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Early View

Task Force Report

ERS Statement on Respiratory Muscle Testing at Rest and during Exercise

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ERS Statement on Respiratory Muscle Testing at Rest and during Exercise

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Take home message: Diverse methods are available for assessment of the respiratory muscles; the technique used should be tailored to the question posed.

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 sixteen years since publication of the previous ATS/ERS statement on respiratory muscle testing in 2002. Key advances were made in the field of mechanics of breathing, respiratory muscle neurophysiology (electromyography, electroencephalography, transcranial magnetic stimulation) and on respiratory muscle imaging (ultrasound, optoelectronic plethysmography, 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 sums up 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.

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 to contribute to the diagnosis, to phenotype patients, to assess treatment efficiency and for 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, respiratory muscle imaging in health and disease states, 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 Clinical Respiratory Physiology, Exercise and Functional Imaging group (04.01), the ERS Rehabilitation and Chronic Care group (01.02), the Physiotherapists group (09.02), representatives from the European Lung Foundation (ELF) and the ERS Science Council. The Task Force received support from the ERS methodologists throughout the project. Three meetings of the Task Force were held, two during the Annual conference of the ERS (September 2016 and 2017) and one in Lausanne in March 2017. All TF members declared and signed conflict-of interest statements at the beginning of the project and updated them at project finalisation or when any new relevant conflict appeared.” “Conflicts of interests were managed according to ERS rules.

Studies that report the evaluation of respiratory muscles (inspiratory and expiratory) and upper airway muscles at rest or during exercise in adults and children with cardiorespiratory diseases have been reviewed, without restrictions on study design. MEDLINE and the Cochrane Library have been searched from 1970 to 2017. Selected references considered of particular relevance were included up to June 2018. Reference lists of all primary studies and review articles have been examined for additional citations. Only studies written in English, or for which an English translation was available, have been 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 functionality worthwhile or clinically important), test response to interventions. Studies that did not meet the inclusion criteria based on title or abstract were excluded. Studies that met the inclusion criteria were retrieved in full ext 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 also information on respiratory muscles evaluation in two particular setting such as paediatrics and the ICU; due to length constraint, these two settings are confined quasi exclusively to the “online supplement” along with more technical and methodological details concerning each section of the manuscript.

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 have to be considered [1]:

1. Pressures reflect barometric pressure difference.
2. In unaltered physiology/anatomy, specific pressures represent entire corresponding spaces. Gravity/shear-stress affect 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 ≥2 (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 setting 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, check via water manometer should be done regularly [1]. Pressure range should be ±300 cmH_2O and resolution ≤0.5 cmH_2O [1].

1.1.2.2 Probes for invasive pressure assessment

Air-filled balloon catheters. They are used to record oesophageal (P_{oes}, ~pleural pressure) and gastric pressure (P_{ga}, ~abdominal pressure) [4]. Specific characteristics need to be considered and standardized preparation 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. These catheters feature 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 (P_{ao})

P_{ao} is usually sampled from side taps ("lateral pressure") located in the mouth piece/tracheal tube/face mask/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 minimize the *Bernoulli* effect [8].

For P_{ao} to estimate alveolar pressure during dynamic respiratory efforts against an obstructed 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 diseases -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 (PImax) or expiratory (PEmax) pressures at the mouth allow a simple assessment of global respiratory muscle strength in a clinical setting [1]. Tests are volitional and require full subjects' cooperation. PImax is usually measured at RV and PEmax at TLC to record the maximum value of three manoeuvres that vary by less than 10% (see online supplement for more details). Nevertheless, measuring PImax at functional residual capacity (FRC) also has the advantages of representing the maximal static inspiratory pressure measured at the "real volume" at which patients breathe tidally; however, it is greatly influenced by the level of lung hyperinflation or the severity of restriction, therefore great attention should be paid under these conditions.

PImax is strongly related to exertional dyspnoea (see figure S4) [9]. The test might also serve as a screening instrument to identify patients with respiratory muscle weakness (see figure 2 and online supplement) [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 PImax and PEmax measurements are summarized in the online supplement tables S2-S8 [11]. Measurements of mouth pressures are used in cooperative children older than 6-8 years of age (table S14) as well as PImax to evaluate global inspiratory muscle strength in the ICU (see online supplement). .

1.2.2 Maximal sniff nasal inspiratory pressure (SNIP)

During SNIP inspiratory pressure is recorded by a pressure transducer connected to a catheter placed in the nostril [12]. The test is performed at functional residual capacity (FRC). The subject is instructed to inhale fast and deep. SNIP has been validated in healthy individuals [12], 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 the online supplement (table S9)**.**

1.2.3 Peak cough flow (PCF)

PCF estimates the effectiveness of mucus clearance and expiratory muscle function in neuromuscular disorders (NMD) [15, 16]. The measurement is performed with subjects seated. An oronasal-mask/mouth-piece 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 maneuvers (<5% variability) and the maximum PCF ($l \cdot min^{-1}$) should be reported [17]. In NMD (manually) assisted PCF might be appropriate [18]. Peak flow meter might overestimate PCF if <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 NMD [17]. Healthy (children) adults achieve PCF~(150)470-600 $l \cdot min^{-1}$; PCF <160 $l \cdot min^{-1}$ is associated

with higher likelihood of extubation/weaning-failure in NMD [17, 19] (see online supplement for more details).

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 non-invasive 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 (hypertrophy of the adenoids, rhinitis, polyps) or lower airway obstruction. Assessments during cough are needed to assess expiratory muscle when glottis function is compromised such as in patients with bulbar amyotrophic lateral sclerosis (ALS). These measurements may also be used to refine the 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 useful in the ICU and in children (see online supplement).

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

Reference values are given in table 2 where available.

In many diseases, pressures produced during sniff and cough are lower than normal, in adults (e.g. heart failure [26], stroke [27], COPD [25], pulmonary fibrosis [25], cystic fibrosis (CF) [28] and NMD [20, 21, 29]) and children with NMD [30, 31]. In a cohort of patients with mixed diagnoses [20], adding SNIP to PImax, 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 PEmax decreased false-positive diagnosis of expiratory muscle weakness by 30% [20].

The use of sniff -P_{di} and cough-P_{ga} was little explored for prognosis. In ALS patients, sniff-P_{di} correlated with SNIP [32] and SNIP <40 cmH_2O was significantly associated with desaturation during sleep and a 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 PEmax and $P_{di,tw}$ were predictors of absolute survival.

After lung volume reduction surgery [34], sniff-P_{di}, SNIP and PImax 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, but sniff-P_{oes}-MRR decreased by 42%, but recovered within 5 min [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 non-invasive 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% to 20% decrease in the supine position (15% which represents twice the CV of the measure could be considered as lower limit of normalcy) [41] (figure 2), while FRC and TLC are usually preserved [40, 41]. In severe bilateral diaphragm weakness, VC is usually approximately 50% 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 to 79% of the predicted value in mildly restricted, up to 30 to 50% of the predicted value in moderate-to-severe restriction), while RV 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], especially ALS, a significant reduction of VC at diagnosis as well as its rate of decline over time are recognized as criteria for initiating non-invasive ventilation [51, 52]. Reduction in VC are also predictive of sleep-disorders breathing, respiratory failure, worse prognosis and response to treatment to a lesser extent, with a 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 the work of breathing (WOB) or the pressure–time product (PTP) of either the oesophageal pressure (PTP_{oes} = reflecting the effort done by all of the respiratory muscles), the transdiaphragmatic pressure (PTP_{di} = reflecting mostly the effort done by the diaphragm) [54], the tension-time index (TTI = PI/PImax*Ti/Ttot) or the oesophageal pressure swing. Details on how these indices are calculated, their physiological underpinning and advantages and disadvantages of their measures are described in the on-line supplement. 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 $cmH_2O \cdot sec \cdot min^{-1}$ while in acute respiratory failure (before receiving mechanical ventilation), the average pressure-time product has been reported to be about 4 times as high [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 in COPD patients (i.e., by GOLD stages) [65] and is sensitive to changes over time and to interventions within patients [65]; in addition, 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 reduction in inspiratory effort decrease exercise-asociated 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} swing [71-73]. Finally, exercises that promote slow and deep breathing have the potential to reduce elastic component of the work of breathing and thereby reduce inspiratory effort [74-76]. In addition, changes in inspiratory duty cycle (decreased Ti/Ttot) 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 second) applied without warning before the individual recognizes the occlusion and reacts (i.e. P0.1) are also a useful but less often utilised index of respiratory centre motor output and will be dealt with in the Online Supplement.

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 contraction causing a 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 the patient has implanted ferrous metal where magnetic stimulation is contraindicated. Technical considerations are: (i) stimulation must be supramaximal, (ii) potentiation resulting from prior contraction must be avoided or standardized, (iii) lung volume must be standardized and (iv) different magnetic stimulation techniques (e.g. cervical, bilateral anterior) yield different results and should be used consistently. A non-invasive 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], with between-occasion variability as much as 6 cmH_2O [79]. Variations in $P_{di,tw}$ with disease are shown in table 3.

Exhaustive exercise in healthy subjects can elicit a drop in $P_{di,tw}$ (showing diaphragm fatigue), while in disease, diaphragm fatigue was reported in some (low back pain) but not in other (COPD, CF, interstitial lung disease - ILD) clinical conditions (see online supplement). Low-frequency diaphragm fatigue is not necessarily related to exercise performance and development of fatigue may not predict clinical outcomes [80].

Normal values are available for neonates [81], infants [82] and children [83] where 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 $P_{di,tw}$-values [84] (or pressure at the endotracheal tube [85]) that are typically lower than those seen in the healthy individuals likely either due to ventilator-induced diaphragm dysfunction or co-morbidity (see online supplement).

1.6 Respiratory muscle endurance testing

Different approaches can be used to assess respiratory muscle endurance,: i) incremental-load testing, ii) constant-load testing and iii) time trials. Different tests were developed within these categories: i) a stepwise load-increase by increasing resistance/threshold load or minute ventilation, ii) sustaining a given resistance/threshold load or hyperpnoea level to task-failure and ii) 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 test loads both inspiratory and expiratory muscles [87].

Since test performance is influenced by breathing pattern, breathing frequency and VT 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.

1.6.1 Maximal incremental-load testing

Resistive/threshold. This test 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) by e.g. 10% of baseline PImax until task failure. Inspiratory muscle endurance can be defined as the pressure of the last completed step.

Hyperpnoea. This test 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

Resistive/threshold. Subjects are instructed to breathe against a sub-maximal load [86, 88, 89] until task failure (Tlim). It has been proposed that the selected load should result in a Tlim 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 Tlim 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.

Hyperpnoea. Subjects breathe at a constant ventilation (40% to 70% MVV) to achieve task failure within 8-12 min.

1.6.3 Time trial

The 10-15-s MVV is too short lasting to assess respiratory muscle endurance. Different protocols exist to test 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 non-invasive and relatively well tolerated. Several studies showed large improvements in respiratory muscle endurance after respiratory muscle training by using these tests (see online supplement).

2. Respiratory muscle neurophysiology

Respiratory muscle neurophysiological testing includes (i) EMG to measure the output of the respiratory motoneurones, (ii) electroencephalography (EEG), which tests the involvement of motor and premotor areas and (iii) 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 [for reviews see 93, 94], neuromechanical coupling during loaded breathing [e.g. 95] and the efficacy of muscle contraction when coupled with measurements of ventilation [e.g. 96, 97]. In the ICU, the EMG signal can be used to trigger and determine the level of assistance during mechanical ventilation, i.e. 'neutrally-adjusted ventilatory assistance' [98]. 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 is usually contaminated with electrocardiogram (ECG) which should be eliminated [99, 100] or excluded from EMG measures. Moreover, respiratory EMG recordings, especially with surface electrodes, are subject to electro-magnetic interference [1, 94, 101], contamination from adjacent muscles and changes in lung volume or posture [1, 102]. However, diaphragm EMG can be quantified with a multi-pair oesophageal electrode [103, 104], usually standardised to a maximal value (table 4). Given its non-invasive 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 [105-108], but may not be useful during exercise testing [109]. 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 [1, 94, 110, 111] (table 4).

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 [103, 112-114] and can be used to assess upper airway resistance [113, 115],

distinguish between central and obstructive sleep apnoea events [112, 113, 116] and exertional breathlessness during exercise [64, 97, 117, 118]. Given increased respiratory motor output to the respiratory muscles in COPD [119, 120] and the relationship between EMG and lung function, respiratory EMG has been taken as a marker for disease severity in stable COPD [104] and to predict COPD exacerbations [106], early hospital admission [108] and the effect of medical interventions [121-123].

In the ICU, recordings of the electrical activity of the crural diaphragm (EAdi) using a dedicated nasogastric tube with EMG electrodes has greatly facilitated bedside monitoring of diaphragm activity in both among paediatric [124] and adult patients [125]. The ratio of actual EAdi to maximum EAdi (EAdi,max) can be used to estimate the patient's effort to breathe [126]. EAdi is a promising tool to monitor diaphragm activity 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 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]. The 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 that cognitive performances were better during mechanical

ventilation than during unsupported breathing [140], in support of the actual role of the cortical activity in sustaining ventilation ['dual tasking paradigm', see also 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

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

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 minimized by careful selection of subjects [147], stimulus threshold, and strict adherence to the available safety guidelines [55] (table 5, table S12).

The validity of TMS critically depends on the appropriate location of EMG electrodes [148] and control of background muscle activity and noise. In the experimental field, 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 [149-151] (see online

supplement). In the clinical field (e.g. stroke, multiple sclerosis), TMS has been used to document the involvement of the respiratory musclesin patients with neurological conditions such as stroke and multiple sclerosis [152-154] (see table S13).

Test-retest reliability of TMS for respiratory muscles has not been published, 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 summarized in the table S13.

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

In stable COPD, intracortical facilitation (ICF) of the diaphragm correlates with inspiratory muscle strength, whereas intracortical inhibition (ICI) correlates with arterial partial pressure of CO_2 [161]. In COPD, the corticospinal pathway to diaphragm is more excitable and ICF of 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, see table S13.

3. Respiratory muscle imaging

3.1 Ultrasound

Since the publication of the last 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 the muscle's activity [165].

The most frequently variables assessed using diaphragm ultrasound are 1) static measurement of end-expiratory diaphragm thickness (Tdi), 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 Tdi 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 (Tdi)

In healthy subjects at rest, intra- and inter-observer reliability of Tdi are high [167-171] and ultrasound estimates of Tdi are correlated to direct anatomical measurements [168]. The lower limit of normal for Tdi 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]. However, it remains uncertain whether a Tdi value below this threshold can be used to identify diaphragm dysfunction. Tdi 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 Tdi values 0.15 cm [176-178]. However, the temporal evolution of Tdi in these patients was related to the change in VC in those with recovery of diaphragm function, suggesting that Tdi can be used to monitor the evolution of diaphragm weakness [176]. In mechanically ventilated patients, Tdi is reproducible [179, 180]. Tdi is not correlated with $P_{ao,tw}$ when patients are receiving assist-control ventilation or pressure-support ventilation [181]. Tdi is a poor predictor of weaning outcome [182-184]. Finally, over the course of mechanical ventilation, Tdi can decrease, increase or remain unchanged [185, 186].

3.1.2 Diaphragm thickening fraction (TF) and ratio (TR)

The measurement of TF is reproducible [179], with a reported lower limit of normal value for TF of >20% in healthy subjects and patients with COPD [167, 172], but this value is possibly more

closely associated with almost complete paresis rather than partial dysfunction, as the mean values for TF in healthy subject can frequently exceed 100% [167].

Diaphragmatic contractions produce both muscle shortening and thickening. The correlation, however, between diaphragm thickening and diaphragm effort is tenuous: ultrasound measurements of diaphragm 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 dimension measurement whereas inspiratory effort results from an active three dimension displacement of muscle volume. In addition, the extent of diaphragmatic thickening for a given level of inspiratory effort varies considerably between subjects and the reproducibility of the measurement is weak, i.e. reproducibility coefficients ranging from 16 to 27% [187].

In critically ill patients receiving pressure support ventilation, TF <29% has been associated with diaphragmatic dysfunction – the latter being defined as $P_{ao,tw}$ < 11 cm H_2O [181]. In addition, diaphragm TF moderately correlates to indices of neural respiratory drive such as P0.1 [188] and has been reported as a predictor of weaning outcome [181, 182, 189] and duration of mechanical ventilation in critically ill patients [181, 189]. In patients with acute exacerbation of COPD, preliminary data suggests that TF is related to failure of non-invasive 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, measurements 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 hemi-diaphragms, focal diaphragmatic eventration, diaphragmatic hernia) and to document paradoxical movements of the diaphragm [200] (see online supplement).

3.2 Optoelectronic plethysmography (OEP)

OEP is an established technique that allows measuring tidal changes in the volume of the chest wall and its compartments [201, 202] (figure 6). 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 regulations were found in severe patients with COPD, interstitial pulmonary fibrosis, and CF adopted by the ventilatory pump to cope with chronic respiratory failure [206].

OEP has been also 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 on chest wall kinematics and inspiratory muscle activity such as laparoscopic surgery [212], Nuss technique for pectus excavatum [213], diaphragm plication for unilateral diaphragm paralysis [214], diaphragm repair in congenital diaphragmatic hernia [215]. More recently, OEP has also been used to evaluate the effects on chest wall kinematics of several interventions such as air stacking [216], breath staking [217], stretching [218], incentive spirometry [219], inspiratory loaded breathing [220] and rehabilitation [221]. OEP has been 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 or computed tomography have been used to assess the position of the diaphragm and/or a hemidiaphragm, particularly to identify diaphragm elevation secondary to weakness or paralysis in patients with myopathies, neuropathies and injured hemidiaphragm [224]

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]. Chest fluoroscopy, although highly ionizing, can also be considered to identify decreased or paradoxical diaphragm motion. However, 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, non-invasive method to assess breathing pattern [226]. The technique is based on the stereoscopic analysis of respiratory-related distortions of a black and white checkered 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, it allows to measure ventilatory activity while preserving resting tidal breathing variability, reducing instrumental observer effect and avoiding any disruptions in breathing pattern induced by the use of pneumotachograph-mouthpiece-nose-clip combination. SLP allows a detailled compartmentalized analysis of thoraco-abdominal behaviour, which is not the case of wearable devices [226]. In children with asthma, SLP can differentiate between those with and without airway obstruction and may identify responses to bronchodilator [230]. Further researches are however required to confirm the clinical applications of SLP.

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, mitochondrial function as well as the consequences of oxidative stress and inflammation (see table 6). These techniques have the potential of being used to monitor interventions aimed at restoring respiratory muscle function in the ICU and the rehabilitation setting.

4.1 Near-infrared spectroscopy (NIRS)

A decade ago a technique combining near-infrared spectroscopy (NIRS) with the light absorbing tracer indocyanine green dye (ICG) was employed to measure intercostal muscle blood flow (IMBF) using the Fick's principle. Guenette et al. [231] were the first to quantify IMBF in healthy subjects during resting isocapnic hyperpnoea at different fractions of MVV. They showed that as ventilation rose, IMBF significanty correlated with the increase in cardiac output, the work of breathing and P_{di}, suggesting that the NIRS-ICG technique was a sensitive indicator of IMBF in healthy humans. Similar results have been reported by Vogiatzis et al. employing the same NIRS-ICG technique to measure IMBF in healthy subjects [232] and COPD patients [233].
Absolute IMBF measurements by 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 catheterization for the injection of ICG [234] (figure 7).
Habazettl et al. [234] compared BFI values obtained from the 7^{th} 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 individuals [234] but also by retrospective data analysis in COPD [233] (figure 7). 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 BFI technique provides a minimally invasive and technically less demanding

alternative than NIRS-ICG to measure respiratory muscle perfusion in humans at rest and during exercise.

4.2 Oxygen cost of breathing

Oxygen cost of breathing (VO_{2RM}) is an index of the energy required for ventilation. For more detailed information on methods of assessment please see online supplement. $VO2_{RM}$ was shown to be increased in women [236, 237] and in obesity [238, 239], post-operatory patients [240], COPD [240, 241], CF [242, 243], asthmatic children [244], sarcoidosis [245] and CHF [246, 247]. This may contribute in these conditions to increase energy cost during activities of daily living adding, particularly in disease imposing a ventilator or cardiac constrain, an extra factor contributing to the reduced exercise capacity characteristic of these morbid conditions. Interestingly, several interventions have been used in different patient populations to reduce WOB with a potential impact on reducing the oxygen cost of breathing namely invasive and non-invasive 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 the last 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, because of localized lung lesions, 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 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 described in detail 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 COPD, where the diaphragm shows increased type I fibres [267] that favours aerobic metabolism [268]. These changes (injury and regeneration cycles), depend mainly on the training 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 COPD patients has been reported by some but not all investigators [256, 259, 273, 274]. Changes in the proportions of fibre types were also observed in 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 in 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 COPD patients [260, 283, 284]. In these patients, mitochondrial isolated from intercostals muscles showed electron transport blockade and excessive production of reactive oxygen species similarly to *vastus lateralis* [259, 284]. In diaphragm muscle, 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 were impaired in patients with sepsis [287]. In turn, animal models of prolonged mechanical ventilation showed 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 severe COPD patients [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 the severe patients [256, 259]. Contractile actin and myosin, creatine kinase, and carbonic anhydrase-3 are oxidatively modified in the diaphragm of severe COPD patients, 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 CPAP for six 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]. However, local inflammation does not play a role in COPD muscle dysfunction: inflammatory cell counts were very low in diaphragm and external intercostals of severe COPD patients and preserved body composition [257]. Expression of mRNA and protein content of tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 are significantly 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 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 (i.e. oxidative stress), 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 disease conditions, from respiratory diseases to neuromuscular disorders, critically ill, 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. Seventeen 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 scientists 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 the 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 masters the use of rarer pieces of equipment available only in specialized centres. In order to fight this regrettable situation, it seems apparent that the 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., ERS, ATS, ACCP) cannot be underestimated.

