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A Novel Method for Noninvasive Estimation of Respiratory Effort during Pressure Support Ventilation

William Pasillas-Lépine^{a,*}, Samuel Tuffet^{b,d}, Charles Soussen^a, Ségolène Gendreau^{c,d}, Mohamed Ahmed Boujelben^{c,d}, Armand Mekontso-Dessap^{c,d}, Guillaume Carteaux^{c,d}

^aUniversité Paris-Saclay, CNRS, CentraleSupélec, Laboratoire des signaux et systèmes, Gif-sur-Yvette, France

^bRéanimation polyvalente, Hôpital Saint Joseph Saint Luc, 20 quai Claude Bernard, Lyon, France

^cAssistance Publique-Hôpitaux de Paris, CHU Henri Mondor, Service de Médecine Intensive Réanimation, Créteil, France

^dParis Est-Créteil, Faculté de Santé, Groupe de Recherche Clinique CARMAS and INSERM U955, Institut Mondor de Recherche Biomédicale, Créteil, France

Abstract

Objective: This paper proposes an initial proof-of-concept validation for a method that estimates the respiratory effort during pressure support ventilation, based solely on the signals provided by a standard commercial ventilator. The study is carried out on a test bench with an Active Servo Lung 5000 mechanical simulator. **Methods:** The asymptotic behavior of the respiratory mechanics during expiration is exploited to analyze its identifiability (the fact that two sets of respiratory mechanics parameters necessarily generate distinct signals). Furthermore, we propose a method of estimation of the patient's respiratory muscle pressure, based on the degree of smoothness of a signal constructed from the airway pressure and flow measurements. **Results:** The proposed method was validated on a commercial ventilator, under a wide range of respiratory mechanics parameters and respiratory efforts. **Conclusion:** Our approach provides a non-invasive estimation of the respiratory effort, which allows for accurately detecting over- and under-assistance. **Significance:** Compared to existing muscle pressure estimation methods, our approach clarifies the conditions under which the respiratory effort of a patient can be estimated and offers a simple way to compute it in real time, without using invasive devices or occlusion-based techniques.

Keywords: Biomedical monitoring, Lung parameter estimation, Mechanical ventilation, Mechanical lung simulator, Muscle pressure, Pressure support ventilation, Respiratory effort monitoring.

1. Introduction

Mechanical ventilation assists or replaces the patient's respiratory effort, ensuring adequate gas exchange. Depending on the clinical condition of the patient, several ventilation modes are available. Pressure support ventilation (PSV) is the most widely used method of assisted ventilation in the world [1]. It provides partial support to the patient, delivering an insufflated volume that is modulated by the patient's respiratory effort [2].

When adjusting the pressure support level, the primary objective of the physician is to adequately unload the respiratory muscles. Indeed, insufficient or excessive respiratory effort during PSV is associated with the risk of developing diaphragmatic dysfunction [3] (ventilation-induced diaphragm injury) and lung injury (patient self-inflicted lung injury) [4, 5], which can lead to an increase of the duration of ventilation [3]. However, during PSV, the measurement of respiratory effort is not easily accessible to the clinician, which can lead to inappropriate adjustments of the pressure support level and thus induce a risk for the patient. The reference method is based on the measurement of the pressure developed by the respiratory muscles [6]. This technique requires the collection and analysis of the esophageal pressure signal by means of an esophageal catheter, which seriously limits its generalization. Alternative

methods have been developed based on occlusion maneuvers of the airway during the inspiratory effort [7, 8, 9] to detect excessive or insufficient respiratory efforts. These methods require an intensivist's intervention to perform the occlusion and some of them may be poorly tolerated if repeated. Therefore, they are not suitable for continuous monitoring [10, 11, 9, 8]. In contrast, a non-invasive, continuous method for estimating muscle pressure would significantly help in monitoring respiratory effort and identifying over- or under-assistance. Vicario *et al.* proposed a method [12], which estimates muscle pressure under mechanical ventilation using ventilator-displayed flow and pressure waveforms. However, it lacks extensive validation across a wide range of respiratory cycles for clinical application. Besides, Al-Rawas *et al.* described a method for estimating respiratory mechanics (resistance and compliance of the respiratory system) during PSV, based on flow and airway pressure signals analysis [13]. The availability of the respiratory mechanics allows for continuous computation of respiratory muscle pressure according to the equation of motion of the respiratory system [14]. Such estimation of muscle pressure using respiratory mechanics values derived from the method proposed by Al-Rawas *et al.* is hereafter referred to as Al-Rawas derived method.

