295]. In contrast, local inflammation does not play a role in COPD muscle dysfunction: inflammatory cell counts were very low in the diaphragm and external intercostals of patients with severe COPD with preserved body composition [257]. Expression of mRNA and protein content of tumour necrosis factor alpha and interleukin-6 are greater in the external intercostals of patients with severe COPD and normal weight than in healthy controls, while muscle mRNA levels of CD18 panleukocyte marker do not differ between patients and controls [296]. In patients with severe sepsis, inflammatory markers are increased in the external intercostals compared to controls [263].

Collectively, respiratory muscle dysfunction in patients with COPD is the result of multiple deleterious factors such as lung hyperinflation (mechanical disadvantage), gas exchange abnormalities, impaired bioenergetics (increased cost of breathing) and biological mechanisms (oxidative stress), and structural abnormalities (sarcomere damage and atrophy), while inflammation does not seem to play a major role [295]. This scenario coexists with adaptive features including a switch towards a more oxidative phenotype (predominance of slow-twitch fibres, increased mitochondrial density and myoglobin content), probably in response to increased mechanical loads.

Conclusion

Respiratory muscle dysfunction is a major clinical concern in a variety of conditions, from respiratory diseases to NMDs, critically ill patients, sports medicine and paediatric populations. Assessment of respiratory muscle function is therefore of critical importance for patient diagnosis, follow-up and for evaluating the effect of therapeutic interventions aimed at improving respiratory function. 17 years after the 2002 ATS/ERS statement on respiratory muscle testing [1], a growing body of literature has emerged and has been discussed in this document, which provides clinicians and investigators with the latest knowledge on this topic. In addition to historical evidence on respiratory muscle strength, endurance and fatigue assessments, new information on imaging technologies and respiratory muscle assessment during exercise have provided important insights into respiratory muscle function, including its integration with brain and cardiovascular function, dyspnoea and exercise tolerance. This document, which has involved experts in the field of respiratory medicine and physiology on the topic of respiratory muscle testing at rest and during exercise, is intended to open up new perspectives in both clinical and research settings. Despite the remarkable advances in respiratory muscle and lung mechanics assessment in the past few decades, this body of knowledge has not been fully translated to the clinical care of individual patients. Although this state of affairs is likely explained by multiple reasons, it is noteworthy that less and less time has been devoted to training in the administration and interpretation of the more advanced tests of respiratory muscle function worldwide. This contributes to a vicious circle in which fewer pulmonologists master the use of less common devices that are available only in specialised centres. To fight this regrettable situation, it seems apparent that new generations of pulmonologists should (again) be intensively exposed to clinical physiology concepts and practices. To reach this intent, the key relevance of the leading societies in our field (*e.g.* the European Respiratory Society, American Thoracic Society and American College of Chest Physicians) cannot be underestimated.

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