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Figures

Figure 1. Pressure recording sites. AbW, abdominal wall; aw, airway; Di, diaphragm; Eq, equipment; Lt, lung tissue; Pab, abdominal pressure; Palv, alveolar pressure; Pao, pressure at airway opening; Pbs, body surface pressure; Ppl, pleural pressure; rc, rib cage. From [1]

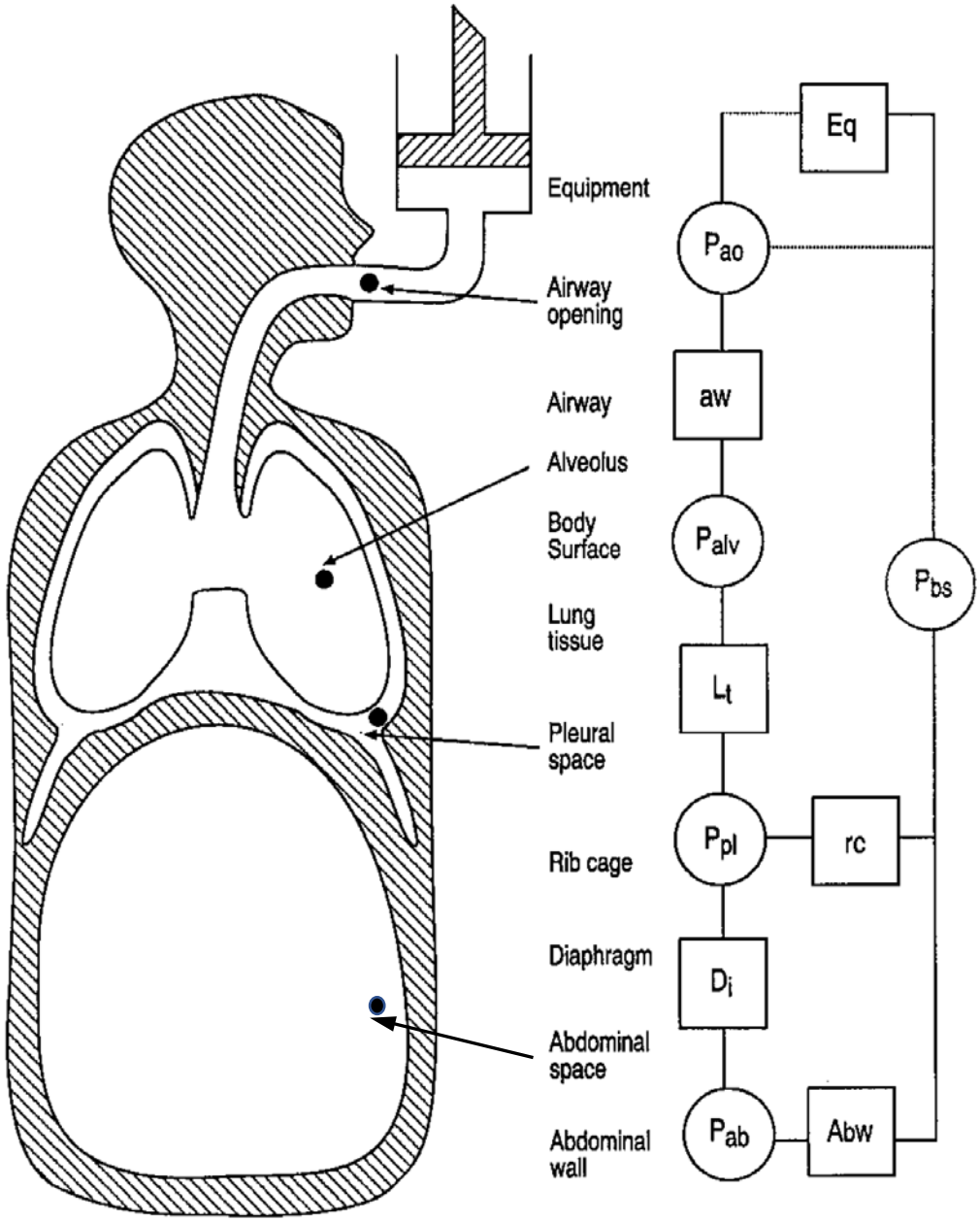

Figure 2. Expert opinion on the suspicion of diaphragmatic dysfunction. The figure describes the current practice of how the members of the Task Force suspect and treat respiratory muscle dysfunction (especially for the unilateral and bilateral diaphragm weakness), outside of the intensive care setting (this is however not intended as a recommendation for clinical practice). In the absence of clearly defined lower limits of normalcy, it has long been accepted that a PImax or sniff-P_{di} or P_{di} max ≥80 cmH_2O in men and ≥70 cmH_2O in women, or/and a sniff nasal inspiratory pressure (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 MIP 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 twitch P_{di} >10 cmH_2O with unilateral phrenic-nerve stimulation or >20 cmH_2O with bilateral phrenic-nerve stimulation also rules out clinically significant weakness [1]. Abbreviations: CT, computed tomography; VC, vital capacity; PImax, maximal inspiratory pressure; TF, thickening fraction of the diaphragm; PSG, polysomnography; CPAP, continuous positive airway pressure; $P_{di,tw}$, twitch transdiaphragmatic pressure; NPPV, noninvasive positive pressure ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; SpO_2, peripheral oxygen saturation. Please refer to the text for more details.

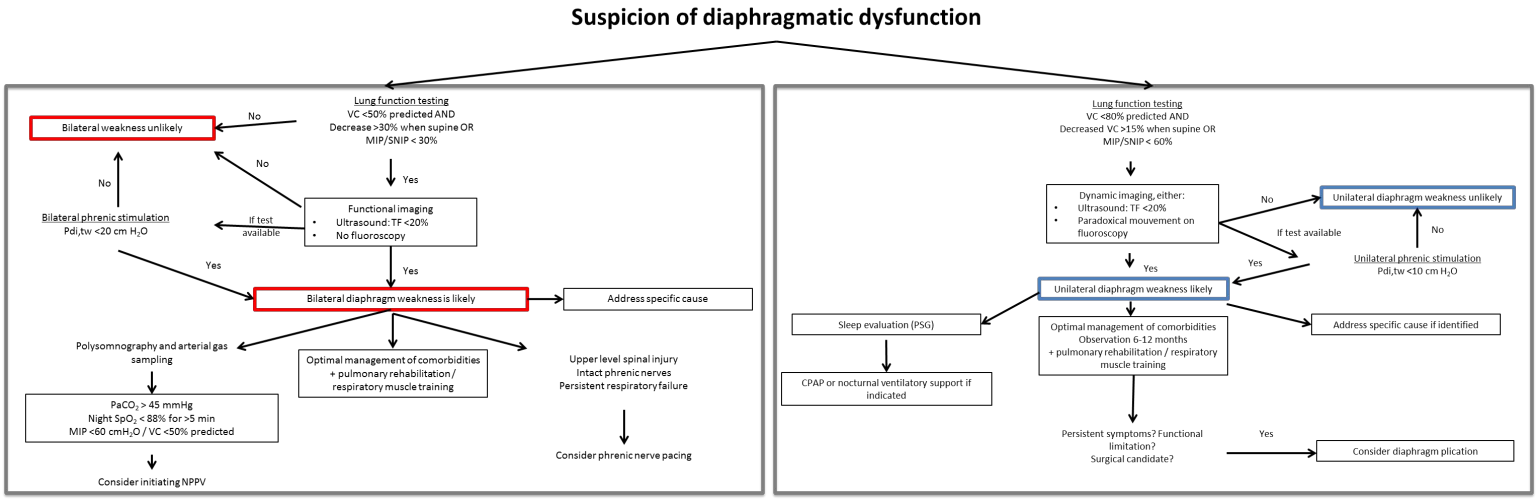

Figure 3. Tidal oesophageal pressure (Poes) swings are shown with varying severity of COPD and in age-matched healthy control subjects. As disease severity worsens, the amplitude of inspiratory and expiratory Poes increases for a given ventilation during exercise. The shaded area represents the tidal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

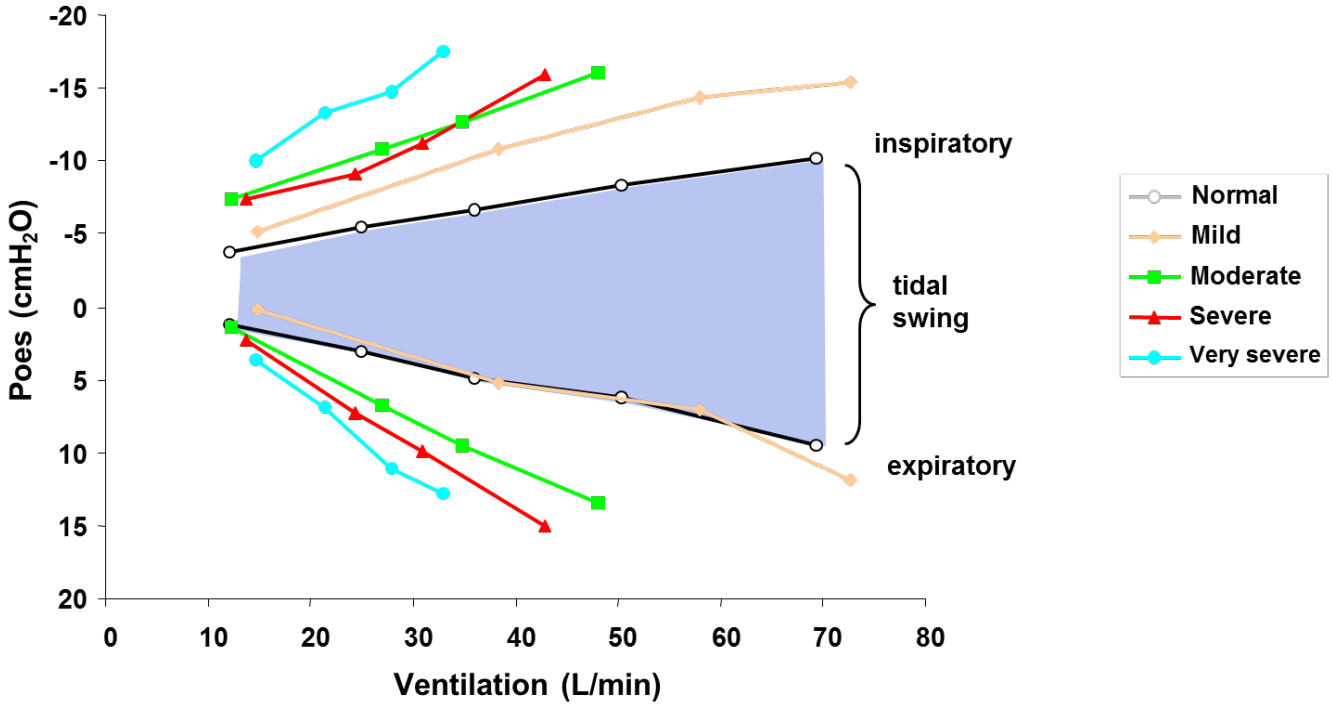

Figure 4. Neurophysiological techniques to assess respiratory muscle control. Schematic of the neural control of the human respiratory muscles. Multiple descending pathways integrate at the respiratory motoneurones (with reflex afferent inputs) and determine the functional output of the muscles. Using 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; Vt: tidal volume

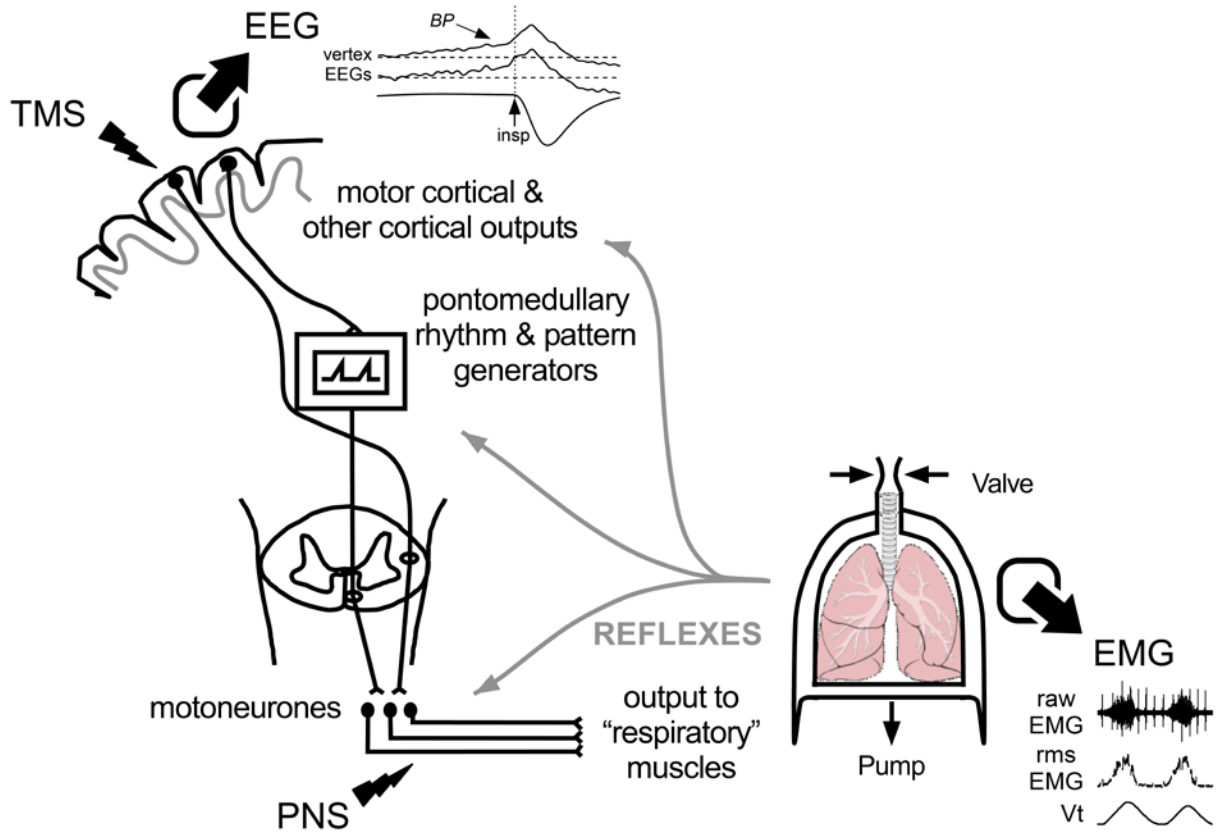

Figure 5. Diaphragm ultrasound assessment. Panel A: when measuring diaphragm thickness and thickening fraction, the use of a linear, high-frequency probe is suggested. The probe is positioned in the sagittal-oblique position at the level of the zone of apposition, and image scanning begins at the mid-axillary 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. Panel B: M-mode image of diaphragm thickening during inspiration. End-expiratory and end-inspiratory diaphragm thicknesses can be directly measured, (red arrows) and thickening fraction (TF) can be determined.

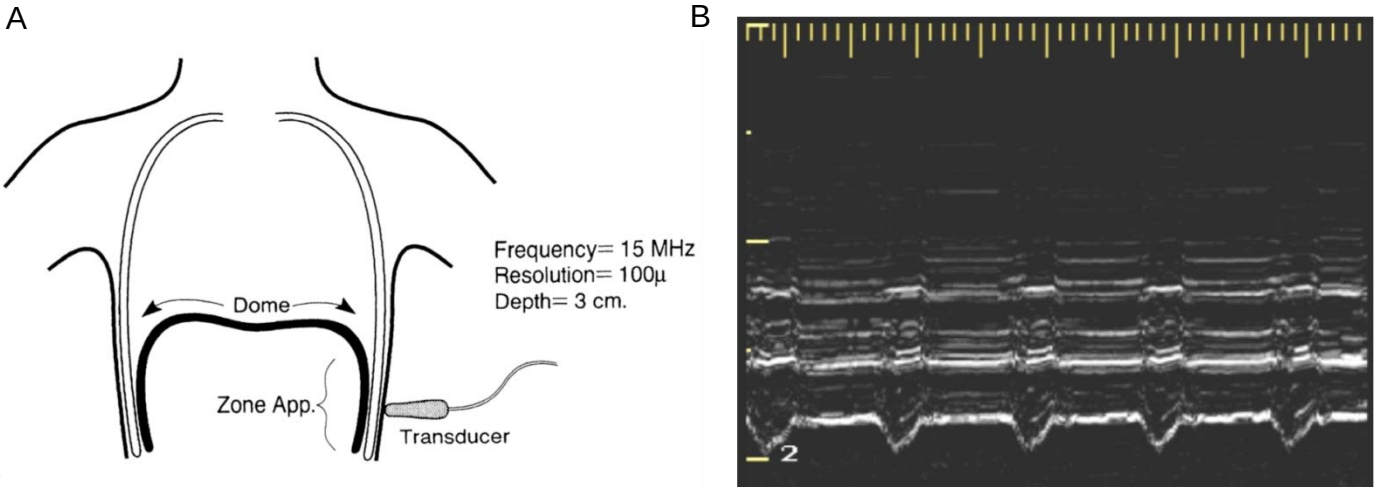

Figure 6. Optoelectronic plethysmography. A number of reflective markers are positioned on the trunk of the subject in selected anatomical reference sites of the rib cage and the abdomen. A set of cameras placed nearby the subject under analysis and dedicated stereo-photogrammetric techniques allow measuring 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 rib cage (rc,p), exposed on its inner surface to pleural pressure, abdominal rib cage (rc,a), and the abdomen (ab), the latter both exposed to abdominal pressure. Total chest wall volume is the sum of the volume of these three compartments ($V_{rc,p}$, $V_{rc,a}$, and V_{ab}).

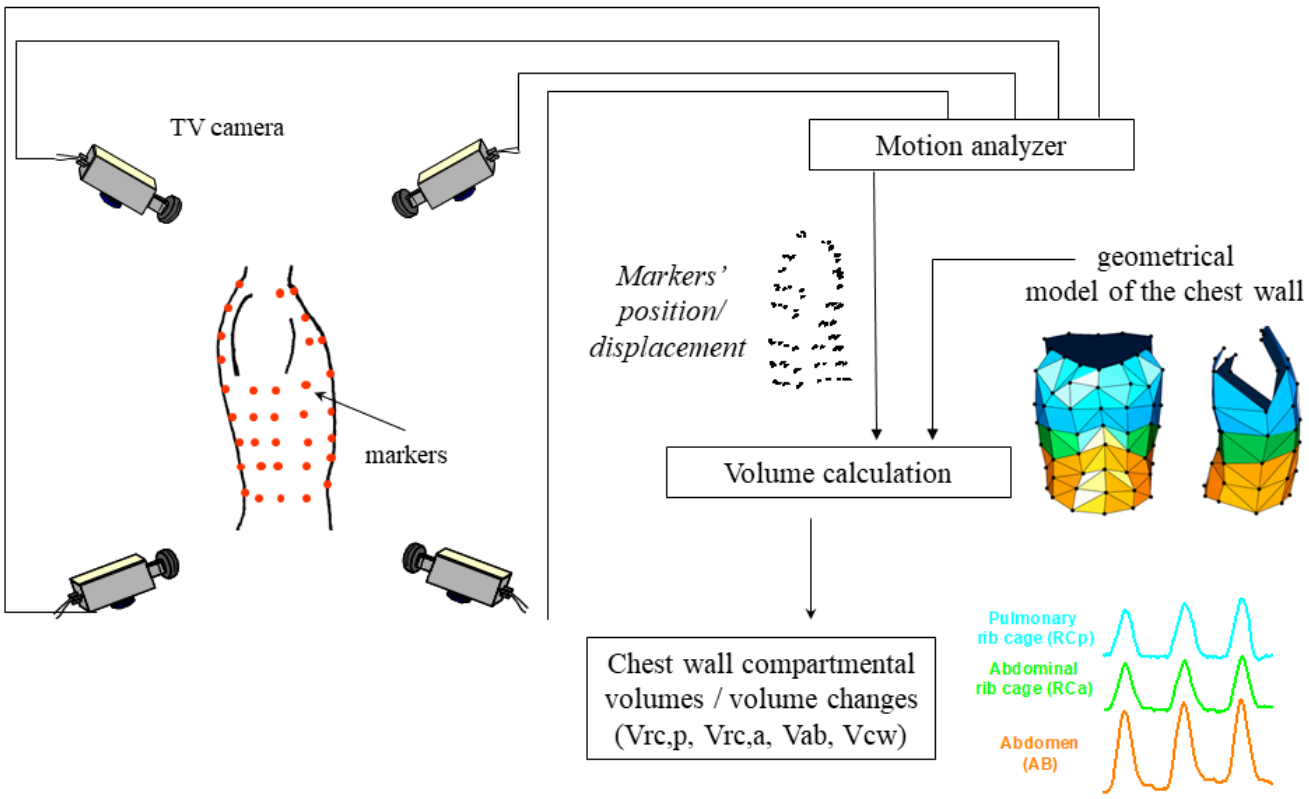

Figure 7. Near-infrared spectroscopy (NIRS). Panel A, Typical example of muscle indocyanine green (ICG) concentration curve recorded by NIRS during exercise. The original tracing (grey line) appears with marked oscillations (at a frequency of 84/min; 1.4 Hz) due to muscle contraction and relaxation during 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. From [234]. Panel 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 COPD. Data calculated from [233].

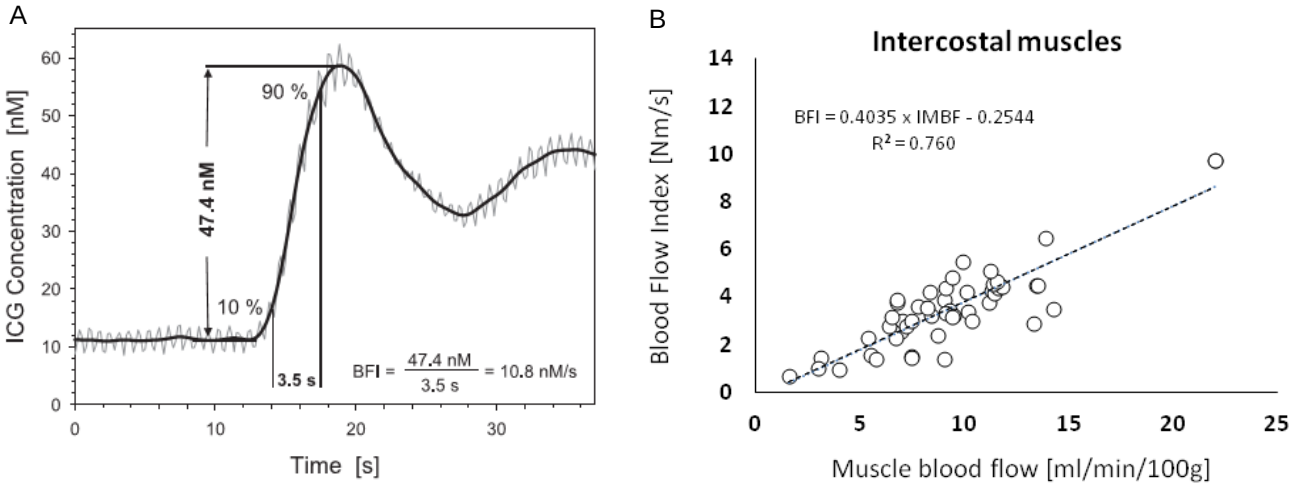

Table 1. Thoracic pressure readings.

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

$P_{aw} = P_{ao} - P_{alv}$

$P_{el(L)} = P_{alv} - P_{pl}$

$= P_L = P_{ao} - P_{pl}$

$P_{rc} = P_{pl} - P_{bs}$

$= P_{cw} = P_{pl} - P_{bs}$

$P_{di} = P_{pl} - P_{ab}$

$P_{abw} = P_{ab} - P_{bs}$

$= P_{cw} = P_{pl} - P_{bs}$

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

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…)	Remarks
Voluntary manoeuvres with mouth pressure						
	PImax	Yes (see 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].	Standardization of lung volumes, mouthpiece, and recorded pressure (peak vs 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.
	PEmax	Yes (see tables S5 and S6)	Reliable peak values usually achieved after 5-6 efforts. Within subject between occasion coefficient of variation around 10%. [21]	Standardization of lung volumes, mouthpiece, and recorded pressure (peak vs plateau) required.		Always to be interpreted in clinical context of symptoms and diagnosis.
	SNIP	Yes (see table S9)	Yes. Possibly less efforts needed for acceptably reliable measurements in comparison to PImax in untrained subjects. [12, 13, 20, 299, 300]	Cautions in subjects with severe nasal congestion. Although SNIP and PImax has a good correlation, the agreement between these two methods is variable. Thus, they are	SNIP in association to PImax reduce 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.

			complementary and not interchangeable in the evaluation of inspiratory weakness		
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 be assessed Especially useful in NMD patients	No direct link between "cut off" values and clinical consequences (e.g. cough assist, etc.).
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 are: P_{di} (37 m): 148±24 (112-204) 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] 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)	CV-P_{di} (healthy adults): 11% [24]	NA	Expert centres 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-yr ventilator-free survival in ALS patients: sniff-P_{di} cut-off 108.5 cmH_2O (sensitivity of 0.85, specificity of 0.98) [33]

	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 centres research	Cough-P_{ga} assessment is helpful for patients with low PEmax 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				

PImax, maximal inspiratory pressure; PEmax, 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. *S* references are detailed in the online supplement references list.