In this paper, we propose a new method for estimating respiratory effort, based solely on the signals provided by stan-

*william.pasillas-lepine@centralesupelec.fr

standard ICU ventilators during a single breathing cycle. We hypothesized that our method enables to estimate the inspiratory muscle pressure during PSV with sufficient accuracy to detect both under-assistance and over-assistance. Consequently, we assessed its performance across thousands of simulated clinical scenarios and compared it to the performance of Vicario *et al.* method and the method derived from Al-Rawas *et al.*.

2. Material and Methods

In this section, we first introduce the mathematical models used to derive the proposed estimation method. We further describe the experimental validation setup and the statistical analysis performed to assess the numerical methods.

2.1. Modeling pressure support ventilation

A standard practice in mechanical ventilation estimation problems (see, *e.g.*, [15] and [16]) is to model the respiratory mechanics using a linear relation

$$P_{ao} = RQ + EV + P_0 + P_{mus} \quad (1)$$

between the *airway pressure* P_{ao} , the *patient muscle pressure* P_{mus} , the *pulmonary volume* V , and the *flow* Q . The *resistance* R , the *elastance* E , and the *offset pressure* P_0 are unknown constant parameters. In contrast, the time varying signals $P_{ao}(t)$ and $Q(t)$ can be measured (they are used by the control system of the ventilator). The volume $V(t)$ is deduced from the flow by integration. Our aim is to recover the signal $P_{mus}(t)$ from a single cycle during pressure support ventilation.

A pressure support ventilation cycle [12] is composed of two phases (Fig. 1). During the *insufflation* phase, the flow Q is positive, while it is negative during the *expiratory* phase. Most often, at the end of expiration the flow vanishes, until the patient starts his effort and generates a positive flow (at t_{str} , with *str* for start). The insufflation phase is then triggered by a threshold on the flow, when $Q \geq Q_{on}$. The time at which the triggering occurs is denoted t_{on} , with $t_{on} > t_{str}$ and $Q(t_{on}) \geq Q_{on}$. The *inspiratory trigger* Q_{on} can usually be adjusted by the clinician. Similarly, the expiration phase is triggered by a threshold on the flow, once the flow has started to decrease and satisfies $Q \leq Q_{off}$, which ends the insufflation phase. The time at which the triggering occurs is denoted t_{off} , with $t_{off} > t_{on}$ and $Q(t_{off}) \leq Q_{off}$. Unlike Q_{on} , which is constant, the threshold Q_{off} is variable. It is defined as a percentage r_{off} of the maximum value Q_{max} reached by the flow during insufflation: $Q_{off} = r_{off} \cdot Q_{max}$. The ratio r_{off} is the *expiratory trigger* (or cycling off criterion). On most modern ventilators, this parameter can also be adjusted by the clinician.

The expiratory trigger r_{off} has a strong impact on the synchronization between the patient and the ventilator. In the ideal case, the time t_{off} (when the expiratory phase is triggered) should coincide with the time t_{end} (when the patient ends his effort). The case where both times are significantly different is called an *asynchrony* and more specifically, a *short cycle* when $t_{end} > t_{off}$ and a *prolonged insufflation* when $t_{end} < t_{off}$. The extreme case where, during the expiratory phase, the muscular effort of the