Table 3. Summary of the main causes of perturbation in $P_{di,tw}$

$P_{di,tw}$ observation	Partitioning	Interpretation	Consider
$P_{di,tw}$ ↑	$P_{oes,tw}$ ↑, $P_{ga,tw}$ ↑	a) Strong patient	
		b) Potentiated muscles	
$P_{di,tw}$ ↓	$P_{oes,tw}$ ↓ $P_{ga,tw}$ ↓	a) True weakness	a) Neurological exam
		b) Submaximal stimulation (e.g. obesity)	b) Is PImax/SNIP strong ? (supports if so)
		c) Medical co-morbidities	c) 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)

$P_{di,tw}$, trandiaphragmatic twitch pressure; $P_{oes,tw}$, oesophageal twitch pressure; $P_{ga,tw}$, gastric twitch pressure; PImax, maximal inspiratory pressure; SNIP, sniff nasal inspiratory pressure; COPD, chronic obstructive pulmonary diseases; PEEP, positive end-expiratory pressure. *S* references are detailed in the online supplement references list.

Table 4. Characteristics of 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, PImax, inspiration to TLC and MVV).	sEMGpara, EMGpara%max	Reference values for men and women, with and without a mouthpiece, raw versus normalised signal [107].	Negligible bias for raw and normalised EMG between recording sessions. Small bias in raw EMGpara for repeat measures in the same recording session [107].	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 non-invasive method to measure neural respiratory drive [105].
	sEMGscal	N/A	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 [101].
For the single motor unit technique recorded with needle or wire electrodes, the peak discharge rate is typically reported.	sEMGdi	N/A 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	Good repeatability between recording sessions and between observers [104].	Not for use in patients with oesophageal varices.	Clinical, research. Used in neurally-adjusted ventilatory	The preferred technique for testing respiratory muscle control during exercise given its specificity

	manoeuvres or evoked response (i.e. oesCMAPdi) [104]			assistance.	and safety advantages. Disadvantage of the normalisation procedure is that 'maximal efforts' can be, in fact, sub-maximal [309].
iEMGdi	No data available for amplitude during quiet breathing. This measure is typically used to compare activity between experimental procedures [e.g. 310].		Usual considerations with needle insertion (bleeding, pain and infection). Risk of pneumothorax can be minimised with appropriate precautions (e.g. ultrasound and on-line 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 (see [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.

Evoked signals Measured as the compound muscle action potential in response to electrical stimulation (ES) 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 [see 110, 312]. Amplitude of CMAP more variable.	Latency is reproducible for both electrical and cervical magnetic stimulation [110].	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 [103] [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 [103, 313]. Good agreement between electrical and unilateral magnetic stimulation for latency and amplitude [103].	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; PImax, maximal inspiratory pressure; TLC, total lung capacity; MVV, maximal voluntary ventilation; SMU, single motor unit; ES, electrical stimulation, CMS, cervical magnetic stimulation; UMS, unilateral magnetic stimulation; CMAP, compound muscle action potential. *S* references are detailed in the online supplement references list.

Table 5. Characteristic of TMS paradigms and related measures

Tests (TMS paradigms)	Main measures	Definition	Physiologic significance	Repeatability/ reliability/ validity	Safety	Setting (clinical, research)
Single-pulse TMS		Non-invasive 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.			Carry 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	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.	excitatory input from local circuits.	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
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 10–25Hz rates can produce partial seizures with or without secondary generalization [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 ≤ 1 Hz stimulation frequency.	Depression of the excitability of the stimulated regions, possibly via LTD.		Research
	High-frequency rTMS	Trains of variable duration at ≥ 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

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. *S* references are detailed in the online supplement references list.

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 polymerase chain reaction	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

ONLINE SUPPLEMENT

ERS Statement on Respiratory Muscle Testing at Rest and during Exercise

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1. Respiratory muscle function

1.1 Airway opening, oesophageal and gastric pressures: technical considerations

1.1.1 Airway opening

In most individuals, changes in airway pressure (P_{ao}) accurately reflect the corresponding changes of alveolar pressure (P_{alv}) generated by respiratory muscle contractions, even during dynamic manoeuvres when it is necessary to have a fast transmission of P_{alv} to the airway opening [1]. The speed of this pressure transmission is affected by the flow resistance of the airways and by the compliance of the extrathoracic airways, and the compliance of the equipment [1]. In practice, however, compressibility of gas in the extra-thoracic airways does not pose a real obstacle to the transmission of P_{alv} to the airway opening [1]. In patients with severe airway obstruction the delay in pressure transmission to the airway opening may cause underestimation of ΔP_{alv} [2].

Measurements of P_{ao} during brief inspiratory occlusions (typically 0.1 second) applied without warning before the individual recognizes the occlusion and reacts (i.e. $P_{0.1}$) are a useful index of respiratory centre motor output [3]. $P_{0.1}$ has three determinants: 1) the neural command, 2) the conduction of the neural signal to the inspiratory muscles and 3) the pressure-generating capacity of the muscle. Accordingly, a high value of $P_{0.1}$ always indicates intense neuroventilatory activity whereas low values may be difficult to interpret. $P_{0.1}$ is measured at the airway opening and accordingly, in presence of intrinsic positive end expiratory pressure (PEEP), $P_{0.1}$ can underestimate respiratory centre motor output.

Being generated by inspiratory efforts, $P_{0.1}$ values represent negative pressures, yet they are usually reported in positive units. In healthy subjects, the values of $P_{0.1}$ usually range between 0.5 and 1.5 cmH_2O during resting breathing [4]. The corresponding values in stable patients with chronic obstructive pulmonary diseases (COPD) range between 2.5 and 5 cmH_2O [4]. $P_{0.1}$ has been used to monitor respiratory centre motor output at rest and during exercise in young and elderly healthy subjects [5], in ambulatory children with cystic fibrosis (CF) [6], in ambulatory patients with COPD [7] and heart failure [8], in patients with neuromuscular disorders [9], during titration of ventilator support [10, 11], and weaning from mechanical ventilation [12] and to predict post extubation respiratory failure [13].

1.1.2. Oesophageal and gastric pressures

Oesophageal pressure (P_{oes}) and gastric pressure (P_{ga}) recordings provide valuable data on respiratory mechanics and respiratory muscle activity [14]. For instance, tidal changes in pleural pressure (ΔP_{pl}) are accurately tracked by tidal changes in P_{oes} (ΔP_{oes}) even in supine position [1].

Swings in P_{oes} are obtained recording inspiratory ($P_{oes,insp}$) and expiratory ($P_{es,exp}$) oesophageal pressures as the most negative and positive pressures during tidal breathing, respectively. The tidal P_{oes} swing ($P_{oes,tid}$) is the amplitude of the waveform between these two points. Other computations of respiratory muscle effort include work of breathing (WOB), pressure time product (PTP) and tension-time index (TTI) *(see 1.4.2 Indices of respiratory muscle effort)*.

P_{oes} measured in supine critically ill patients is often greater than what many assume to be likely pleural pressures [15]. Factors that contribute to this finding may include the weight of mediastinal contents and a concurrent variable elevation of pressure within the coelomic cavity [15]. These mechanism, however, have been put into question by recent experimental findings in lung-injured pigs and human cadavers [16].

Simultaneous recordings of P_{oes} and P_{ga} can be plotted against each other to obtain the so called "pleural pressure-abdominal pressure diagram" [17]. With this diagram, it is possible to estimate the relative contributions of the diaphragm, rib cage inspiratory muscles, and abdominal muscles to breathing [18]. The diaphragm also indicates how these muscles are coordinated during ventilation under different conditions [18]. In addition, simultaneous measurements of P_{oes} and P_{ga} permit the calculation of transdiaphragmatic pressure ($P_{di} = P_{ga} - P_{oes}$) [18]. Measurement of P_{di} is especially helpful in the diagnosis of severe weakness or paralysis of the diaphragm (see below). The ratio of P_{ga} over P_{di} is an estimator of diaphragm contribution to the tidal breathing [1]. A negative ratio suggests diaphragm dysfunction.

Despite data showing its usefulness in critically ill patients, P_{oes}, P_{ga} and P_{di} are still hardly used in the clinical setting [2]. This is partially due to technical issues, such as the insertion and proper placement of the catheters, the feasibility of obtaining accurate measurements, and the interpretation of the measurements.

1.2 Voluntary tests of respiratory muscle strength

1.2.1 Maximal static inspiratory (PImax) and expiratory (PEmax) mouth pressure

Measurements of maximal static respiratory pressures during forceful inspiratory and expiratory efforts against an occluded airway reflect global inspiratory and expiratory muscle strength [18]. When the airway is occluded and the glottis is open, mouth pressure equals P_{alv} and reflects the pressure across the entire respiratory system [1].

PImax and PEmax vary with lung volume. This is because of the force–length relationship of the respiratory muscles and the varying contribution of passive elastic recoil pressure of the respiratory system [18]. Other sources of PImax and PEmax variability include the type of mouthpiece used, the evaluated pressure (peak or plateau) and the number of trials performed. To standardize the measurement of PImax and PEmax, it has been recommended to measure the former at or close to residual volume (RV) and the latter at or close to total lung capacity (TLC), although measuring PImax at functional residual capacity can also be an option closer to operational lung volume [19].

Recordings of PImax and PEmax should be obtained by an experienced operator, who should strongly urge subjects to make maximum inspiratory (*Mueller manoeuvre*) and maximal expiratory (*Valsalva manoeuvre*) efforts. During testing, subjects are normally seated. They need coaching to prevent air leaks around the mouthpiece. Once the operator is satisfied, the maximum value of three inspiratory manoeuvres or three expiratory manoeuvres that vary by less than 10% is recorded. The system requires a small leak (approximately 2-mm internal diameter and 20–30 mm in length) to prevent glottic closure during the PImax manoeuvre and to reduce the use of buccal muscles during the PEmax manoeuvre.

Ideally, inspiratory and expiratory pressures must be maintained for at least 1.5 s. This allows to record and report the maximum pressure sustained for 1 s. Pressure transducers should be connected to a computer screen to give feedback to the subject being tested through the display of the pressure-time curves and for the computations of the 1-sec plateau pressure. For clinical use, flanged mouthpieces are recommended even though they result in somewhat lower pressure values, especially for PEmax [19].

Reliability of the test is good if at least 5 attempts are performed, and better after an initial warm-up of the respiratory muscles [19-21]. Peak values should typically be achieved after 5-6 efforts for PEmax [21], and after 9 efforts for PImax [20].

In the previous ATS/ERS statement on respiratory muscle testing, a PImax of less than -80 cmH_2O was proposed as a practical threshold to exclude clinically important inspiratory muscle

weakness [19]. Alternatively, weakness can be defined based on the lower limit of the normal PImax using specific equations. In such a case, the presence or absence of respiratory muscle weakness is critically dependent upon the specific predictive equation being used [22]. For example, in a study of more than 1500 subjects, Rodriques et al. [22] reported that the prevalence of weakness ranged from 33.4 to 66.9% according to the reference equation being used. In addition, the investigators noted how some predictive equations do relate better to clinical and physiologic indicators of respiratory muscles weakness. These observations suggest that there are specific predictive equations that might be particularly useful in screening patients for advanced respiratory neuromuscular assessment (see tables S2 and S4 for more details) [22].

PImax can be affected by specific training [23]. Learning effects need to be acknowledged and sufficient baseline trials (at least 5 manoeuvres) have to be performed. Exercise of relatively short duration (<30 min) at high or maximal intensity (>75% VO_2max) results in reductions in PImax both in trained and in untrained individuals [24, 25]. These observations have been interpreted as a sign of exercise-induced respiratory muscle fatigue. Reductions in PImax have also been reported following marathon running in non-elite athletes who typically run for more than 3 h at a moderate exercise intensity (<70% VO_2max) [26].

Paediatrics. Measurements of PImax and PEmax are restricted to cooperative children older than 6-8 years of age (table S14). Alternative techniques (airway pressure during crying as a surrogate for both in- and expiratory mouth pressures and mouth whistle pressure as a surrogate for PEmax) are described below. The minimal number of measurements has not been validated in children. As children may be unable to comply with technical quality standards, peak inspiratory and expiratory pressures may then be used as simpler tests, and have shown their usefulness to predict severe chest infection in children with neuromuscular disease (NMD) [27].

In children, maximal pressures increase with age, and, as in adults, are greater in males than in females [28]. By 11-12 years of age, adult PImax values are reached in both sexes. Normal values have been established in large series of children of different ethnicities [28-32]. Maximal pressures measured in infants and children are surprisingly high compared to adults. This seems to be related to the small radius of curvature of the rib cage, diaphragm, and abdomen, that according to the Laplace relationship, converts small tensions into relatively high pressures [33]. Recordings of PImax and PEmax have a limited value in children with NMDs disease (Duchenne) because they are too difficult to perform [34].

In infants, mouth pressures generated during crying may provide an index of global respiratory muscle strength [35, 36]. The firm application of a rubber cushion mask against the face of an infant is generally sufficient to provoke crying efforts. An artificial leak in the mask prevents glottic closure. Only peak pressures can be recorded during crying. Mean peak crying PImax was -118 ± 21 cmH_2O in a large group of healthy infants between the age of one month and two years and was independent of age and sex [36]. In some studies, mean peak crying PEmax was 125 ± 35 cm H_2O and was related to body weight [36]. The main advantage of this test is its simplicity. Moreover it is valuable in the assessment of infants with NMD [35].

Mouth whistle pressure (PmW) is a simple and reproducible test to evaluate expiratory muscle strength in patients with amyotrophic lateral sclerosis (ALS) without bulbar dysfunction [37]. In children, PmW has the great advantage of its simplicity, audible feedback, playfulness and non-invasiveness. Aloui et al. [38] recently reported that PmW was closely related to oesophageal whistle pressure and gastric whistle pressure in children with NMDs. This observation confirms that noninvasive mouth pressure is a reliable reflection of P_{oes} and P_{ga} measurements in children and young adults with NMD. PEmax and PmW were also highly related although with wide limits of agreement, mainly due to greater differences for the highest values. Indeed a good agreement between the two tests was found to detect expiratory muscle weakness with 92% of the children being diagnosed as having muscle weakness by both tests.

ICU. Bendix and Bunker were among the first investigators to suggest that MIP might provide a useful reflection of respiratory reserve [39]. Patients who generate a PImax of -20 cmH_2O during a 30-s occlusion of the airway are considered to display sufficient recovery from neuromuscular blockade to tolerate transfer to the recovery room. In a classic study, Sahn and Lakshminarayan [40] reported that all patients with a PImax more negative than -30 cmH_2O were successfully weaned, whereas all patients with a PImax less negative than -20 cmH_2O failed a weaning trial. Unfortunately, the accuracy of PImax in predicting weaning outcome varies considerably among studies. This is not surprising considering that studies differ in the technique for PImax recording (duration of occlusion), design (prospective, retrospective), methods of weaning (T-tube, pressure support, intermittent mandatory ventilation), definition of weaning success and failure. In patients requiring short-term mechanical ventilation, PImax commonly does not differentiate between weaning success and weaning failure patients [41-45]. Measurements of PEmax are not routinely used in intubated patients.

Voluntary manoeuvres are not always possible in the ICU due to poor patient cooperation. Other parameters may therefore be considered:

Airway pressure contour. Airway pressures of mechanically ventilated patients are continuously monitored. Any deviation from the relaxed configuration may indicate active contraction of inspiratory muscles.

Breathing pattern. Tidal volume (VT), respiratory rate (RR) and minute ventilation are easy to measure in intubated patients, and their values are continuously displayed on virtually all modern ventilators. Rapid shallow breathing is common in critically ill patients. Several challenges are susceptible to induce rapid shallow breathing including increased respiratory load, chemoreceptor stimulation, altered neuromechanical transmission, anxiety, fear and cortical influence. In the context of separation from mechanical ventilation, rapid shallow breathing is more likely to appear in patients failing a weaning attempt. Accordingly, RR/VT ratio is used as a predictor of weaning failure [41].

1.2.2 Maximal sniff nasal inspiratory pressure (SNIP)

The amplitude of a SNIP is not specific of diaphragm contraction because sniffing results from the coordinated action of several inspiratory muscles [46]. The high correlation between SNIP and P_{oes} usually reported in healthy individuals [47, 48] is reduced in patients with airflow obstruction [47, 48] or individuals with nasal obstruction [49]. SNIP measurements in different populations are reproducible and, compared to PImax, are less prone to learning effects [50, 51]. In healthy subjects [52] and in patients with COPD [53], SNIP values have good within subject and between occasion repeatability.

The agreement between SNIP and PImax is variable. It has been suggested that, in the evaluation of inspiratory muscle weakness, these two tests should be regarded as complementary and not interchangeable [49, 54].

SNIP is often recorded in the seated position. To avoid air leaks, one nostril is completely occluded by the pressure sensor (plug), while the other nostril is kept open. Often both nostrils are tested with 1 to 3 SNIP runs and the nostril conducive to the higher values is used for further testing.

Starting from functional residual capacity (FRC), subjects are instructed to make a short and fast sniff such that the peak pressure is not sustained. The duration of the sniff should be less than

500 ms. Usually, 10 trials are sufficient to reach a plateau in SNIP values – and the highest value is selected [50]. More than 10 tests might be necessary when the SNIP value is below normal or to follow disease progression.

SNIP have been successfully recorded in healthy individuals [51, 52, 55, 56], in patients with a variety of disease process including patients with COPD [53, 57, 58] and patients with NMDs [59-61].

The precision of SNIP to reflect swings in P_{oes} is good in healthy individuals [62, 63], is reduced in patients with airflow obstruction [47, 48] and in patients with nasal obstruction [49]. The repeatability of SNIP, even in patients with COPD, is good [53]. As described previously, the precision to reflect the oesophageal pressure is good in healthy subjects without severe nasal congestion. Although airflow obstruction is another limiting factor decreasing the correlation with P_{oes}, SNIP has achieved good repeatability even in COPD patients [53].

There is a lack of studies on the prognostic role of SNIP in respiratory diseases. In a retrospective study in patients with severe COPD, SNIP was a better predictor of mortality than inspiratory capacity (IC)/TLC [58]. This topic merits further studies, considering that even patients with mild COPD display a reduced SNIP [57].

SNIP is less frequently used than PImax. In one study conducted in patients with moderate to severe COPD, inspiratory muscle training improved the perception of well-being and PImax, but not SNIP [64]. Lung volume reduction surgery results in greater SNIP one month after surgery; improvements in SNIP, however, do not correlate with improvements in exercise capacity, dyspnoea and lung function [65].

Four groups of investigators have published reference values for healthy adults [55, 56, 66, 67], and one group has published reference values for healthy children [68] (see table S9). Higher SNIP values were found in males and, in most studies, there is a positive correlation with age [55, 56, 67, 68]. The lower limit of normality was around -70 cmH_2O in males and -60 cmH_2O in females, which was in agreement with the previous ATS/ERS statement [19]. However, these limits were significantly reduced in Japanese and Taiwanese individuals [56, 66]. Accordingly, when assessing a given individual, reference values obtained from the individual's population of origin should be used.

Paediatrics. SNIP is a natural and simple manoeuvre that most children > 2 years of age can easily perform [68-71]. SNIP values in healthy children (> 6 years old) are similar to those

measured in healthy adults [68]. In healthy children and in children with inspiratory muscle weakness, SNIP provides a reasonable estimate of the inspiratory muscle strength [72].

The main limitation of SNIP is the underestimation of the inspiratory muscle strength in case of nasal obstruction (e.g., enlarged adenoids, nasal polyps), severe respiratory muscle weakness and airway obstruction (e.g., cystic fibrosis) [69].

Because of its simplicity, SNIP should be part of the routine evaluation of muscle strength in children with NMDs. SNIP was one of the 4 respiratory lung or muscle parameters that declined significantly with age in boys with Duchenne muscular dystrophy [34]. In these boys, SNIP declines earlier than PEF [73].

ICU. SNIP measurements are impossible in intubated patients, since there is no communication between the airway and the nostril (see below on the use of flap valves connected to the endotracheal tube to mimic sniff testing in intubated patients [74]).

1.2.3 Peak cough flow (PCF)

Peak cough flow (PCF) – also known as cough peak expiratory flow – has been described as early as 1966 [75]. The effectiveness of mucus clearance depends on an adequate PCF [76]. The act of coughing consists of the following steps: i) inhalation ranging from 50% of VT to 50% of VC [77], ii) tight glottic closure, iii) contraction of the expiratory muscles with the attendant rise in intrathoracic pressure to around 70 cmH_2O to 400 cmH_2O [77], iv) glottic reopening with biphasic turbulent air blast – with an initial peak (i.e., peak cough flow or PCF) occurring within 30-50 ms after the glottic opening, followed by a flow-plateau phase of 200-500 ms when airflow is approximately 50% or less of PCF [76, 78]. The effectiveness of mucus clearance depends on an adequate PCF [76].

PCF is usually measured with a hand-held, portable peak flow meter (PFM) [79]. While sitting up straight [79], subjects are instructed to inhale maximally and put the PFM mouthpiece in their mouth and seal their lips and teeth tightly around the mouthpiece. Then, subjects are instructed to cough as hard as they can. Usually, subjects repeat the procedure until they generate three PCF readings with <5% of each other. The highest of these three values is then reported [79].

There is a strong correlation and narrow limits of agreement between PCF values assessed via the pneumotachograph of a spirometer and the PCF values recorded with a portable PFM [79]. When PCF is <270 $l \cdot min^{-1}$, peak flow can be overestimated by the PFM [79].

PCF has been proposed to monitor expiratory muscle weakness and potential bulbar involvement in patients with NMD [80]. PCF <270 $l \cdot min^{-1}$ have been associated with increased of pulmonary complications during respiratory tract infections in patients with NMDs [79, 81]. The indication of manual / mechanical exsufflator/insufflator therapy is – among other criteria – based on PCF values in patients with NMD.

Precise threshold values for PCF are not available [79]. Healthy subjects have been reported to reach mean PCF values of approximately 468 to 588 $l \cdot min^{-1}$ (significantly lower values for women than men); patients with NMDs achieve lower PCF values according to the type and stage of the disease [79, 82].

Paediatrics. Reference PCF values are available for children [83] (table S14). As for PImax and PEmax, children with NMDs can find it difficult to perform PCF manoeuvres – this is why in these children PCF values not necessarily correlate with age [34]. The PCF threshold for successful mucus expectoration in children with NMD has been reported to be >160 $l \cdot min^{-1}$ [27].

ICU. Intubated patients cannot close their glottis. Accordingly, intubated patients cannot properly cough. This means that in these patients it is impossible to measure PCF. Intubated patients, however, can huff [84]. The strength of a huff can be quantified measuring peak expiratory flow (PEF) during the huff. Cooperative patients can generate huffs. In non-cooperative patients (e.g., delirious, psychiatric conditions etc.), huffing can be induced using aerosolized normal saline solution [84]. In intubated patients, PEF less than 35 $l \cdot min^{-1}$ [85], 60 $l \cdot min^{-1}$ [86], 70 $l \cdot min^{-1}$ [87], or 80 $l \cdot min^{-1}$ [88], have been associated with extubation failure. This wide range of PEF thresholds plus the fact that all studies were single-centred in specific patient population prevent the widespread adoption of this measurement in clinical decision making in intubated patients.

1.3 Voluntary manoeuvres with oesophageal and gastric pressures

Recordings of P_{oes} and P_{ga} signals during voluntary manoeuvres such as a sniff and a cough are useful in assessing respiratory muscle strength when non-invasive measures fail to provide clinically meaningful information due to anatomical, functional or behavioural causes. P_{oes} recordings during a sniff are particularly useful when SNIP yields suspiciously low values such in patients with upper airway obstruction (hypertrophy of the adenoids, rhinitis, polyps) or lower

airway obstruction (children with CF) [69]. P_{ga} recordings during a cough are needed, for example, when the glottis function is compromised [89] such as in patients with bulbar ALS [90].

In patients without the above specific impairments, assessment of P_{oes} and P_{ga},may not be necessary as SNIP and PCF correlate well with these measures [91]. However, intra-thoracic and -abdominal pressures may be used to refine the diagnosis [21, 54]. In many subjects the value of sniff-P_{di} is greater than that of PImax [92] and the value of cough-P_{ga} is greater than that of PEmax [21].

For both sniff and cough, strong patient encouragement is required to achieve maximal performance. Multiple attempts with adequate breaks (30 s) are needed to reach a plateau [93]. It is advisable to perform more than 3 and up to 10 attempts after a plateau is reached. Visual feedback on a computer screen is a simple and engaging tool to motivate subjects, particularly children [69].

A sniff is usually reported as the pressure difference between baseline and peak pressure. In addition, it is possible to calculate the sniff's maximal relaxation rate (MRR) – i.e., maximal decrease in pressure or dP/dt. The sniff's MRR can be give information on respiratory muscle function including early fatiguing state, selective fiber recruitment, muscle function in patients with thyroid diseases and in malnourished patients [59, 94]. Because MRR is pressure-dependent, the MRR is normalized by dividing by dP/dt by peak pressure [95]. This allows to compare the MRR of sniffs of varying intensity [95].

In adults, the average within-subject, between-occasion CV is higher for sniff-P_{di} (11%) [93] than for cough-P_{ga} (6.9%) [21] (table 2 in main text). No such values are available for children. For sniff-MRR, only individual within-subject, between-occasion CVs have been reported, and they range from 6% to 26% [96].

In a study of 64 subjects (37 males, 27 females), Man et al. [21] reported reference values for sniff-P_{oes}, P_{ga}, and P_{di}. No reference values for cough-P_{ga} are yet available. The range between individuals is quite large and reported ranges in healthy subjects are given in table 2 (main text).

In many disease states, pressures produced during a sniff (e.g., sniff-P_{oes}) and during a cough (i.e., cough-P_{ga}) are lower than normal both in adults [21, 54, 91] and children [38, 71, 97], as are non-invasive measures of static (PImax, PEmax) or dynamic (SNIP, PCF) respiratory muscles strength and function. Thus, it is important to know what additional diagnostic information on

respiratory muscle function can be obtained by measuring pressure signals using balloon (or other pressure-tip) catheters. For example, patients with multiple sclerosis [91] generate a significantly lower cough-P_{ga} (109±46 cmH_2O) than controls (150±34 cmH_2O). In turn, cough-P_{ga} can be predicted by measuring PCF. This favours the use of the less invasive technique (PCF) than the more invasive one (cough-P_{ga}).

In patients with lung disease, including patients with COPD [96], pulmonary fibrosis [96], CF [69] and patients with systemic lupus erythematosus who develop 'shrinking' lung syndrome [96], sniff-P_{oes} recordings help avoid underestimation of inspiratory muscle strength by use of SNIP or PImax only. In patients with heart failure, a reduced sniff-P_{di} (103±21 cmH_2O) correlates with reduced cardiac output [98].

Sniff-P_{oes} may underestimate diaphragm dysfunction, e.g. in patients with bilateral diaphragm paralysis [99], who increasingly recruit rib cage and neck muscles during a sniff manoeuvre. In patients with unilateral diaphragm paresis, Verin et al. [100] observed a significant reduction in sniff-P_{oes}. This reduction was positively correlated with the time elapsed from onset of symptoms to respiratory muscle testing [100].

In a large cohort of patients with mixed diagnoses (156 NMD, 94 dyspnoea of unknown origin, 45 COPD, 37 rheumatologic disease and 81 other diseases), Steier et al. [54] assessed to which extent adding P_{oes} or P_{ga} would improve diagnosis of respiratory muscle weakness. These authors reported that using a single test such as PImax or PEmax, tends to overdiagnose respiratory muscle weakness. Measuring both, PImax *and* SNIP, reduced the false-positives by 20%, while adding sniff-P_{oes} *did not* significantly improve the rate of false-positive tests. When diagnosing expiratory muscle weakness, adding cough-P_{ga} to PEmax decreased false-positives by 30% [54]. In accordance with the previous study, Tzani et al. [82] reported that adding cough-P_{ga} (53% positive) to PEmax (51% positive) and PCF (27% positive), reduced positive cases to 20%.

Man et al. [21] have assessed the value of adding cough-P_{ga} measurement in a mixed group of 99 patients with respiratory muscle weakness. They found that cough-P_{ga} had a much better positive predictive value (94%) than PEmax (58%). In fact, 43% of patients with low PEmax had normal cough-P_{ga} while of 105 patients with low cough-P_{ga}, only 6% had normal PEmax. These results suggest that cough-P_{ga} may be useful to exclude expiratory muscle weakness in patients with reduced PEmax.

Voluntary manoeuvres are not always sufficient to elucidate the pathophysiological mechanisms. For example, compared to healthy controls, in patients with hemispheric stroke [101], sniff-P_{oes} (58±37 vs. 109±29 cmH_2O), sniff-P_{di} (63±41 vs. 121±39 cmH_2O) and voluntary cough-P_{ga} (99±62 cmH_2O vs. 209±62 cmH_2O) are lower than normal. In contrast, P_{ga} during a reflex cough is not significantly different (179±78 vs. 208±77 cmH_2O) than normal. These results suggest that the voluntary initiation of muscle contraction contributing to lower values.

The value of sniff-P_{di} and cough-P_{ga} as prognostic tools has been marginally studied. In 98 ALS patients, Morgan et al. [61] assessed whether SNIP and sniff-P_{di} could predict the risk of desaturation during sleep and the hazard ratio for death. Sniff-P_{di} correlated well with SNIP ($r=0.9$, $p>0.01$) and SNIP values <40 cmH_2O were associated with desaturation during sleep (no such correlation for FVC or PImax). The hazard ratio for death in this group of patients was 9.1 (95% CI 4 – 20.8). These results suggest that it is unnecessary to record sniff-P_{di} in ALS patients to assess their prognosis.

Polkey et al. [60] reported that sniff-P_{di}, sniff-P_{oes} and transdiaphragmatic twitch pressure elicited by magnetic stimulation of the phrenic nerves ($P_{di,tw}$) could predict ventilation-free survival in a group of 78 ALS patients – i.e., for 3-yr ventilation-free survival, sniff-P_{di} cut-off was 108.5 cmH_2O with a sensitivity of 0.85 and a specificity of 0.98. In the same study, PEmax and particularly $P_{di,tw}$ were predictors of survival [60].

Sniff-P_{di}, sniff-P_{oes} and $P_{di,tw}$ and cough-P_{ga} are seldom used to assess response to interventions. After lung volume reduction surgery, for example, sniff-P_{di} [65, 102], SNIP [65], PImax [65, 102] and $P_{di,tw}$ [103] increased significantly. In patients with COPD completing an exhaustive treadmill walk, sniff-P_{oes} did not change from pre-exercise values [104]. Sniff-P_{oes}-MRR, however, decreased by 42%, and recovered within 5 min of rest [104]. This transient decrease in sniff-P_{oes}-MRR suggests development of inspiratory muscle fatigue.

Paediatrics. The measurement of P_{oes} and P_{ga} during voluntary manoeuvres such as sniff and cough is particularly useful in children (table S14). As noted, SNIP can underestimate inspiratory muscle strength in patients with upper airway obstruction (hypertrophy of the adenoids, rhinitis, polyps) and lower airway obstruction (children with CF) [69]. Accordingly, in these patients, a low SNIP value should prompt measurement of sniff-P_{oes}.

The measurement of P_{oes} and P_{ga} may also evidence diaphragmatic dysfunction as shown in children with collagen type VI (ColVI) myopathies [97] and selenopathies [105].

Expiratory muscle strength can be measured during a maximal cough (P_{ga}-cough) [21, 38, 71]. Visualization of the P_{ga} signal during the cough on a computer screen is a simple and playful tool to motivate a child to perform a maximal manoeuvre [21, 38, 71].

ICU. In intubated patients instrumented with oesophageal and gastric balloons it is possible to record maximal P_{oes} ($P_{oes,max}$) and maximal transdiaphragmatic pressure ($P_{di,max}$) during forceful inspiratory efforts. $P_{oes,max}$ can be used to evaluate global inspiratory muscle strength while $P_{di,max}$ can be used to evaluate diaphragmatic strength. In most patients without diaphragmatic paralysis the contribution of P_{ga} to P_{di} during a maximal inspiratory effort is minimal-to-none (see figure 4 in Laghi et al. [106]). Accordingly, in most intubated patients, a simple PImax can give similar information afforded by $P_{oes,max}$ and $P_{di,max}$.

Intubated patients cannot sniff naturally because the upper airway is bypassed by the endotracheal or tracheostomy tube. To overcome this obstacle, Goldstone et al. [74] used a flap valve in 19 alert and cooperative intubated patients. The flap valve occluded flow during inspiration thereby allowing patients to generate a "sniff-like" inspiratory waveform. In the study, 14 out 19 patients were able to perform sniff-like manoeuvres. Unfortunately, the investigators did not report the sniff-P_{oes} or sniff-P_{di} values recorded in the study nor the intra or inter-observer reproducibility of sniff pressures. What role sniff manoeuvres may play in the assessment of respiratory muscle function in intubated patients remains to be determined.

1.4 Respiratory muscle-related mechanics of breathing

1.4.1 Pressure-related measurements during inspiratory capacity (IC)

IC is the maximal volume of air that can be inhaled to TLC after a quiet exhalation to end-expiratory lung volume (EELV). The main determinants of resting IC in patients with COPD include the magnitude of the resting EELV (inverse relation), the strength of the inspiratory muscles, and the combined elastic properties of the lung and chest wall [107-124]. Resting IC is an indirect measure of lung hyperinflation only in patients with COPD whose TLC is not decreased to less than the lower limit of normal; e.g. no coexistent inspiratory muscle weakness, lung or chest wall restriction. In patients with milder airway obstruction and in some patients with very advanced COPD, TLC and EELV may rise in tandem to a similar extent thus preserving IC [125]. In patients with COPD and moderate obesity, expiratory reserve volume

and EELV are diminished to a greater extent than TLC leading to preservation or increase in IC compared with normal weight individuals with similar forced expiratory volume in 1 second (FEV_1) [126].

IC represents the operating limits for VT during exercise in elite athletes and patients with respiratory disorders. In obstructive lung disorders (COPD), TLC and IC are reduced "from below" with an increase in EELV. In restrictive lung disorders (interstitial lung diseases, inspiratory muscle weakness, chest wall restriction), TLC and IC are reduced "from above" without an increase in EELV. Regardless of the underlying disorder, and in the absence of inspiratory muscle weakness, a reduced IC indicates close proximity of VT to TLC – at the upper less compliant reaches of the respiratory systems s-shaped pressure-volume relaxation curve where the inspiratory muscles are under a significant disadvantage [127]. In these patients early mechanical constraints (and high VT/IC ratios) are evident at relatively low exercise intensity and correlate with increased ratings of dyspnoea [116, 118-120, 128]. In patients with asthma [109, 113], pulmonary arterial hypertension (PAH) [110, 112] and in patients with chronic heart failure (CHF) [115], airway dysfunction with the resultant progressive reduction in IC during exercise (dynamic lung hyperinflation) have important mechanical and sensory consequences [120].

IC's repeatability and reliability, its predictive, discriminative and evaluative value and its minimal clinical important difference (MCID) have been extensively described elsewhere [123].

The accuracy and construct validity of serial IC measurements during exercise to track change in EELV has been confirmed in a number of studies in COPD. One large retrospective analysis examined test re-test repeatability of IC during rest and exercise in 463 patients with moderate to severe COPD entered in multi-center, multi-national clinical trials designed to test efficacy of bronchodilators. Within-subject coefficient of variation (%) for IC at rest, at a standardized time during exercise during exercise and at peak exercise was 9.5%, 10.8% and 11.6%, respectively. Intra-class correlation (with 95% confidence interval) for IC at rest, standardized time and peak exercise was 0.89 (0.87- 0.91), 0.88 (0.86-0.9) and 0.87 (0.85-0.89), respectively. While IC measurements have been shown to be robust in diverse international clinical research settings, data are lacking on its reliability as an evaluative instrument in clinical practice.

The ratio of IC to total lung capacity (TLC) has been shown to predict respiratory and all-cause mortality and the risk and severity of exacerbations [129-131]in COPD population studies. There

is good evidence that lung hyperinflation and attendant reduction in IC is closely linked to the degree of breathlessness (dyspnoea) experienced by patients with COPD during physical activity. Although exercise limitation is multi-factorial in COPD respiratory mechanical factors are undoubtedly important. In this context, resting IC is a good predictor of peak ventilatory capacity and peak oxygen uptake in COPD. Moreover, therapeutic reversal of lung hyperinflation, with improvement of IC, has been shown to be associated with improved dyspnea and exercise endurance.

Cross-sectional studies have confirmed that significant differences in IC are discernable across quartiles of severity of airway obstruction based on spirometry. Thus, the IC provides additional information about the individuals exercise capacity and dyspnea beyond simple spirometry.

In multiple clinical trials, bronchodilators of all classes and duration of action have been shown to increases IC. Generally, bronchodilator-induced improvements in resting IC range from 0.2-0.4L or 10-15% of the baseline value. Besides bronchodilator therapy, any intervention that reduces inspiratory neural drive and thus breathing frequency such as hyperoxia, helium-oxygen, or exercise training (by delaying metabolic acidosis) has the potential to reduce the rate of increase of EELV during exercise (by prolonging expiratory time), thereby improving dyspnea by delaying the onset of mechanical limitation. Changes in IC during exercise have also mirrored improvement in dynamic respiratory mechanics following lung volume reduction procedures in COPD and following bi-ventricular pacing in patients with congestive heart failure.

IC measurement is simple, safe and easy to perform. IC manoeuvres are carried out at the end of a steady-state resting baseline period (approximately 3 minutes) until at least 2 reproducible efforts are achieved (i.e., ±100 mL or within approximately 10% of the largest acceptable value). IC measurements at rest should not be performed closer than 1 minute apart, and measurements should not be repeated until breathing has returned to the pre-manoeuvre pattern.

As is the case with other spirometric and plethysmograhic indices, no minimal clinically important difference values has been clearly established for indirect measurements of lung hyperinflation such as IC. From experience to date, a post-intervention change in IC of ~0.2L at rest or at a standardized time during exercise (or ~15% predicted) could be considered clinically meaningful. More specifically, such changes have been consistently associated with increased exercise endurance time by at least 60 seconds or in the order of 20-30% in patients with moderate to severe COPD.

The IC manoeuver is reliable in evaluating dynamic hyperinflation during cardiopulmonary exercise testing (CPET) in patients with COPD, asthma, PAH and CHF. This because TLC does not change during exhaustive cycle exercise neither in healthy subjects [132] nor in patients [114, 117, 133, 134].

A dynamic decrease in IC during exercise can be caused by true dynamic hyperinflation or by impaired inspiratory muscle performance (weakness/fatigue). Previous published studies have assessed the reliability of IC manoeuvres by comparing dynamic peak inspiratory P_{oes} values during IC manoeuvers, and clearly demonstrated that IC-P_{oes} values were remarkably preserved during exercise and independent of exercise intensity and ventilation in COPD [118, 119, 135], CHF [133] and PAH [117] (figure 3). The contention that these patients were able to inhale to a lung volume close or equal to TLC was bolstered by the evidence that end-exercise static lung compliance was remarkably preserved compared with pre-exercise static lung compliance, suggesting that the elastic recoil pressure of the lung does not change during exercise in PAH. The P_{oes} at IC is remarkably preserved during exercise and it is independent of exercise intensity and ventilation in COPD [118, 119, 135], CHF [133] and PAH [117] (figure 3). These observations suggest that exercise-induced changes in EELV can indeed be reliably monitored with IC manoeuvres. That patients are able to inhale to a lung volume close or equal to TLC is further supported by the finding that pre and end-exercise static lung compliance are constant. This finding suggests that in healthy subjects [136], and in patients with COPD [135], PAH [117], and CHF [133] the elastic recoil pressure of the lung does not change during exercise.

Exercise-induced inspiratory muscle fatigue, if present, does not seem to be sufficient to contribute to decreases in IC during exercise because of the stable IC-P_{oes} during CPET (figure S1) and identical sniff-P_{oes} values pre/post-exercise in these patients.

Although IC-P_{oes} and sniff-P_{oes} measures during CPET can rule out a potential inspiratory muscle fatigue, their predictive, discriminative and evaluative value along with their respective MCID have not yet been described. Further studies are therefore needed in this regard.

1.4.2 Indices of respiratory muscle effort

Computation of tidal swings in P_{oes} and P_{di}, work of breathing (WOB), pressure–time product (PTP) and tension-time index (TTI) can be used to assess the pressure output of the respiratory muscles [137].

In common usage, the expression WOB is often understood to be synonymous with breathing effort [138]. WOB, however, is technically defined in the mechanical and not biologic sense. Mechanical work (W) occurs when pressure (P) changes the volume (V) of matter: W = P x V. In the case of the respiratory system, mechanical (external) WOB can be calculated by measuring the generation of intrathoracic pressure (i.e., change in P_{pl}) due to contraction of the respiratory muscles and the displacement of gas volume [137]. In spontaneously breathing subjects, tidal changes in P_{pl} can be estimated measuring changes in P_{oes} [137].

PTP is calculated as the time integral of the area between P_{oes} and the recoil pressure of the chest wall (PTP_{oes}) or as the time integral of the area between baseline P_{di} (resting end-expiratory P_{di}) and P_{di} during the inspiratory effort (PTP_{di}) [138]. PTP_{oes} reflects the effort done by all of the respiratory muscles and PTP_{di} reflects mostly the effort done by the diaphragm [139, 140].

TTI is an estimate of inspiratory effort relative to respiratory muscle strength. Generally speaking, TTI is calculated as the product of respiratory duty cycle (inspiratory time divided by the time of a total respiratory cycle ot T_I/T_{TOT}) and mean inspiratory pressure per breath divided by the maximum inspiratory pressure [138]. The effort done by all of the respiratory muscles, or TTrc, is calculated as the product of mean inspiratory P_{oes} divided by $P_{oes,max}$ and T_I/T_{TOT}: $TTrc = (P_{oes}/P_{oes,max}) \times (T_I/T_{TOT})$. The effort done by the diaphrgm, or TTdi, is calculate as the product of mean inspiratory P_{di} divided by $P_{di,max}$ and T_I/T_{TOT}: $TTdi = (P_{di}/ P_{di,max}) \times (T_I/T_{TOT})$.

Measurements of WOB or PTP have been used to estimate the energy dissipated or consumed by the respiratory muscles [140]. Under specific experimental conditions PTP is more closely related to respiratory muscle oxygen consumption than WOB [141]. PTP is obtained by multiplying the integral of pressure over time for each breath by the respiratory frequency. In spontaneously breathing subjects P_{di} is usually measured to calculate PTP since it seems to better reflect oxygen cost of breathing than PTP estimates derived from measurements of P_{oes} [142]. Measurements of WOB underestimate respiratory oxygen consumption during isometric contractions [143]. In addition, WOB does not account well for the duration of muscular contraction. PTP circumvents some of these limitations of WOB [141]. PTP has been used to quantify respiratory muscle effort in healthy subjects [144, 145] and patients with respiratory disorders [106, 146-148].

When computing WOB and PTP, it is recommended to include that portion of WOB and PTP necessary to expand the chest wall. This can be accomplished directly by measuring the

compliance of the chest wall or indirectly by assuming that the compliance of chest wall amounts to 4% of the predicted vital capacity (VC) per cmH_2O [15]. Because the pressure necessary to expand the chest wall during tidal breathing is usually small, some investigators ignore its contribution to WOB or PTP.

PTP can be separated into several components: effort made to overcome intrinsic PEEP such as in patients with COPD, effort to inflate the chest and, in the specific case of mechanichally ventilated patients, the effort to trigger the ventilator [137]. An important technical challenge in the computation of PTP is the accurate identification of the beginning of inspiratory effort, particularly when intrinsic PEEP is present [2]. This because patients with intrinsic PEEP often recruit the expiratory muscles during exhalation [149]. Sudden relaxation of the expiratory muscles at the end of exhalation causes a sudden decrease in P_{oes} that can be easily confused with the sudden decrease in P_{oes} that accompanies inspiratory muscle contractions [137]. To correct for expiratory muscle contribution to intrinsic PEEP and to better define the beginning of inhalation, it is useful to record gastric pressure (P_{ga}) [149].

Under specific experimental conditions PTP is more closely related to respiratory muscle oxygen consumption than WOB [141]. Anotherhe PTP_{oes} of healthy subjects at rest is around 100 $cmH_2O \cdot sec \cdot min^{-1}$ [138]. The PTP_{oes} of patients with COPD at rest is twice that in healthy subjects [150]. The average PTP_{oes} of patients in acute respiratory failure can be 4 to 6 times higher than in healthy subjects [138, 151]. During spontaneous breathing trials, increases in respiratory effort reflected by increases in PTP_{oes} are predictive of weaning failure [151].

A simplified strategy to monitor inspiratory effort consists in measuring the tidal swing in P_{oes} during inspiration (figure 3). These tidal swing in P_{oes} is computed by recording inspiratory ($P_{oes,insp}$) and expiratory oesophageal pressures ($P_{es,exp}$) as the most negative and positive pressures during tidal breathing, respectively. The tidal P_{oes} swing ($P_{oes,tid}$) is the amplitude of the waveform between these two points, and is expressed as an absolute value and relative to $P_{oes,max}$ ($P_{oes,tid}/P_{oes,max}$) and can serve as an index of global respiratory muscle effort [152]. $P_{oes,tid}$ is less precise than measurements of $PTP_{di.}$ It has however been successfully applied as bedside monitoring tool in sleep studies [153], and during weaning trials [154]. Swings in P_{oes} (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) [151, 154]. Swings in P_{oes} can also serve as a useful index of global respiratory muscle effort during exercise in patients with

chronic respiratory disease [155]. Increases in $P_{oes,tid}$ swings relative to stable tidal volume responses are related to the perception of dyspnoea in patients during exercise [118, 155].

TTrc and TTdi have been used to identify potentially fatiguing contractions of the respiratory muscles [156]. Healthy subjects cannot sustain indefinetly respiratory loads that require the generation of a TTrc greater than 0.30 [157] or a TTdi greater than 0.15, 0.18 [158] (In healthy subjects, a sustained increase in TTdi above 0.15 leads to diaphragmatic fatigue even before task failure [158, 159].) Reliable calculation of TTrc and TTdi is critically dependent on an accurate measurement of overall inspiratory muscle strength and diaphragmatic strength, respectively [158]. Unfortunately, in critically ill patients $P_{di,max}$ often underestimates maximum diaphrgmatic strength [106]. This is because critically ill patients are unable to activate completely the diaphragm during "maximum" voluntary inspiratory maneuvers [106]. Such underestimation of $P_{di,max}$ necessarily produces an overestimation of TTdi – one of the reasons why patients who fail a trial of weaning from mechanical ventilation not develop low-frequency fatigue of the diaphragm despite generating TTdi above 0.15 [106].

Variable resistive and elastic unloading of respiratory muscles by either continuous positive airway pressure or inspiratory pressure support can reduce inspiratory effort. Reduced effort has been associated with reduced dyspnea and improvements in exercise capacity in patients with COPD [128, 146, 160]. Reductions in the resistive WOB and dynamic hyperinflation by helium-hyperoxia also reduce inspiratory effort and dyspnea [128, 161]. Finally, breathing exercises that promote slow and deep breathing can reduce elastic resistance during breathing and thereby reduce inspiratory effort [162-164]. In addition, changes in inspiratory duty cycle (decreased Ti/Ttot) induced by these breathing techniques can further reduce PTP by reducing inspiratory time per minute [165].

1.4.3 Flow-Volume Loop to Evaluate Expiratory Flow Limitation (FV Loop-EFL)

The flow-volume (FV) loop technique permits the evaluation of expiratory flow limitation at rest [166] and during exercise [167]. Evaluation of the expiratory limb of the maximum FV loop can also be used to assess expiratory muscle weakness. Severe expiratory muscle weakness is indicated by a sudden decrease in maximum expiratory flow toward residual volume [90]. The FV loop technique permits the evaluation of expiratory flow limitation at rest [166] and during exercise [167]. Evaluation of the expiratory limb of the maximum FV loop may also be used to

assess expiratory muscle strength. Severe expiratory muscle weakness is indicated by a sudden decrease in maximum expiratory flow toward residual volume [90].

Expiratory flow limitation (EFL) can be assessed by positioning the resting and the exercise tidal FV loops within a pre- or post-exercise maximum FV taking care that the tidal FV loop starts from end-expiratory lung volume [167]. EFL is present when the expiratory limb of the tidal FV loop encroaches or exceeds the expiratory limb of the resting maximum FV loop [166]. The severity of EFL can be quantified calculating the percentage of VT that encroaches or exceeds the expiratory limb of the maximum FV loop

Performing forced expiratory manoeuvres to generate the maximum FV loop is safe in the general population [168, 169].

Although the FV loop technique is widely used, there are many methodological limitations that can impact the validity of the technique. These include thoracic gas compression artifacts [170, 171], presence of exercise-induced bronchodilation [170] or exercise-induced bronchoconstriction [172], differences in the time and volume history preceding maximal and tidal exhalations [173-175], time-constant inequalities [176, 177], and poor patient cooperation and effort. Accurate alignment of the tidal and maximal expiratory FV loops during exercise also depends on the accuracy of inspiratory capacity manoeuvres. Studies in obstructive pulmonary diseases show that EFL is over-estimated using the FV loop method compared to the negative expiratory pressure (NEP) technique (see below) [178-183].

1.4.4 Negative Expiratory Pressure (NEP)

NEP permits the evaluation of expiratory flow limitation at rest and during exercise [184]. NEP can also assist in the evaluation of patients with suspected increased upper airway collapsibility NEP permits the evaluation of expiratory flow limitation at rest and during exercise [184] and possibly upper airway collapsibility [185, 186].

During normal exhalation, a negative pressure is quickly applied at the airway. If EFL is present, the resulting expiratory flow is not greater than the expiratory flow of the preceding tidal exhalation [182, 184, 187, 188]. EFL can be quantified using the 3-point score or the 5-point score system [189]. EFL can also be quantified by examining the percentage overlap between the NEP breath and the preceding control breath(s) [190].

NEP is a safe, non-invasive procedure that causes no discomfort [184].

NEP has been validated against direct measurement of iso-volume, flow-pressure relationships in mechanically ventilated patients [190].

In patients with COPD, EFL is poorly reproducible when it is assessed using the percentage overlap NEP method [180, 189]. In contrast, EFL is highly reproducible in patients with and without COPD when EFL is assessed using the 3-point score or 5-point score NEP system [189, 191].

The use NEP has been primarily limited to the research setting. The presence of EFL identified using the NEP technique has been associated with dyspnoea on exertion in patients with COPD [184], exercise limitation [181], and as an indicator of worsening COPD [192]. NEP has also been used in healthy infants [193], in children with asthma and CF [194], in patients with CHF [195], obstructive sleep apnoea syndrome (OSAS), in obese patients without OSAS [196]. It has been used in chronic heart failure patients [195], obstructive sleep apnoea syndrome (OSAS) patients and obese non-OSAS patients [196], in cervical spinal injured patients [197], and obese subjects [198], in patients with restrictive disorders [175, 199], in elite athletes [175, 199] and in the ICU [190].

NEP may help determine whether maximal expiratory flow has been achieved, if not, decreased flows may be suggestive of expiratory muscle weakness or lack of coordination of expiratory muscles but there is no data on it being used this way.

1.4.5 Inspiratory Flow Reserve (on the flow volume loop)

Maximal inspiratory flow-volume curves are universally recorded during of standard pulmonary function testing. This is a standard procedure with minimal safety concerns [19, 200].

Maximal inspiratory flow-volume curves can be reduced as a result of extrathoracic upper airway obstruction and, in the effort-dependent regions of the curve, as a result of respiratory muscle weakness, poor effort, and poor performance of the manoeuvre [19, 201]. Only a small percentage of tests indicate abnormalities including inspiratory muscle weakness [202]. However, visual examination of the maximal inspiratory flow-volume loop may suggest weakness [19, 203]. The maximal inspiratory flow-volume loop has greater variability than the VC manoeuvre and reference values for inspiratory flow may present problems with interpretation [19]. Inspiratory flow oscillations (saw-tooth) can suggest upper airway and surrounding muscular abnormalities. By looking at peak expiratory flow, slope of ascending limb

of the maximal expiratory curve, drop in forced expiratory flow near residual volume, and inspiratory flow at 50% VC, better predictability may be achieved [203]. The maximal inspiratory flow-volume loop has greater variability than the VC manoeuvre and reference values for inspiratory flow may present problems with interpretation [19]. Inspiratory flow oscillations (saw-tooth) may potentially suggest upper airway and surrounding muscular abnormalities [19, 204] including neuromuscular diseases, Parkinson's disease, laryngeal dyskinesia, pedunculated tumours of the upper airway, tracheobronchomalacia and upper airway burns [202]. Inspiratory flow oscillations have also been reported in snorers without OSAS, in patients with OSAS and in about 10% of healthy individuals [202]. Unfortunately, inspiratory flow-volume curves are not sufficiently sensitive to diagnose upper airway obstruction. This because lesions must narrow the tracheal lumen to less than 8 mm (i.e., a reduction of the tracheal by at least 80 percent) before abnormalities in the flow-volume curves can be detected [202].

As already noted, the quality of maximal inspiratory flow-volume curves depends on patient motivation and cooperation. Moreover, there are more specific tests of muscle weakness than maximal inspiratory flow-volume curves including recordings of VC, SNIP and Pditw [205, 206]. In clinical practice it is useful to use a battery of respiratory muscle tests (PImax, PEmax) and pulmonary function tests (VC, FVC, and less so maximal voluntary ventilation -MVV) to assess respiratory muscles weakness [207, 208].

1.4.6 Maximum Voluntary Ventilation (MVV)

MVV ($l \cdot min^{-1}$) is produced voluntarily in 12 to 15 s during standard pulmonary function testing as described in the ATS/ERS statement [200] or estimated as forced-expiratory volume in 1 s (FEV_1) × 35 or 40 [19]. During the MVV manoeuvre the breathing rate should be between 70 and 110 breaths$\cdot min^{-1}$ using a tidal volume of approximately 50% FVC [201].

Mechanical aspects of chest wall and lung tissue can affect the MVV value other than respiratory muscle function (i.e., stiff chest wall or lung-restrictive components, and obstruction of airways) [206]. Further, MVV has poor specificity, is highly effort dependent, and uncomfortable for patients to perform [201]. MVV depends on motivation and can be tiring for some patients [19]. MVV is no longer recommended in the evaluation and management of patients with respiratory muscle weakness or for inspiratory and expiratory respiratory muscle endurance testing [19, 201].

1.5 Evoked manoeuvres

Measurements of trandiaphragmatic pressure elicited by electrical of magnetic stimulation of the phrenic nerves or $P_{di,tw}$ can be used to evaluate diaphragmatic contractility. When the glottis is kept open, swings in P_{oes} may be evident in the upper airway (i.e. the mouth or, if the patient is intubated, the endotracheal tube). Stimulation of the thoracic nerve roots with simultaneous measurement of P_{ga} is used to evaluate the main expiratory muscles, i.e. the abdominal muscles.
With respect to pressure measurements, electrical stimulation of phrenic nerves is insufficiently reliable and has too much limitations [209]. Nowadays, phrenic nerve stimulation is usually done using magnetic stimulators unless patients have pacemakers or other implanted electronic devices. In these patients electrical stimulation is preferred [210].
Several important factors need consideration since they may change the amplitude of $P_{di,tw}$

i. Nerve stimulation must be supramaximal to be reliable and needs special consideration in obesity (insulation) or with muscle activity (the activation threshold of motor nerve axons increases after minutes of repetitive use [211, 212]). Confirming supramaximality requires accurate measurement of the electromyographic signal, or the amplitude of $P_{di,tw}$ elicited by the stimulation. Supramaximal stimulation of the thoracic nerve roots is difficult to obtain using currently available technologies.
ii. Prior contractile activity may lead to a 'falsely high' $P_{di,tw}$ through a phenomenon known as twitch potentiation [213]. For this reason, stimuli are ideally done after a minimum rest of 10 min, and for many research studies after 20 min. If changes immediately after an activity such as exercise are of interest to avoid recovery of muscle fatigue [214], one option is to assess potentiated muscle contractility both before and after the exercise. This, however, bears the risk of 'incomplete' potentiation if the volitional maximal inspiratory contractions used to elicit potentiation are in fact submaximal, as is often the case even for trained subjects [215].
iii. A change in lung volume affects diaphragm length and pressures, e.g. hyperinflation leads to diaphragm shortening which reduces $P_{di,tw}$ [216], mainly through a reduction in the oesophageal pressure twitch ($P_{oes,tw}$) [217]. Thus, to obtain reproducible measurements, the person should be relaxed at consistent end-expiratory lung volume. Also, interpreting changes over time should be done with caution if a patient has received

interventions which might change lung volume [218]. Typically a change of 0.3 cmH_2O/unit % VC may be considered a reasonable correction factor [219].

iv. A choice of magnetic stimulation techniques for phrenic nerves is available, including cervical stimulation [220], anterior mediastinal stimulation [221], and uni- [222] or bilateral anterior simulation [222]. Most specialist units prefer the latter as it more reliably provides supramaximal stimulation. Magnetic phrenic nerve stimuli may also be applied as single [145] or paired [223] stimuli of different stimulation frequency, the latter having the advantage in some research environments that both lung volume and fatigue can affect the magnitude of $P_{di,tw}$ elicited as a function of interstimulus interval [219, 223]

A non-invasive estimate of $P_{di,tw}$, may be obtained by measuring pressure change in the upper airway or mouth ($P_{mo,tw}$), reflecting $P_{oes,tw}$ quite closely [42, 224-226]. Whilst this obviates the need to pass oesophageal and gastric balloons, most investigators have found it necessary to make a small inspiratory or expiratory effort to ensure the glottis is open [225, 227], and this may be conveniently done using an electronically triggered valve to close the airway briefly during stimulation [224, 228]. In interpreting the result, it should be recalled that the overall signal is smaller (typically $P_{oes,tw}$ is around 50% of $P_{di,tw}$) and 'noise' (e.g. due to cardiac contraction) is constant. Furthermore, $P_{oes,tw}$ (and therefore $P_{mo,tw}$) is more influenced by lung volume than $P_{di,tw}$ [219].

In several diseases, muscle weakness is seen with values below the cut-off value of 18 cmH_2O previously suggested for diagnosis of diaphragm weakness [54], in particular in more severe stages of disease.

In the context of exercise, a drop in $P_{di,tw}$ at the end of exhaustive exercise, showing diaphragm fatigue (generally defined as $\geq$10-15% reduction in $P_{di,tw}$), is seen in about 70% of healthy subjects, while in disease, diaphragm fatigue was reported in some (COPD [229], low back pain [230]) but not in other (COPD [231], CF [232], heart failure -HF- [233], interstitial lung disease -ILD- [234]) studies suggesting that other factors may be equally or more important in limiting performance. Although pre-exercise respiratory muscle fatigue impairs exercise performance [235, 236], development of low-frequency fatigue is not directly related to performance in health [237] and it does not predict outcomes in the clinical arena [106]. Abdominal muscle contractility is assessed mainly in the context of development of expiratory muscle fatigue

during exercise. Resting gastric twitch pressure ($P_{ga,tw}$) values have a slightly higher variability (CV 9-10%) [238] than is known for $P_{di,tw}$ (6%) [238]. $P_{ga,tw}$ decreases by up to 20% after expiratory muscle activity such as volitional heavy breathing [144, 238] or exercise [239] in the healthy. In patients, results are less uniform with some studies showing a $P_{ga,tw}$ decrease after exercise (ILD [234]) while others do not (COPD [229]).

Paediatrics. A straightforward and non-volitional way to test the strength of the diaphragm is to measure $P_{di,tw}$ [71, 240-244]. Magnetic stimulation most easily stimulates large nerve fibres so there comes a point where in small humans (i.e. children and neonates) it may become hard to ensure supramaximality. There are of course often aesthetic objections from parent or practitioners to nerve stimulation in young children though this is possible and acceptable in experienced hands (table S14).

Normal values are available for neonates [242], infants [240] and children [245].

$P_{di,tw}$ has been shown to be decreased in neonates with diaphragmatic paralysis [243], in children with NMD and diaphragmatic weakness [71].

$P_{di,tw}$ has been measured in infants with abdominal wall defects and congenital diaphragmatic hernia [246, 247] and in children after liver transplantation [244].

Lung hyperinflation and a poor nutritional status were associated with low $P_{di,tw}$ values in children with CF [241].

ICU. In critically ill, intubated patients, it is possible to assess diaphragmatic contractility measuring $P_{di,tw}$ elicited by electrical or magnetic stimulation of the phrenic nerves [248]. The use of electrical stimulation in intubated patients, however, is fraught with technical limitations and, for all practical purposes, it has been abandoned [248].

Glottic closure cannot arise in a patient with an endotracheal tube. Accordingly, in ventilated patients, there is a good correlation between twitch airway pressure ($P_{ao,tw}$) and $P_{di,tw}$ [42, 249]. The limits of agreement between the two measurements, however, are wide, meaning that a particular $P_{ao,tw}$ is a poor predictor of $P_{di,tw}$ [42, 249]. Yet, measurements of $P_{ao,tw}$ are extremely reproducibleand, therefore, can be used to track changes in diaphragmatic contractility in ventilated patients [42].

Measurements of $P_{ao,tw}$ and $P_{di,tw}$ elicited by magnetic stimulation of the phrenic nerves have given major insights on diaphragmatic contractility in the critical care setting. These include the objective demonstration that intubated patients cannot maximally recruit the diaphragm during

"maximal" voluntary inspiratory manoeuvres, that weaning failure is not caused by diaphragmatic fatigue and that patients who require mechanical ventilation develop profound diaphragmatic weakness [106, 250-253].

Experimental evidence suggests that, in critically ill patients, acquired diaphragm weakness variably defined as a $P_{ao,tw} < 11$ cmH_2O [250] or $P_{di,tw} \leq 10$ cmH_2O [253] might be associated with excess morbidity and mortality [250-253]. First, Dres et al. [251] and Supinski et al. [253] reported that the mean duration of mechanical ventilation remaining at the weaning phase is about four to six days for patients without diaphragmatic weakness and seven to twelve days for patients with diaphragmatic weakness. These results contrast with those of Laghi et al. [106] and Demoule et al. [250] and Jung et al. [252] who reported that weaning outcome [106, 252] and duration of mechanical ventilation [250] were not associated with diaphragmatic weakness. Of note, the threshold of $P_{ao,tw}$ that optimally predicts weaning failure seems lower than the threshold defining diaphragm weakness (7 cmH_2O versus 11 cmH_2O, [254]). Second, mortality ranges from 7% to 16% for patients without weakness and it is nearly 50% for patients with diaphragmatic weakness [250, 253]. Third, in mechanically ventilated patients, diaphragm weakness is a far stronger predictor of ICU mortality than comorbidity index, extent of organ failure (including severity of lung functional abnormalities), age, gender and steroid use [255]. Whether diaphragmatic weakness is marker of disease severity or it is causally related to worse outcomes in critically ill patients remains to be determined [256].

1.6 Respiratory muscle endurance testing

Inspiratory muscle endurance to an external load

External loading protocols are frequently used to measure respiratory muscle endurance. The load is usually incremental or constant, and is to be sustained until symptom limitation – endurance time or Tlim [257]. The load itself can be (1) a flow resistive, in which the pressure required of the muscles is dependent on the flow rate across the resistance; (2) a threshold load in which a finite pressure is required to open a valve that allows flow – i.e., the pressure at the airway opening generated by the respiratory muscles is relatively constant and independent of both volume and flow; or (3) a hybrid between flow resistive loads and threshold loading (tapered flow resistive loading). During the latter type of loading, an initial threshold load has to be overcome. Then, the pressure is flow-dependently tapered down to accommodate length

tension characteristics of the respiratory muscle. The result is an iso-flow (i.e. iso-velocity) contraction.

Inspiratory endurance tests often used in recent years include threshold loading [257, 258], and tapered flow resistive loading [259]. Since muscle performance is influenced by breathing pattern (both timing components and inspiratory volumes) it has been recommended to control these parameters during testing [257, 260]. Such control of breathing pattern adds complexity to the procedure. This is why measurements of inspiratory muscle endurance have been regarded, until recently, to be beyond the scope of routine clinical practice [261]. Some investigators argue that the need to control breathing pattern during endurance testing might be overcome by recording mouth pressure, flow and inspiratory volumes during the test [19]. External work performed during the test (integrated from inspiratory volumes and mouth pressure) has been put forward as the most important determinant of Tlim, regardless of the pattern of breathing [19]. With the introduction of new handheld devices that record continuously flow, volume, and pressure responses, it is now easier to monitor breathing pattern and external WOB during endurance tests [259, 262]. This has opened the possibility to implement well controlled endurance tests into standard clinical evaluation of different interventions.

Generally speaking, inspiratory muscle endurance tests to external loads require development of large pressures swing and, concurrently, ventilatory requirements remain unchanged or modestly increase [19]. Such conditions are similar to those of weight lifting, with relatively low velocities of shortening. In contrast, hyperpnoea endurance tests (see below) are more like activities of running with large velocities of shortening and participation by a large number of synergic muscle groups.

The incremental threshold loading technique was first described in the late 1980s [263, 264]. In concept, it was designed to resemble a Bruce protocol, which is popular for incremental, whole body exercise testing. Before the test, the subject's PImax is measured by standard techniques. Then he/she is instructed to inhale against an external load of approximately 30–40% of PImax. Every 1 to 2 min, the load is increased by approximately 5–10% of PImax, until the load cannot be tolerated. The maximum inspiratory mouth pressure sustained for the full 1-min or 2-min interval is considered the peak pressure (Ppeak).

The incremental test holds strong appeal as a measure of inspiratory muscle function because it is well tolerated and provides a clear outcome variable. Moreover, it is sensitive to disease states

and clinical treatment [265, 266]. Unfortunately, the extent to which the results from incremental tests represent endurance or strength is not entirely clear. Strictly speaking, it is not a test that has been proven to be a direct measure of endurance, just as an incremental exercise test is not generally considered an endurance test. An interesting observation during incremental tests is that peak external work reaches its highest value somewhere during the first stages of the test and then falls precipitously before attaining Ppeak, while oxygen consumption and pressure development are still rising [263]. This means that efficiency and ability to generate inspiratory flow and inspiratory volume are falling during the final stages of the test. Peak external work performed during the test may be a useful measurement of the dynamic capacity of the muscles of the chest wall to perform external work. This value might be as important clinically as the measure of endurance by Ppeak.

In contrast, during a constant load test patients are asked to breathe against a sub maximal inspiratory load until Tlim. It has recently been shown that if inspiratory loads are selected that result in a Tlim of less than 7 min at baseline, post-intervention test durations can be limited to 15 min without important ceiling effects [257, 259]. Data from a recent multicentre RCT demonstrated a large effect size in endurance time (0.77) measured with this constant load protocol in response to inspiratory muscle training (figure S2) [267]. Longer baseline Tlim data have previously been shown to result in ceiling effects when the post-test was limited to 15 min [257]. This lowered effect sizes of a constant load test (small to medium effect size of 0.44) in comparison to an incremental test (medium to large effect size of 0.68) in response to inspiratory muscle training [257]. Based on these data it seems reasonable to choose an external load that limits baseline test duration to 5-10 min in order to subsequently be able to limit post-test duration to 15-20 min without important ceiling effects. Standardized breathing instructions should be provided and post intervention tests should be repeated using an identical load. Improvements in Tlim and total external work performed during the tests can be recorded as main outcomes of the test.

Typical changes in breathing parameters observed during breathing against external loads after training interventions include the following: patients are able to generate higher inspiratory flow rates against equivalent external loads resulting in shorter inspiratory time, as well as being able to increase inspiratory volume and work per breath [262]. While shortening inspiratory time could be interpreted as a breathing pattern adopted to reduce the load on the muscles it also

reflects the ability of the muscle to perform faster contractions against high external resistances (i.e. improvements in muscle power). The increases in inspiratory volume and external work are also suggestive of a breathing pattern that increases load on the respiratory muscles.

Hyperpnoea endurance test

Hyperpnoea endurance tests consist in reproducing hyperpnoea as induced by intense physical exercise, without the addition of any inspiratory or expiratory load. Of the hyperpnoea endurance tests that address endurance of in- and expiratory muscles, the easiest to perform is the MVV since this test is of brief duration where the naturally occurring hypocapnia can be tolerated while all other tests need specific equipment assuring normocapnia.

Maximum voluntary ventilation (MVV). For assessment of MVV, subjects are asked to breathe at a maximal possible speed and depth, usually for 12 s (sometimes 10 s or 15 s), and the value is then given in $l \cdot min^{-1}$. From a physiological point of view a 12-second test is, however, far too short to assess intramuscular processes associated with endurance.

Improvements to MVV reported in the context of respiratory or whole-body exercise training are likely to include a large neuro-muscular, task-learning component. For example, respiratory muscle training shown to improve MVV by 14% [268] to 184% [269]. Furthermore, the main determinants of MVV for athletes were identified to be gender, FEV1 and PEF [270] while the amount of physical training did not contribute to MVV.

Maximal sustainable ventilation (MSV). Testing MSV, i.e. the maximal ventilation that can be sustained for an extended period of time, is a more meaningful measure respiratory muscle endurance than MVV. Unfortunately, there is no established protocol on how to perform MSV testing. Theoretically, several tests with decreasing levels of ventilation should be performed up to exhaustion to determine an intensity that could be sustained for an ‘infinite duration’, in analogy to critical power for whole-body endurance. For a detailed description of the methodologies used, the reader is referred to the previous ATS/ERS statement [19]. In brief, after assessment of MVV [271], subjects are asked to breathe at 70-90% MVV with visual feedback and adjustment of the intensity in the first minutes such that a maximal ventilatory level can be sustained for 10-15 min [272-274].

Tests based on prolonged hyperpnoea require special equipment to provide normocapnic conditions and visual feedback; of note, different resistances of these systems can affect test results [268, 273-275].

Using MSV testing, investigators have reported decreased respiratory muscle endurance in patients with heart failure [276] compared to healthy subject. In addition, when conducting MSV testing using the same protocol and equipment, it is possible to document improvements in respiratory muscle endurance following hyperpnoea training in healthy subjects [277, 278], in patients with chronic heart failure [279] and in patients with COPD [275]. Finally, improvements in MSV have been reported in healthy subjects at high altitude [280].

When compared to changes in MVV after respiratory muscle training, the size effect of changes in the MSV is larger than that of MVV [281].

Maximal incremental hyperpnoea. Loading the respiratory muscles by hyperpnoea of stepwise incremental intensity is gaining popularity. Most commonly, subjects are instructed to breathe at 20% MVV for 3 min and then to increase ventilation by 10% MVV every 3 min up to the highest %MVV that can be sustained for 3 min [19]. Ventilatory levels achieved in this test have been compared to levels in the traditional MSV-test and have been found to be of similar size [276, 279]. After hyperpnoea training, respiratory muscle endurance assessed with maximal incremental hyperpnoea improves by 52% in obese subjects (range ~19 to ~28 min) [282] and by 12% in spinal cord injury patients (range from ~15 min to ~18 min) [283]. Maximal incremental hyperpnoea requires special equipment is required yet, in recent years, commercial devices have become available and normal values have been established in a large study of 160 healthy subjects from young to old age [284].

Maximal constant-load hyperpnoea. Respiratory muscle endurance can be tested with constant-load hyperpnoea ranging from 40% MVV in spinal cord injured patients to 70% MVV in healthy individuals. Large inter-subjects differences, even in healthy subjects, can lead to very different Tlim for a given level of constant-load hyperpnoea. Improvements in Tlim following hyperpnoea training has been reported to increase by 168-630% in healthy subjects [269, 285-287], by 65-250% in patients with COPD [288, 289], by 103% in CF patients [290], by 256% in spinal cord injured patients [291], and by 265% in obese subjects [292]. Figure S3 shows the improvement in Tlim during constant-load hyperpnoea following respiratory muscle endurance training based on a meta-analysis of nine previous studies

Paediatrics. Endurance indexes are rarely calculated on a routine basis in children despite the fact that they may be informative. Diaphragmatic and oesophageal tension-time index decline significantly as boys with Duchenne muscular dystrophy get older [34].

2. Respiratory muscle neurophysiology

The respiratory muscles contract phasically throughout life to maintain ventilation. Their precise neural control is important for co-ordinated activity of 'pump' muscles that generate intrathoracic pressures and 'valve' muscles that maintain airway patency (figure 4).

During resting breathing, rhythmic inputs that arise from pacemaker cells in the medulla [293] are transmitted to respiratory motoneurones in the spinal cord. This automatic control for ventilation is sensitive to increased carbon dioxide levels, for example during exercise. Additional inputs arising from cortical networks including motor and premotor areas [294] also act on respiratory motoneurones, for example, via corticospinal pathways.

Respiratory muscle neurophysiological testing can be achieved with the use of (i) EMG to measure the output of the respiratory motoneurones, (ii) electroencephalography (EEG), which tests the involvement of motor and premotor areas and (iii) transcranial magnetic stimulation (TMS) which assesses the neural pathways to the respiratory muscles.

2.1 Electromyography (EMG)

The validity of respiratory EMG recordings depends on the (i) ability of the EMG technique to accurately reflect the activity in the target respiratory muscle and (ii) that the activity recorded accurately reflects the neural control of the respiratory muscles.

Respiratory muscle EMGs are usually contaminated with electrocardiogram (ECG) which can be eliminated with the gating technique [295, 296] and, less often, with other techniques including subtraction of the ECG template from EMG [296]. Respiratory muscle EMGs, especially with surface electrodes, are also subject to power line and electro-magnetic interference particularly in the ICU [19, 297, 298]. A common problem for surface recordings of respiratory muscles EMGs is signal contamination from adjacent muscles or artefactual effects due to changes in lung volume or posture [19]. Diaphragm EMG recorded via a multi-pair oesophageal electrode is less

susceptible to lung volume and posture artefacts than diaphragm EMG recorded via surface electrodes [299, 300]. Intramuscular recordings are much less susceptible, but not immune [301], to contamination from neighbouring muscles and thus are superior to surface recordings to reflect respiratory neural drive. A major benefit of the single motor unit technique is that recordings do not need to be normalized to maximal efforts.

Respiratory EMG can be used to monitor neuromuscular function and changes in respiratory motor output after interventions such as CO_2 inhalation, drugs, exercise and change in respiratory load. There is linear relationship between $P_{di,tw}$ and compound muscle action potential (CMAP) recorded from oesophageal or surface electrodes [302]. Quantification of diaphragm EMG with a multi-pair oesophageal electrode [302, 303] is a superior measure of respiratory motor output than pressure measurements, as the latter, can be affected by muscle length changes and, in the case of the P_{ao} signal, by airway resistance [108]. Given that surface and oesophageal respiratory EMG values change with electrode placement and subject dimensions, they are usually standardized to a maximal value (see table 4), a reasonable strategy if subjects can achieve maximal or near maximal voluntary muscle recruitment [e.g. 304]. For intramuscular recordings when assessing respiratory motor output using the single motor unit technique, the caveats include regional differences in activity, for example between the dorsal and ventral regions of the dorsal external intercostal muscle [305] and that muscle force is achieved via both rate coding and motor unit recruitment and the balance between these two processes of increasing force can vary between respiratory muscles [306]. For evoked responses, normal values of phrenic nerve conduction time are well established with both electrical and magnetic stimulation of the phrenic nerve [19, 297, 307, 308].

Tables S10 and S11 summarise the results for studies that have evaluated peak EMG (typically standardised to a maximal value) during breathing at rest and during exercise in cardiorespiratory disorders. The amplitude of compound muscle action potentials of the diaphragm elicited by phrenic nerve stimulation are usually reduced in most NMDs (e.g. motoneurone disease), latencies, however, are prolonged in only some NMDs (e.g., demyelination) [see 302]. Spectral analysis of respiratory EMG to detect respiratory muscle fatigue [19, 297, 309] is usually limited to research rather than clinical practice.

ICU. In the ICU, recording of the electrical activity of the crural diaphragm (EAdi) using a dedicated nasogastric tube with EMG electrodes has greatly facilitated bedside monitoring of

diaphragm activity in paediatric [310] and adult patients [311]. The ratio of actual EAdi to maximum EAdi (EAdi,max) can be used to estimate the patient's effort to breathe [312]. EAdi is a promising tool to monitor diaphragm activity especially during weaning from mechanical ventilation [313]. Of note, EAdi,max varies widely between subjects so that there is no clear reference range for EAdi. Neurally adjusted ventilatory assist (NAVA), is a novel ventilator mode that synchronizes ventilation to EAdi [314, 315].

2.3 Transcranial magnetic stimulation (TMS)

Depending on the selected coil, current amplitude, duration, and direction, a focal or non-focal magnetic field will depolarize neurons or their axons. TMS can be applied with different paradigms (i.e. single-pulse, paired-pulse and the neuroplasticity-inducing repetitive TMS (rTMS)) to obtain measures that explore distinct neurobiological and neurochemical processes (table 5).

TMS does not appear to cause long-term adverse neurological, cardiovascular, hormonal, motor, sensory, or cognitive effects in healthy subjects. Delivering a single-pulse (<1 Hz) of TMS to the brain is very safe [316] (table 5, table S12*)*.

The validity of TMS depends on the appropriate location of EMG electrodes and control of background muscle activity and noise. In the laboratory, single and paired-pulse TMS have been used to study the diaphragm's corticospinal pathways in healthy subjects. Insights into the role of the cerebral control of breathing at rest, during exercise and inspiratory loading have been obtained using single-pulse TMS [317, 318] and by repetitive pulse TMS [319, 320]. Clinically, TMS is used to document respiratory muscle involvement in various disease states, e.g. extention of diaphragm's response to TMS on the paralyzed side in stroke patients [321], abnormalities of diaphragm's response to TMS in patients with multiple sclerosis [322] or ALS [323] (see also table S13).

In patients with stroke, respiratory muscle function, assessed by measuring PEmax induced by TMS, represents a simple bedside technique to assess airway clearance and evaluate aspiration risk [324].

Regarding plasticity-related TMS measures, there are conflicting results concerning motor evoked potential (MEP) amplitude changes (increase in genioglossus -GG- or decrease in submental muscle) in response to rTMS trains [325, 326].

Widespread disease-related alteration of corticomotor excitability (as documented by changes in a hand muscle first dorsal interosseous) have been documented in cardiorespiratory diseases including OSAS [327] and COPD [328].

In OSAS, a reduction of cortical excitability (i.e. MEP amplitude and latency, cortical silent period (CSP) duration) recorded in first dorsal interosseous was related to the metabolic changes induced by OSAS [329, 330]. Although some TMS studies indicate an increase in cortical-motoneuronal excitability in some upper airway and respiratory muscles [331, 332] [325, 326], no difference or a wide-spread defect in the conductivity or excitability of the corticomotor system was documented in hand muscles [329, 330, 333-335] in OSAS patients during wakefulness. Regarding plasticity-related TMS measures, there are conflicting results concerning MEP amplitude changes (increase in GG or decrease in submental muscle) in response to rTMS trains [336, 337], whereas other studies reported a widespread lack of response in first dorsal interosseous MEPs characteristics in OSAS patients after the application of high-frequency rTMS [335] or continuous theta-burst stimulation [338].

During acute exacerbation of COPD, motor threshold (MT) and central motor conduction time (CMCT) recorded in first dorsal interosseous was increased compared to controls [339], with conflicting results in CSP duration [328, 339]. Some TMS parameters recorded in first dorsal interosseous correlated with variables of pulmonary function and arterial blood gases [339]. Intracortical inhibition (ICI) of first dorsal interosseous was less pronounced in the acute-exacerbation COPD group compared to controls [328].

Effects of some interventions on TMS outcomes are summarized in table S13. In awake healthy or OSAS subjects, hyperoxic CO_2-induced hyperventilation was associated with heightened chest wall/diaphragm corticomotor activation, as evidenced by decreased motor threshold and increased MEP amplitude, without modulating GG or *abductor pollicis brevis* MEP responses or scalene CSP duration [340-343]. Inspiratory resistive breathing facilitates the diaphragm response to TMS while it does not increase the automatic drive to breathe [344]. In healthy subjects, non-invasive ventilation can depress diaphragm motor cortex excitability [345]; whereas in COPD patients, an acute effect of non-invasive ventilation was observed with a

reduction of diaphragm MEP amplitude, with no effect on ICF or ICI, implying an effect of neuromechanical feedback at brainstem or spinal level [346]. In acute-exacerbation COPD patients, 3 to 4 months of O_2 therapy could normalize motor threshold (resting and active) and ICI impairment and prolong CSP duration in first dorsal interosseous [328].

3. Respiratory muscle imaging

3.1 Ultrasound

Paediatrics. In children, diaphragmatic movement can be assessed by either fluoroscopy or ultrasound. The latter is gaining popularity as it does not require radiation and its bedside availability [347]. Normal, impaired, missing, or even paradoxical diaphragmatic motion can be visualized in real time by ultrasound, and the documentation can be achieved using M-mode [348]. For neonates and infants, a subxiphoid transverse view is preferred as both right and left hemi-diaphragms can be seen at the same time and it is easier to evaluate a paradoxical movement. For older children, each hemi-diaphragm is evaluated separately with either a (more lateral) subcostal or intercostal approach. Ultrasound is also used to evaluate lobulated-shaped hemi-diaphragms [348, 349] to assess whether the finding results from focal diaphragmatic eventration, a potential diaphragmatic hernia, or a rare thoracic kidney/spleen. Most cases of diaphragmatic hernia can be diagnosed by plain radiographs. But when the herniated viscera do not contain air, ultrasound can be used to show herniated fluid-filled bowel loops or herniated liver with the “waist” sign through the diaphragmatic defect

3.2 Optoelectronic plethysmography (OEP)

OEP is an established technique that allows measuring the variations of the volume of the chest wall and its compartments during breathing [350, 351].

Contraction of the diaphragm expands the rib cage (RCa) compartment and the abdominal (AB) compartment. Rib cage muscles, including the intercostals, the parasternals, the scalenes and the neck muscles, mostly act on the pulmonary rib cage compartment (RCp) and are both inspiratory and expiratory. The abdominal muscles act on RCa and AB and are expiratory. In disease states,

when each muscle group contracts alone or the contraction of one group is predominant compared to the contraction of other groups result in asynchronies between compartments or complete "paradoxical" motion. These abnormal movements can be quantified by discernible phase shifts between compartments (V_{RCp}, V_{RCa}, and V_{AB}) [352-354].

The accuracy of OEP has been evaluated by comparing chest wall volume with lung volume variations measured by a spirometer or integrating a flow measurement at the airway opening. These assessment have been performed in a variety of conditions including newborns at rest [355] (accuracy −2.0%), quiet breathing, slow VC manoeuvres [350], incremental exercise on a cycle ergometer [356] (with a coefficient of variation of the two signals lower than 4%), during cycling exercise [357] (2.4±3.9%), in patients with respiratory muscle dysfunction [358]. Intra-observer and inter-observer reliability was evaluated at rest and during exercise [359], with intraclass correlation coefficient values >0.75 and error values <10%. The possibility to track end-expiratory volume variations by OEP on a breath-by-breath basis has been evaluated during incremental exercise (compared with simultaneous measurements of IC [360], with a mean difference between equal to 7.0±5.8% or 35±24 ml) and in mechanically ventilated patients at different levels of external PEEP [361].

OEP has been extensively used to evaluate total and compartmental volume variations during exercise in patients with COPD. It was found that the patients with more severe COPD experienced dynamic hyperinflation during incremental exercise, but 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 [360, 362, 363], some having a progressive and significant increase in end-expiratory volume of the chest wall ("early hyperinflators") and other having an increase in end-expiratory volume only at higher levels of exercise ("late hyperinflators").

Three distinct patterns of breathing and chest wall volume changes to cope with chronic respiratory failure have been found in patients with severe COPD, interstitial pulmonary fibrosis, and CF [364].

OEP has been also used in the study of patients with several NMDs. In awake patients with Duchenne muscular dystrophy, abdominal motion during resting breathing while supine is an important indicator of the degree of respiratory muscle impairment, of disease progression and an early indicator of nocturnal hypoxemia [365]. A reduced abdominal contribution to VT during

resting breathing is also associated with inefficient cough [366]. In addition, a reduced abdominal contribution to VT is a specific and early marker of diaphragm weakness in adolescent and adult patients with Duchenne muscular dystrophy who present either no sign or only mild nocturnal oxygen desaturation [367]. Mild initial modifications of thoraco-abdominal motion have been described in Limb-girdle muscular dystrophy, Becker muscular dystrophy, facioscapulohumeral dystrophy [368] and in ALS [369]. A negative or reduced contribution of V_{RCp}, indicative of inspiratory ribcage muscle weakness, is a distinctive feature of spinal muscle atrophy type1 and type 2 since infancy [370].

4. Respiratory muscle structure, perfusion and metabolism

4.2 Oxygen cost of breathing

Oxygen cost of breathing (VO_{2RM}) is an index of the energy required for ventilation. During rest, respiratory muscles use 1-2% of the total body oxygen uptake (VO_2) resulting in an approximate VO_{2RM} of around 2.5 $ml \cdot min^{-1}$. During exercise, ventilation and the WOB increase in proportion to the metabolic demands [371]. VO_{2RM} during maximal exercise represents ≅10% of whole-body maximal oxygen uptake [372-374] or even >15% in endurance-trained men [372]. Oxygen cost of breathing of the respiratory muscles in humans is mostly measured using indirect methods by measuring ventilation and VO_2 at rest followed by an increase in ventilation (voluntarily, by CO_2 breathing or by the addition of dead space) [375]. By extrapolating the changes observed in VO_2 and ventilation, the oxygen cost of breathing is estimated [376]. However, different approaches were used in the past with considerable variability [377]. As ventilation rises, the WOB also increases. Using a wide range of ventilation values, the CV of the method ranges from 4.3 to 5.7% [378].

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Table S1. Summary of relative contraindications and the main reasons to avoid respiratory muscle testing

Contraindication	Reason to avoid respiratory muscle testing
Recent surgery (thoracic / abdominal / brain / ear, nose, throat)	Rupture site of injury, avoid pain, discomfort
Pneumothorax	Worsen pneumothorax, avoid discomfort and pain
Myocardial infarction	Induce further infarction leading to cardiac arrest
Ascending aortic aneurysm	Rupture of aneurysm, catastrophic/fatal event
Haemoptysis	Pulmonary emboli or myocardial infarction
Pulmonary embolism	Death, hypoxia leading to respiratory failure
Acute diarrhoea / stress incontinence	Discomfort, embarrassment, infection risk
Severe hypertension (systolic >200 mmHg, diastolic >120 mmHg)	Risk of blackout/collapse, rupture of cerebral blood vessels, etc.
Confused/demented patients	Tests are volitional and need full patient cooperation
Patient discomfort	Vomiting, diarrhoea, cold sores, common cold
Infection control issue	Contagious infections (norovirus, tuberculosis, flu)

Based on Cooper [379]

Table S2. Reference values for maximal inspiratory pressure (PImax) measurements performed at residual volume

Reference	**Study population**	**Reference values (equation),** cmH_2O	**LLN (Lower Limit Normality),** cmH_2O
Sclauser Pessoa et al. [380]	Based on 22 studies (n=840; 426 men, 414 women see Tables S7 and S8 for details) that measured PImax in accordance with 2002 ATS/ERS statement [19] (either flanged or tube mouthpiece)	See table S3	-
Rodrigues et al. [22]	Based on 6 most cited publications of reference values for PImax [32, 381-385]. 3 references providing higher normal values are recommended [381, 382, 385] (see below for details of three recommended studies).		See table S4
Bruschi et al. [382]	n=669 subjects (290 male / 379 female) from 18-70 years.	LnPImax = 4.02 – (0.26 x sex) – (0.004 x age) + (0.47 x body surface area)	
Neder et al. [385]	n=100 subjects (50 male / 50 female) from 20 to 80 years.	Male = 155 – (0.8 x age) Female = 110 – (0.49 x age)	
Black and Hyatt. [381]	n=120 subjects, (60 male / 60 female) from 20 to 74 years.	Male = 143 – (0.55 x age) Female = 104 – (0.51 x age)	
Evans et al. [386]	Based on 5 studies [383, 387-390] using 2002 ATS/ERS statement [19] and flanged mouthpiece	Male = 120 – (0.41 x age) Female = 108 – (0.61 x age)	Male = 62 – (0.15 x age) Females = 62 – (0.50 x age)

Table S3. Reference values for maximal inspiratory pressure (PImax) measurements obtained at residual volume for different age groups

	Men		Women	
Age group, years	**Studies, n/sample size, n**	**PImax, cmH_2O, mean (95% CI)**	**Studies, n/sample size, n**	**PImax, cmH_2O, mean (95% CI)**
18–29	6/96	128.0 (116.3–139.5)	6/92	97.0 (88.6–105.4)
30–39	6/69	128.5 (118.3–138.7)	6/66	89.0 (84.5–93.5)
40–49	6/72	117.1 (104.9–129.2)	6/71	92.9 (78.4–107.4)
50–59	5/61	108.1 (98.7–117.6)	5/60	79.7 (74.9–84.9)
60–69	5/65	92.7 (84.6–100.8)	5/66	75.1 (67.3–82.9)
70–83	5/63	76.2 (66.1–86.4)	5/59	65.3 (57.8–72.7)

From Sclauser Pessoa et al. [380]

Table S4. Absolute maximal inspiratory pressure (PImax) values obtained at residual volume associated with "higher" likelihood of inspiratory muscle weakness, by sex and age

Age (yrs)	PImax (cmH_2O)	
	Men*	Women+
< 40	63	58
40-60	55	50
61-80	47	43
> 80	42	38

* n = 164 (< 40 y), 302 (40-60 y), 365 (61-80 y), and 35 (> 80 y). + n = 140 (< 40 y), 293 (40-60 y), 387 (61-80 y), and 43 (> 80 y). From Rodrigues et al. [22]

Table S5. Reference values for maximal expiratory pressure (PEmax) measurements performed at total lung capacity

Reference	**Study population**	**Reference values (equation),** cmH_2O	**LLN (Lower Limit Normality),** cmH_2O
Evans et al. [386]	Based on 4 studies [32, 203, 383, 385] using 2002 ATS/ERS statement [19] and flanged mouthpiece	Male = 174 – (0.83 x age) Female = 131 – (0.86 x age)	Male = 117 – (0.83 x age) Females = 95 – (0.57 x age)
Neder et al. [385]	n=100 subjects (50 male / 50 female) from 20 to 80 years. Flanged mouthpiece.	Male = 165 – (0.81 x age) Female = 115 – (0.61 x age)	
Black and Hyatt. [381]	n=120 subjects, (60 male / 60 female) from 20 to 74 years. Tube mouthpiece.	Male = 268 – (1.03 x age) Female = 170 – (0.53 x age)	
Bruschi et al. [382]	n=669 subjects (290 male / 379 female) from 18-70 years. Tube mouthpiece.	LnPEmax = 4.54 – (0.35 x sex) – (0.003 x age) + (0.24 x body surface area)	

Table S6. Reference normal ranges for maximal expiratory pressure (PEmax) measurements performed at total lung capacity

Reference	Numbers		PEmax (cmH_2O)		Mouthpiece
	Male	**Female**	**Male**	**Female**	
Ringqvist et al. [391]	106	94	239 ± 46	164 ± 30	Tube
Black and Hyatt [381]	60	60	233 ± 42	149 ± 27	Tube
Rochester and Arora [392]	80	121	215 ± 45	138 ± 68	Tube
Bruschi et al. [382]	290	379	140 ± 30	96 ± 20	Tube
Enright et al. [383]	244	292	175 ± 46	118 ± 37	Flanged
Leech et al. [393]	325	50	154 ± 82	94 ± 33	Flanged
Wilson et al. [32]	80	480	147 ± 34	93 ± 17	Flanged
Neder et al. [385]	50	87	141 ± 22	100 ± 11	Flanged
Vincken et al. [203]	46	60	140 ± 38	89 ± 24	Flanged

Table adapted from previous 2002 ATS/ERS statement [19] adding data from studies included in review from Evans et al. [386]

Table S7. Characteristics of participants from studies included in the review from Sclauser Pessoa et al. (PImax n=22; PEmax n=17) [380]

Reference	Pressures	Age, years (range)	Height, cm (mean±SD)	Weight, kg (mean±SD)
Cook et al., [33]; n=32 (23M/9F)	PImax and PEmax	M: 18–64; F: 18–32	M: 179; F: 164	NR
Ringqvist et al. [391]; n=200	PImax and PEmax	18–83	Reported according to age	Reported according to age
Black and Hyatt [381]; n=120,	PImax and PEmax	20–74	NR	NR
Leech et al. [393]; n=595 (252M/343F)	PImax and PEmax	15–35	Reported according to age	Reported according to age
Wilson et al. [32]; n=135 (48M/87F)	PImax and PEmax	18–49 >50	M: 179±6; F: 163±7	M: 74.5±8.5; F: 61.4±9
Camelo et al. [394]; n=60 (30M/30F)	PImax and PEmax	20–49	M: 170±7.7; F: 160.2±6.2	M: 70.0±10.8; F: 56.0±9.1
Vincken et al. [203]; n=106 (46M/60F)	PImax and PEmax	16–79	M: 172±7; F: 160±7	M: 74±9; F: 59±10.0
McElvaney et al. [395]; n=104	PImax and PEmax	>55	M: 174±7; F: 161±6	M: 107±10; F: 112±12
Bruschi et al. [382]; n=669	PImax and PEmax	18–70	NR	NR
Enright et al. [383]; n=2871	PImax and PEmax	>65	M: 173.2±6.59; F: 158.8±6.30	M: 79.5±11.6; F: 66.2±12.5
Enright et al. [396]; n=228 (112M/176F)	PImax and PEmax	>65	M: 171.25; F: 157	M: 79.7; F: 65.7
Johan et al. [397]; n=452 (277M/175F)	PImax and PEmax	20–80	M: 164–167*; F: 155–157*	M: 64.1–67.21; F: 53.6–
Pande et al. [398]; n=273 (153M/120F)	PImax	20–65	M: 165.6±6.1; F: 153.5±5.2	M: 62.5±11.7; F: 57.5±10.9
Harik-Khan et al. [384]; n=267	PImax	<40 – >75	M: 164.2±7.3; F: 177.6±6.6	M: 64.7±11.9; F: 81.7±13.3
Neder et al. [385]; n=100 (50M/50F)	PImax and PEmax	20–80	M: 168.4±6.2; F: 157.1±7.1	M: 73.8±10.7; F: 62.5±10.8
Hautmann et al. [387]; n=504	PImax	18–82	M: 176.9±6.82; F: 164.9±6.37	M: 78.3±10.9; F: 66.4±10.8
Wohlgemuth et al. [390]; n=252	PImax and PEmax	18–80	Reported according to age	Reported according to age
Windisch et al. [389]; n=490	PImax	10–90	M: 179.5±7.7; F: 166.4±7.0	M: 77.9±11.2; F: 66.0±10.9
Sachs et al. [399]; n=1755	PImax	45–84	M: 172; F: 158	M: 80.45; F: 68.18
Simões et al. [400]; n=140 (70M/70F)	PImax and PEmax	20–89	Reported according to age	Reported according to age
Costa et al. [401]; n=120 (60M/60F)	PImax and PEmax	20–80	Reported according to age	Reported according to age
Gopalakrishna et al. [402]; n=250	PImax and PEmax	20–70	M: 165.70±7.56; F: 155.99±5.81	M: 64.62±9.73; F:

NR, not reported; M, male; F, female

Table S8. Technical aspects in 22 studies that influence maximal respiratory pressures (PImax (n=22) from residual volume and PEmax (n=17) from total lung capacity) [380]

Reference	Mouthpiece	Small leak (size)	Pressure evaluated	Time of PImax	Trials, n	Criterion for stopping
Cook et al. [33]	Tube	NR	Peak (PImax and PEmax)	Without control	Min of 2	NR
Ringqvist et al. [391]	Tube	Yes (2 mm)	Peak (PImax and PEmax)	Max 1.5 s	Min of 5	Highest value
Black and Hyatt [381]	Tube	Yes (2 mm)	Peak (PImax and PEmax)	Min of 1 s	Min of 2	Highest value
Leech et al. [393]	NR	Yes (0.90 mm)	Peak (PImax and PEmax)	NR	Max of 3	Highest value
Wilson et al. [32]	Flanged	Yes, size NR	Peak (PImax and PEmax)	Min of 1 s	Min of 3	2 identical readings
Camelo et al. [394]	Tube	Yes (2 mm)	Peak (PImax and PEmax)	Min of 1 s	Min of 4	Highest value
Vincken et al. [203]	Flanged	Yes (1.27 mm)	Plateau (PImax and PEmax)	Min of 1 s	Min of 4	Highest 2 values within 5% difference
McElvaney et al. [395]	Tube	Yes (0.6 mm)	Peak (PImax and PEmax)	Min of 1s	Min of 3	Highest 3 values within 5% difference
Bruschi et al. [382]	Tube	Yes (1.06 mm)	Peak (PImax and PEmax)	Min of 1 s	Min of 5	Highest value
Enright et al. [383]	Tube	Yes (1 mm)	Peak (PImax and PEmax)	2 s	3–5	Highest 2 values within 10% difference
Enright et al. [396]	Tube	Yes (1 mm)	Peak (PImax and PEmax)	2 s	5	Highest 2 values within 10% difference
Johan et al. [397]	Flanged	Yes, size NR	Peak (PImax and PEmax)	Min of 1 s	3–5	Highest value of 3 similar trials
Pande et al. [398]	NR	Yes (1.27 mm)	Peak (PImax)	Min of 2 s	NR	Highest value
Harik-Khan et al. [384]	Tube	Yes (1 mm)	Peak (PImax)	2 s	Max of 5	Highest 2 values within 10% difference
Neder et al. [385]	Flanged	Yes, size NR	Peak (PImax and PEmax)	Min of 1 s	3–5	Highest value. <10% of 3 trials
Hautmann et al. [387]	NR	Yes, size NR	Plateau (PImax)	Min of 2 s	Min of 7	Highest value
Wohlgemuth et al. [390]	Face mask	Yes (2 mm)	Peak (PImax and PEmax)	Min of 1 s	Min of 3	Highest value varying 5%
Windisch et al. [389]	Flanged	Yes (2 mm)	Peak and plateau (PImax)	Min of 1 s	Min of 7	Highest 2 values within 10% difference
Sachs et al. [399]	Tube	NR	Plateau (PImax)	Min of 1 s	5	Highest 2 values within 10% difference
Simões et al. [400]	Tube	Yes (2 mm)	Plateau (PImax and PEmax)	About 1 s	Min of 3	Highest value <10% of all trials
Costa et al. [401]	NR	Yes (2 mm)	Peak (PImax and PEmax)	Min of 1 s	Min of 3	Highest value <10% of 2 trials
Gopalakrishna et al. [402]	NR	NR	Peak (PImax and PEmax)	Min of 1 s	Min of 3	Highest 2 values within <10% difference

NR, nor reported

Table S9. Reference values maximal sniff nasal inspiratory pressure (SNIP)

Reference	**Study population**	**Reference values (equation),** cmH_2O	**LLN (Lower Limit Normality),** cmH_2O	**Mean LLN,** cmH_2O
Araujo et al. [55] Reference values for SNIP in healthy subjects in Brazil – multicentre study.	243 healthy individuals (20-80 years), Brazil	(Males) SNIP= -0.47(age) + 135.6 (Females) SNIIP = – 0.36(age) +110.1	(Males) = -0.47(age) +135.6 – 44.9 (Females) = – 0.36(age) +110.1 – 30.5	(males) = 69.2 (females) = 61.9
Kamide et al. [56] SNIP in healthy Japanese subjects: mean values and LLN.	223 healthy Japanese (20-70y)	(males) SNIP = -0.67 (age) + 104.65 (females) SNIP = 2.31 (BMI) + 10.26	(males) LLN = -0.67 (age) + 104.65 – 43.78 (females) LLN = 2.31 (BMI) + 10.26 – 31.32	(males) = 32.9 (females) = 28.8
Uldry and Fitting [67] Maximal values of sniff nasal inspiratory pressure in healthy subjects.	168 healthy subjects (20-80 y), Europe	(males) SNIP = -0.42 (age) + 126.8 (females) SNIP = -0.22 (age) + 94.9	(males) LLN = -0.42(age) + 126.8 – 39.0 (females) LLN = -0.22 (age) + 94.9 – 28.0	
Huang et al. [66] SNIP does not decrease in elderly subjects.	119 healthy volunteers (18-69y), Taiwan	(males) SNIP = 21.10 + 1.24(body weight) (females) SNIP = 19.44 + 5.65(BMI) -2.06(Body Fat%)	(males) LLN = 21.10 + 1.24(body weight) – 50.16 (females) LLN = 19.44 + 5.65(BMI) -2.06(Body Fat%) – 33.81	(males) 60.33 cmH_2O (females) 52.05 cmH_2O
Stefanutti et al. [68] Sniff Nasal inspiratory pressure - Reference values in Caucasian Children.	180 healthy children (6-17y), Europe	(Boys) SNIP = 3.3(age) + 70 (Girls) 93 ± 23cmH_2O	(Boys) SNIP = 3.3(age) + 70 – 39.8 cmH_2O (Girls) SNIP = 93 ± 23 cmH_2O	

Table S10. Summary of prognostics, discriminative, clinical meaningful difference and evaluative information of endorsed EMG techniques at rest in cardiorespiratory disease.

Disease	Variable	Reference	Subject Characteristics	Protocol	Prognostic information	Discriminative	Minimal clinically important difference	Evaluative: pharmacological interventions	Evaluative: non-pharmacological interventions	Cautions
COPD	SMUdi SMUpara SMUscal	De Troyer et al. [403] Gandevia et al. [404]	Severe COPD patients Vs. Controls	Resting breathing			↑ peak discharge rate. In COPD, 79% of SMUdi discharged at >15Hz compared to < 5% of SMUdi for controls		Elevated discharge rate of di SMUs 'recovers' towards normal following LVRS [405]	
COPD	iEMGscal iEMGscm	De Troyer et al. [406]	Severe COPD	Resting breathing			Strong insp activity in scal, but minimal in SCM			
COPD	iEMGabdo	Ninane et al. [407]	COPD Vs. Controls	Resting breathing	Degree of activity related to airflow obstruction (i.e. FEV1)		Exp activity in TA in COPD but not controls			
COPD	oesEMGdi %max	Jolley et al. [303]	COPD Vs Controls	Resting breathing	Degree of activity related to airflow obstruction (i.e. FEV1 %pred, VC and IC)		↑EMGdi % max in COPD			
COPD	sEMGpara%	Murphy et	COPD	Resting		Discriminated				

	max	al. [408] Suh et al. [409]		breathing		between patients who deteriorated or improved. Discriminated between patients who were readmitted to hospital or not.		
Obesity	oesEMGdi %max	Steier et al. [410]	Obese subjects Versus Controls	Resting breathing in different postures	Degree of muscle activity thought to be related to PEEPi as PEEPi and EMGdi %max ↓ with CPAP		↑EMGdi % max in obese, worsened by supine posture (cf seated)	
Asthma	sEMGpara % max	Steier et al. [411]	Controlled asthmatics Versus Uncontrolled asthmatics Versus Controls	Resting breathing, awake and asleep	Low predictive value for AHI in sleep	↑EMGpara %max in uncontrolled asthma cf to controlled asthma.	↑EMGpara % max in wakefulness and sleep and more variable cf controls.	
CF	sEMGpara % max oesEMGdi %max	Reilly et al. [412]	Cystic Fibrosis Versus Controls	Resting breathing (and exercise)	sEMGpara %max and oesEMGdi %max related to degree of airway obstruction, hyperinflation, dynamic lung compliance		↑sEMGpara% max and ↑oesEMG% max cf to controls	
OSA	oesEMGdi %max	Steier et al. [413]	OSA versus Controls	Resting breathing			↑oesEMGdi % max cf to	Effect may be, in

		He et al. [414]		during sleep	controls	part, due to ↑BMI [410]
OSA	oesEMGdi %max	Xiao et al. [415]	OSA	Hypopnoeic and apnoeic events during sleep	No different in oesEMGdi % max for events with and without aroudal. ↑oesEMGdi % max at end of hyponoeic cf apnoeic events.	
ILD	oesEMGdi %max	Faisal et al. [155]	Mild-mod ILD versus COPD versus Controls	Resting breathing	↑oesEMGdi % max in ILD and COPD cf to controls	

COPD: chronic obstructive pulmonary disease; SMUs: single motor units; di: diaphragm; Para: parasternal intercostal muscles in the second space; Scal: scalene; SCM: sternocleidomastoid muscle; i: intramuscular; EMG: electromyography; multi: multiunit recordings; Abdo: abdominal muscles; LVRS: lung volume reduction surgery; inspiratory: inspiratory; exp: expiratory; TA: transversus abdominis; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; ILD: interstitial lung disease; oes: oesophageal; max: maximal.

Table S11. Prognostics, discriminative, clinical meaningful difference and evaluative information of EMG techniques tested during exercise in cardiorespiratory disease.

Disease	Variable	Reference	Subject Characteristics	Exercise protocol(s)	Prognostic information	Discriminative	Minimal clinically important difference	Evaluative: pharmacological interventions	Evaluative: non-pharmacological interventions	Cautions
COPD	oesEMGdi	Qin et al. [416]	Severe COPD versus control	Constant load treadmill						
COPD	oesEMGdi	Luo et al. [417]	Mod-severe COPD	Constant versus incremental treadmill			EMGdi similar at end of both types of exercise			
COPD	oesEMGdi %max	Guenette et al. [418]	Mild COPD versus Controls	Incremental cycle			↑EMGdi % max in COPD cf controls			
COPD	oesEMGdi %max	Jolley et al. [419]		Cycle to exhaustion		↑EMGdi in those patients who stopped because of breathlessness and not leg fatigue				
COPD	oesEMGdi %max	Jolley et al. [420]	Severe COPD patients	Incremental cycle and treadmill	Exertional breathlessness related to EMGdi %max		EMGdi % max related to breathlessness			
COPD	oesEMGdi %max	Qin et al. [421]	Severe COPD +/- inhlaed tiotropium (muscarinic receptor antagonist)	Constant cycle				↓EMGdi at rest with tiotropium, improved 'efficiency' of neural respiratory drive during exercise and prolonger exercise duration.		

COPD	oesEMGdi%max	Qiu et al. [422]	COPD (range of severities)	Constant rate treadmill versus Tai Chi	Similar EMGdi in both forms of exercise
ILD/COPD	oesEMGdi %max	Faisal et al. [155]	Mild-mod ILD versus COPD versus Controls	Incremental cycle	Similar ↑EMGdi in ILD and COPD at rest and during exercise cf controls
Non-COPD smokers	oesEMGdi %max	Elbehairy et al. [423]	Smokers (normal lung function) Versus Controls	Incremental cycle	↑EMGdi % max cf controls, mainly due to lower EMGdimax in smokers
CF	sPara % max	Smith et al. [424]	Cystic Fibrosis Versus Controls	Incremental shuttle walk test	sEMGpara%max related to exercise performance (VO2 peak), but not as strongly as lung gas transfer.
CF	sPara %max oesEMGdi %max	Reilly et al. [412]	Cystic Fibrosis Versus Controls	Incremental cycle exercise test to exhaustion	sEMGpara %max and oesEMGdi %max related to breathlessness
Obesity COPD	oesEMGdi %max	Ciavaglia et al. [425]	Obese with moderate COPD	Incremental cycle Versus treadmill	Similar oesEMGdi %max in 2 exercise types, but resulted in different transdi pressures.

Abbreviations: as for Table S10

Table S12. Conditions that may increase the risk of adverse effects of transcranial magnetic stimulation (relative contraindications of TMS) [426]

Pregnancy (effects on pregnant women are unknown);	Personal or family history of seizures, including febrile seizures as an infant;
Metal implants in the head;	Previous brain neurosurgery;
Cardiac pacemakers;	Unstable major medical conditions;
Poorly-controlled migraine headaches;	Medications that lower seizure threshold;
History of major head injury;	Neurological disorders;
History of stroke;	Major psychiatric disorders.

Table S13. Summary of characteristics and relevant results from TMS studies

Disease	Reference	Subject characteristics	Sample size (M)	Age ± SD (y)	Coil; Muscle; Hemisphere	Protocol	Meaningful clinical difference of variables measured	Prognostic/ discriminative information	Evaluative of intervention information
OSAS	Demoule et al. [427]	Healthy subjects	13 (7M)	22-43	Circular; DI; Vertex.	Single-pulse TMS; Paired-pulse TMS; Awake;	1. MEP in response to paired-TMS were obtained in 8 subjects; 2. ISI<5 ms resulted in significant inhibition; whereas >6 ms were facilitatory (maximal, 15 ms); 3. DI pattern matched that of the biceps brachii.		
	Civardi et al. [329]	OSAS patients vs. Controls	7 (4M) 9 (5M)	32.7±12.7 36.4±10.3	Circular; FDI; right	Single-pulse TMS; Awake/ sleep	1. MEP lat: NS between groups, (↑only during sleep); 2. MEP amp: NS, (↓only during sleep); 3. MT: NS; 4. CSP: ↑in OSAS	↓of MEP during sleep related to ↓of SaO_2.	
	Grippo et al. [330]	OSAS patients vs. Controls	10 (9M) 10 (8M)	56 (31-67) 47 (31-61)	Circular; FDI; dominant	Single-pulse TMS; Awake every 2 hours (10:00h-18:00)	1. MEP lat: NS; 2. MEP amp: NS (ratio); 3. CMCT: NS; 4. MT: NS; 5. CSP: ↑in OSAS	↓of MEP related to↑of $PaCO_2$	
	Wang et al. [428]	Healthy subjects	13 M	42±12	Circular or figure-of-eight; GG/DI/APB; Vertex or dominant.	Single-pulse TMS; Awake; Facilitation manoeuvre with tongue protrusion, inspiratory resistance or deep inspiration.	1. GG MEP precedes that of DI; 2. The sequence of GG and DI activation is not modified by respiratory or non-respiratory manoeuvres; 3. GG and DI are differently influenced by these manoeuvres in terms of MEP lat and MT.		

Sériès et al. [429]	Healthy subjects	9 M	46±8	Figure-of-eight; GG/ LVP/ PG/ alae nasi/ DI/APB; dominant	Single-pulse TMS; Awake; TMS stimuli during different respiratory conditions.	1. A concomitant response of the 4 studied upper airway muscles exist in the majority of cortical stimuli; 2. The response of these muscles was independent of the DI; 3. Significant relationships existed between the facilitated MEP amp/lat of alae nasi, PG, LVP and the corresponding values of GG.		
Sériès et al. [332]	OSAS patients vs. Controls	13 M 8 M	49±6 49±5	Circular; GG/ DI/ APB; dominant	Single-pulse TMS; Awake; Tongue protrusion facilitation	1. MEP lat: ↓in DI and GG during protrusion in OSAS; 2. MEP amp: ↑in GG during inspiration and ↑in ABP during tongue protrusion in OSAS; 3. MT: ↑difference between GG and DI during respiration in OSAS	Correlation between GG latencies and AHI	
Wang et al. [331]	OSAS patients vs. Controls	12 M 12 M	49±4 51±6	Figure-of-eight; GG; dominant	Single-pulse TMS; Awake	1. MEP lat: ↓in OSAS; 2. MEP amp: NS; 3. CMCT: ↓in OSAS;	Correlation with AHI, saturation, apnea time	
Joo et al. [334]	OSAS patients vs. Controls	45 M 44 M	47.2±9.7 47.2±5.4	Figure-of-eight; FDI; dominant	Single-pulse TMS; Paired-pulse TMS; At rest	1. MT: ↑in OSAS; 2. CSP: ↑in OSAS; 3. ICI: NS; 4. ICF: NS;		
Borel et al. [340]	Healthy subjects	10 M	32±9	Double cone coil (non-focal); GG/ DI/ LCW;	Single-pulse TMS; Awake; Hypercapnic stimulation.	1. MEP lat: NS in DI/LCW/GG during CO_2-induced increase in ventilation drive; 2. MEP amp: ↑in DI/LCW during CO_2 stimulation; NS in GG; 3. MT: ↓in DI/LCW during CO_2 stimulation; ↑ in GG.		CO_2-induced hyperventilation is associated with heightened LCW/DI

				Vertex.				corticomotor activation without modulating GG MEP response.
Opie et al. [335]	OSAS patients vs. Controls	13 (11M) 11 (9M)	42.6±10.2 43.0±10.3	Figure-of-eight; FDI/ADM; dominant	cTBS; Paired-pulse TMS; Awake	1. MT: ↑at rest, NS for active; 2. ICI: NS		Lack of response to cTBS in OSAS
Das et al. [338]	OSAS patients vs. Controls	13 (10M) 12 (8M)	47.7±9.7 46.2±10.5	Figure-of-eight; FDI; Dominant	rTMS; Single-pulse TMS; Awake	1. MEP lat: NS; 2. MEP amp: NS; 3. CMCT: NS; 4. MT: ↑at rest in OSAS; 5. CSP:↑in OSAS		Lack of response to high-frequency rTMS over M1 in OSAS (not in controls).
Melo-Silva et al. [325]	OSAS patients	14 (11M)	50±14	Figure-of-eight; Submental; non-dominant	Single-pulse TMS (acute); PNMS; Awake and sleep	1. MEP lat: NS wakefulness vs. sleep; 2. MEP amp: NS wakefulness vs. sleep; 3. MT: ↑in submental during sleep (NREM).	Cortico-bulbar excitability of submental muscles ↓ during NREM.	Brief recruitment of submental muscles with TMS during sleep improves upper airway mechanics without arousing patients from sleep.
Melo-Silva et al. [326]	OSAS patients	10 (9M)	51±13	Figure-of-eight; Submental; non-dominant	Single-pulse TMS (consecutive); PNMS; Awake and sleep	1. MEP lat: NS wakefulness vs. sleep; 2. MEP amp: NS wakefulness vs. sleep; 3. MT: ↑in submental during sleep		TMS-induced consecutive twitches reduced flow limitation during sleep in OSAS.

	Lanza et al. [333]	OSAS patients vs. RLS patients vs. Controls	14 (8M) 12 (4M) 14 (5M)	57.9±6.02 61.7±11.4 64.4±5.37	Figure-of-eight; FDI; dominant	Paired-pulse TMS;	1. MEP lat: ↑in OSAS; 2. MEP amp: ↓in OSAS; 3. CMCT: ↑in OSAS; 4. MT: ↑at rest in OSAS; 5. CSP: NS; 6. ICI: NS (ratio).	
	Rousseau et al. [336]	OSAS patients	10 M	48±11	Figure-of-eight; GG/DI; Non-dominant	rTMS; Single-pulse TMS; PNMS; Awake	1. MEP lat: NS in GG and DI; 2. MEP amp: ↑in GG from the second to the last rTMS expiratory train twitch; NS in DI.	rTMS applied during expiration induced corticomotor facilitation.
	Rousseau et al. [337]	OSAS patients	9 (8M)	55.9±9.7	Figure-of-eight; Submental/DI; Non-dominant	rTMS; Single-pulse TMS; Sleep	1. MEP lat: NS in Submental and DI; 2. MEP amp: ↓in submental from the first to the subsequent rTMS-induced twitch; NS in DI. 3. MT: ↑in submental during NREM sleep.	rTMS does not provide any improvement of airflow-limited breaths.
	Borel et al. [343]	OSAS patients vs Controls	12 M 9 M	48±10 45±10	Double cone coil (non-focal); GG/DI ; Vertex.	Single-pulse TMS; Awake; Hypercapnic stimulation.	1. MEP lat: ↓in DI during CO_2-induced increase in ventilation drive; NS in GG; 2. MEP amp: ↑in DI during CO_2-induced increase in ventilation drive; NS in GG.	No difference in CO_2-induced responses between OSAS patients and controls.
COPD	Oliviero et al. [328]	AE-COPD patients vs. Controls	4 8	64.8±13 70.4±10	Figure-of-eight; FDI; dominant	Single-pulse TMS; Paired-pulse TMS; Awake.	1. MT: NS (rest and active); 2. CSP: ↓ in AECOPD; 3. CMCT: NS; 4. ICF: NS; 5. ICI: : ↓in AECOPD	O_2 therapy normalized FDI MT (resting and active) and ICI, also prolonged CSP duration in AE-COPD.

Hopkinson et al. [430]	COPD (stable outpatients) vs. Controls	9 7	60.9±8.3 60.4±7.1	Double cone coil (non-focal); DI/Quadriceps/Rectus abdominis/ External oblique ; Vertex	Single-pulse TMS; Paired-pulse TMS; Awake; Voluntary facilitation.	1. MEP amp: at rest, ↑(DI and abdominis) in COPD; at facilitation, DI response ↑during 20% inspiratory efforts; no further ↑with >20% efforts in COPD, whereas further↑in controls at 40%-60% of inspiratory effort. 2. MT: ↓(DI and abdominal) in COPD; 3. CSP: ↓(DI and abdominal) in COPD; 4. ICF: ↓in COPD.	
Sharshar et al. [345]	Healthy subjects	6 (5M)	35 (25-45)	Double cone coil (non-focal); DI (costal and crural); Vertex	Single-pulse TMS; Paired-pulse TMS; PNMS; Awake; Isocapnic NIV intervention.	1. MEP amp: ↓(costal and crural) during NIV; 2. ICI/ICF: MEP amp↑during NIV at facilitatory ISI (> 9 ms)	Depression of diaphragm motor cortex excitability during NIV.
Locher et al. [344]	Healthy subjects	6 (4M)	22-25	Circular coil (non-focal); DI/ APB; Vertex.	Single-pulse TMS; CMS; Awake; Inspiratory resistive breathing.	1. MEP lat: ↓in DI after resistive breathing; NS in APB; 2. MEP amp: NS in DI or APB.	Inspiratory resistive breathing facilitates the diaphragm response to TMS while it does not increase the automatic drive to breathe.

Mohamed-Hussein et al. [339]	AECOPD vs. Controls	41 M 30 M	62.1±8.5 53.6±13	Figure-of-eight; FDI; dominant	Single-pulse TMS; Paired-pulse TMS; Awake;	1. MT: ↑(resting and active) in AECOPD; 2. CMCT: ↑in AECOPD; 3. CSP: ↑in AECOPD.	Correlation between TMS parameters (MT, CMCT and CSP) and pulmonary function tests (FVC, FEV_1%, FEV_1), arterial blood gases (pH, PaO_2, HCO_3) and serum chloride and potassium.	
Hopkinson et al. [346]	Unventilated COPD outpatients vs. Ventilated COPD outpatients	8 M 6 M	61±9 62±6	Double cone coil (non-focal); DI/ Rectus abdominis; Vertex	Single-pulse TMS; Paired-pulse TMS; Awake; Acute NIV intervention on 6 users of nocturnal home NIV.	1. MEP amp: NS between groups; Acute isocapnic NIV↓(DI) MEP amp; 2. MEP lat: NS; 3. ICF: NS; 4. ICI: NS.	Correlation between ICI and inspiratory muscle strength; between ICF and $PaCO_2$.	A reduction of DI MEP during NIV, without change in response to paired stimuli.
Straus et al. [341]	Healthy subjects	13 (10M)	22-35	Circula coil (non-focal); DI/ABP; Vertex	Single-pulse TMS; Awake; Hyperoxic CO_2 stimulation;	1. MEP lat: ↓in DI during (5% and 7%) CO_2-induced increase in ventilation drive; NS in APB; 2. MEP amp: ↑in DI during CO_2-induced increase in ventilation drive; NS in GG. 3. CMCT: ↓(DI) with increased concentration of CO_2; NS in APB.		Increasing the ventilatory neural drive through CO_2 inhalation facilitates the response of the DI to TMS
Luu et al. [342]	Healthy subjects	10 (7M)	29.2±7.1	Circular coil (non-focal); Scalenes and parasternal intercostal muscle; Vertex	Single-pulse TMS; Awake; End-tidal CO_2 stimulation;	1. CSP: NS by end-tidal CO_2.		Changing end-tidal CO_2 did not independently affect the duration of CSP in scalenes.

Central respiratory paralysis patients (ICU)	Duguet et al. [431]	Central respiratory paralysis patients: 1. Long-term ventilator depended; 2. Paralysis for less than 10 weeks	11 (7M) 16 (12M)	22.9±16 39.0±20	Circular coil (non-focal); DI/ APB; Vertex.	Single-pulse TMS; PNMS; Awake and free of sedative and psychotropic drugs;	1. TMS failed to elicit DI EMG and ABP EMG responses in the 11 patients; 2. No (DI/ APB) response of TMS in 6 subjects who had not recovered any ventilator activity at 1 year; 3. A (DI) EMG response to TMS was recorded in 9/10 cases (with usual latencies) who exhibited spontaneous ventilator respiration at 1 year.	DI response to TMS could predict the recovery of spontaneous ventilator activity within 1 year. (Specificity: 100%, sensitivity:90%).
Stroke (Impaired respiratory muscle function)	Harraf et al. [324]	Acute ischemic stroke patients; vs. Controls	15 (7M) 16 (8M)	68.9±9.8 75.8±7.0	Double cone coil (non-focal); DI (costal and crural); Vertex	Single-pulse TMS; PNMS; Awake; Gastric (P_{gas}) and esophageal (P_{oes}) pressures were measured simultaneously with MEP by TMS.	1. TMS P_{gas}: ↓following TMS at injured compared with uninjured hemisphere in stroke patients; 2. Correlations between PCFR and P_{gas} or PEmax; 3. Correlations between P_{gas} and PEmax in stroke patients.	Measurement of PEmax following TMS may assess airway clearance and complement existing methods to evaluate aspiration risk in acute stroke patients.

ABP: abductor pollicis brevis muscle; ADM: abductor digit minimi muscle; AECOPD: acute exacerbation of COPD; AHI: apnea-hypopnea index; CMCT: central motor conduction time; CMS: Cervical magnetic stimulation; COPD: chronic obstructive pulmonary disease; CSP: cortical silent period; DI: diaphragmatic muscle; FDI: first dorsal interosseus muscle; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; GG: genioglossus muscle; ICF: intracortical facilitation; ICI: intracortical inhibition; ISI: interstimulus interval; ICU: intensive care unit; LCW: lower chest wall; M: male; M1: primary motor cortex; MEP amp: MEP amplitude; MEP lat: MEP latency; MEP: motor evoked potentials; MT: motor threshold; NIV: isocapnic volume cycled ventilation delivered noninvasively; NS: not significant; OSAS: obstructive sleep apnea syndrome; PCFR: peak voluntary cough flow rates; PEmax: maximum static expiratory pressure; PNMS: phrenic nerve magnetic stimulation; RLS : restless legs syndrom; rMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; TBS: theta burst stimulation; TMS Pgas: TMS gastric pressure twitch.

Table S14. Advantages and limitations of the different respiratory muscle tests in children (adapted from [38, 432]).

	Volitional / Non volitional	Specificity of the test for a specific (type of) muscle	Advantages (+) / Limitations (-)
Non invasive tests			
Breathing pattern	NV	No	(+)Can be performed at any age (-)Requires quiet breathing (sleep in infants)
Lung volumes Vital capacity (sitting and supine) Residual volume Total lung capacity	 V V V	 Inspiratory and expiratory Expiratory Inspiratory	(+)Easy to perform, largely used in children > 4–8 years old; sensitive for assessing progress in moderate to severe respiratory muscle weakness (-)Requires cooperation; poor specificity for the diagnosis of respiratory muscle weakness
Maximal static pressures	V	Inspiratory (PImax) Expiratory (PEmax)	(+)Simple but difficult to perform, largely used in children > 6–8 years old (-)Requires full cooperation
Sniff nasal inspiratory pressure (SNIP)	V	Inspiratory	(+)Natural maneuver, easy to perform in children > 2 years old, playful, visual feedback (-)Requires cooperation; glottic closure or airway characteristics may prevent adequate equilibration; not reliable in case of rhinitis or hypertrophy of the adenoids
Peak cough flow / peak expiratory flow	V	Expiratory	(+)Easy to perform, largely used in children > 4–8 years old (-)Requires cooperation
Mouth pressure during a maximal whistle	V		(+)Natural maneuver, easy to perform in children > 2 years old, playful, audible feedback (-)Requires cooperation, lack of reference values
Crying mouth pressure	V	Inspiratory and expiratory	(+)Easily to perform in the newborn (-)High variability; glottic closure should be prevented
Tension time index	V	Inspiratory muscles (TTmus)	(+)Evaluates muscle endurance (-)Requires the measurement of occlusion pressure (P0.1), PImax/SNIP and breathing pattern
Invasive tests			
Breathing pattern with P_{oes} and P_{ga}	NV	Diaphragm	(+)Can be performed at any age (-)Mildly uncomfortable, requires quiet breathing (sleep in infants)
P_{oes} and P_{di} during a maximal sniff	V	Inspiratory and diaphragm	(+)Natural maneuver, easy to perform in children > 2 years old, playful, visual feedback (-)Mildly uncomfortable; requires cooperation; values may be less than maximal static values because of

			shortening of the inspiratory muscles
P_{ga} during a maximal cough	V	Expiratory	(+)Natural maneuver, easy to perform, can be performed in children > 2 years old, playful, visual feedback (-)Mildly uncomfortable; requires cooperation; lack of reference values
P_{oes} and P_{ga} during a maximal whistle			(+)Natural maneuver, easy to perform in children > 2 years old, playful, audible feedback (-)Mildly uncomfortable; requires cooperation, lack of reference values
Crying P_{di}	V	Diaphragm	(+)Can be performed in the newborn (-)Mildly uncomfortable; high variability
Tension time index	V	Diaphragm (TTdi) Inspiratory muscles (TTes)	(+)Evaluates muscle endurance (-)Mildly uncomfortable; requires the measurement of PImax/Sniff and breathing pattern
Sleep study			
Polysomnography / polygraphy	NV	No	(+)Can be performed at any age (-)Labor-intensive, expensive, limited accessibility

V: volitional, NV: non volitional, P_{oes}: esophageal pressure, P_{ga}: gastric pressure, P_{di}: transdiaphragmatic pressure, PImax: maximal static inspiratory pressure, PEmax: maximal static expiratory pressure, TTmus: non invasive tension time of the respiratory muscles, P0.1: pressure generated in the first 100 milliseconds of inspiration against an occluded airway, SNIP: Sniff nasal inspiratory pressure, TTdi: tension time index of the diaphragm, TTes: tension time index of the inspiratory muscles.

Figures

Figure S1. Tracings of lung volume (Volume) and oesophageal pressure (P_{oes}) from inspiratory capacity (IC) manoeuvres taken during resting breathing, at 60watts (iso-WR) and peak-exercise from one representative PAH patient who reduced IC (or increased end-expiratory lung volume, i.e., EELV) during exercise (PAH-H, *upper left panel*) and one who increased IC (or reduced EELV) (PAH-NH, *lower left panel*). Please note that, regardless of changes in IC during exercise, dynamic peak inspiratory P_{oes} recorded during IC maneuvres ($P_{oes,IC}$) is remarkably preserved in both PAH-H (upper left panel) and PAH-NH (lower left panel). Maximal and tidal flow-volume loops (average data) are shown at rest and at peak-exercise in PAH-H (upper right panel) and PAH-NH (lower right panel). Tidal flow-volume loops are provided at rest (solid line) and at peak-exercise (dashed line). Note a significant decrease in dynamic inspiratory capacity during exercise in PAH-H compared with PAH-NH. Abbreviations: TLC=total lung capacity.

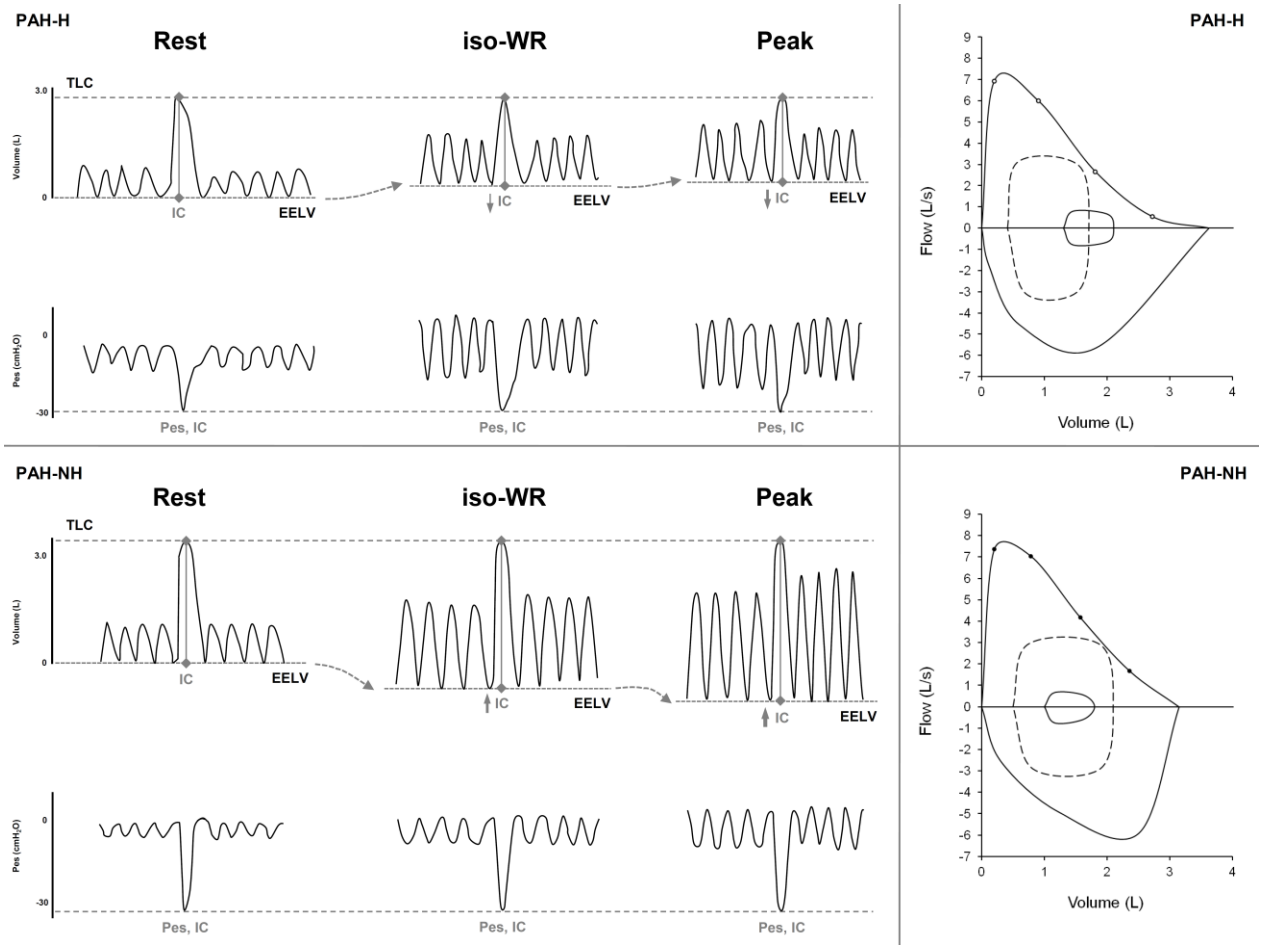

Figure S2. Improvements in inspiratory muscle endurance capacity assessed by incremental (Pmax) or constant load (Tlim) tests in response to inspiratory muscle training (IMT) in patients with chronic obstructive pulmonary diseases. MTL = mechanical threshold loading, TFRL = tapered flow resistive loading.

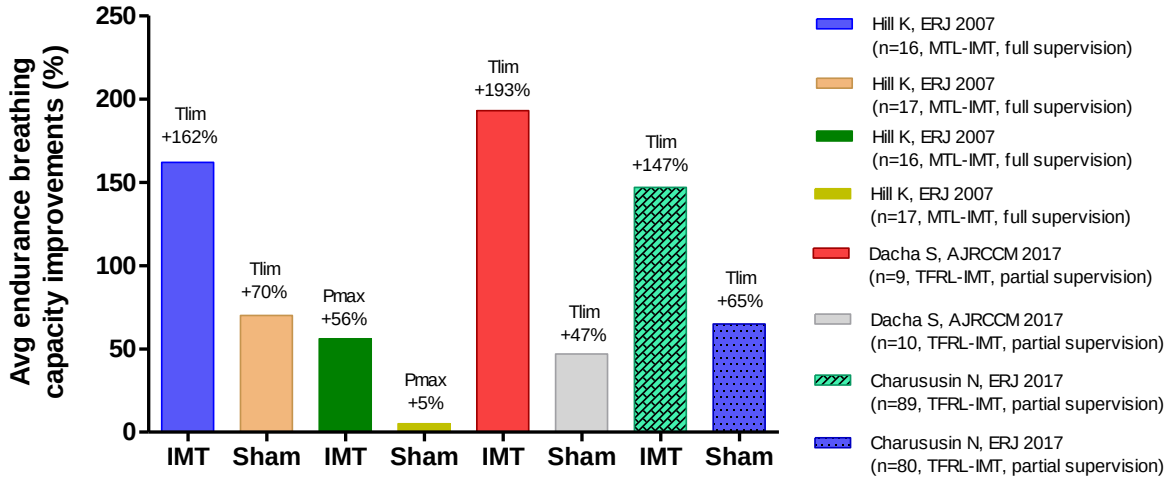

Figure S3. Changes in respiratory muscle endurance measured by a constant-load hyperpnoea test following respiratory muscle endurance training (RMET) or a control period (CON, no training) in healthy subjects. From [433].

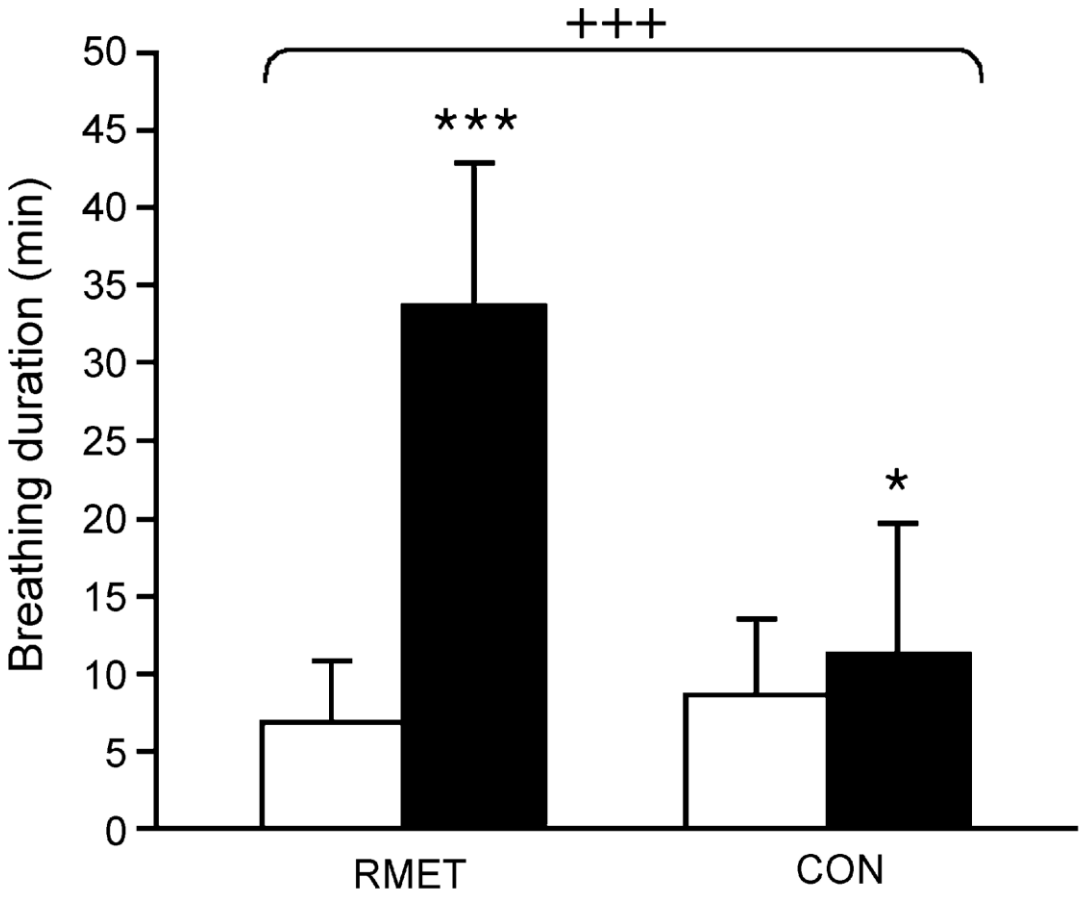

Figure S4. Dyspnoea score perceived during cycling according to maximal inspiratory pressure (PImax) and forced expiratory volume in 1 second (FEV1) based on data collected in 550 subjects exercised for clinical purposes and grouped [434].