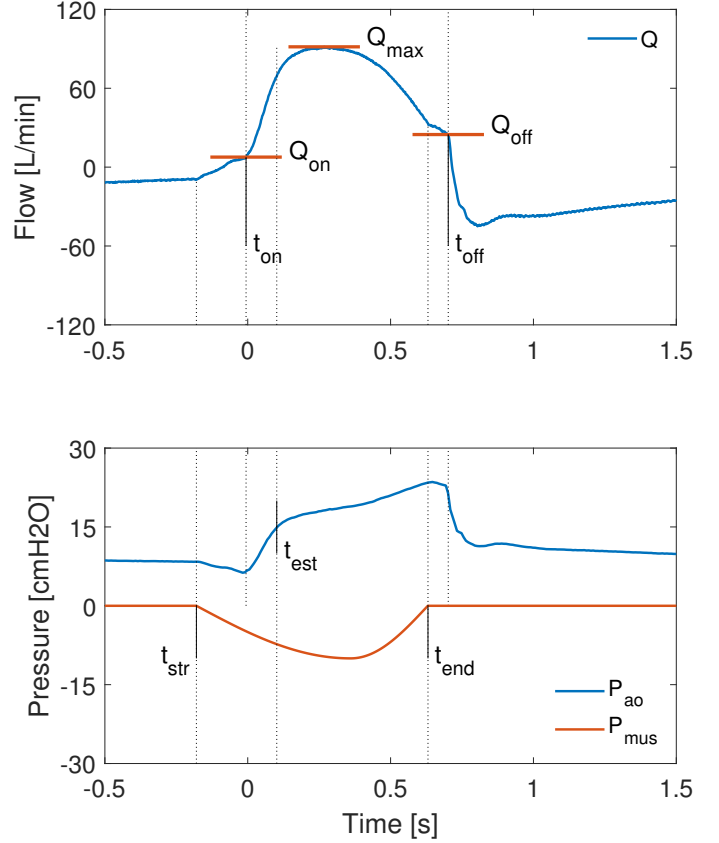


Figure 1: Pressure support ventilation cycle on a Puritan-Benett 980 ventilator, connected to an ASL5000 artificial lung simulator. The thresholds Q_{on} and Q_{off} trigger the beginning and end of the insufflation phase. The corresponding times at which the trigger occurs are denoted t_{on} and t_{off} , respectively. The threshold $Q_{off} = r_{off} Q_{max}$ depends on the maximal value of the flow Q_{max} . The start and end of the patient's effort are denoted t_{str} and t_{end} , respectively. The estimation method proposed in this paper exploits the smoothness of the muscle pressure at t_{est} .

patient is not able to trigger a new insufflation cycle is called an *ineffective effort*.

2.2. Expiration asymptotic regime

In addition to the threshold-based controller described in Sect. 2.1 (which triggers the inspiratory and expiratory phases of the ventilator), pressure support also includes a proportional controller of the airway pressure [17]. The *flow reference* Q_{ref} associated with this proportional regulation is given by

$$Q_{ref}(t) = K(t) (P_{flt}(t) - P_{ao}), \quad (2)$$

where the *filtered reference* P_{flt} is a smoothed version of a piecewise constant *pressure reference* P_{ref} and K is a *proportional gain*. While the pressure reference has always distinct values during insufflation and expiration, on some ventilator models, the gain K might remain constant. During each phase, the dynamics of P_{flt} is designed in order to converge towards P_{ref} either exponentially or in finite time. The ventilator valves are then controlled in order to drive the actual flow Q toward its reference Q_{ref} .

On most ventilators, the clinician can adjust the gain and the convergence speed of the pressure reference filter during the inspiratory phase, via the *slope* (or settling time) parameter of the ventilator interface [18]. During expiration, the reference P_{ref} corresponds to the *positive end-expiratory pressure* (PEEP) while, during insufflation, the difference between P_{ref} and the PEEP determines the level of *pressure support*.

Consider a time interval where the respiratory effort of the patient is constant. Once the filtered pressure has converged towards its reference, equation (2) can be rewritten by replacing Q_{ref} with Q , and P_{flt} with P_{ref} . This allows us to compute the asymptotic line towards which the volume and flow converge in the volume/flow phase plane. Indeed, combining equations (1) and (2) in this asymptotic regime yields

$$\begin{aligned} P_{ref} &= \frac{1}{K} Q + P_{ao} \\ &= \left(R + \frac{1}{K} \right) Q + EV + P_0 + P_{mus}. \end{aligned} \quad (3)$$

Observe that the multiplying factor $R + \frac{1}{K}$ differs from the airway resistance. It includes a term related to the proportional gain K .

A direct consequence of (3) is that during expiration, once the muscle pressure has vanished, the flow converges to the following asymptote

$$Q = \alpha V + \beta \quad (4)$$

with

$$\alpha = \frac{-E}{R + \frac{1}{K_{exp}}} \quad \text{and} \quad \beta = \frac{P_{peep} - P_0}{R + \frac{1}{K_{exp}}}, \quad (5)$$

where K_{exp} refers to the value of $K(t)$ during the expiratory phase. Indeed, in this situation P_{mus} vanishes and P_{ref} is equal to P_{peep} . The constant $-1/\alpha$ identifies with the *Expiratory-Time Constant* (ETC)– see, e.g., [19].

Hereafter, we exclude patient pathologies inducing a nonlinear expiration asymptote (like expiratory flow limitation [20]) and assume that the patient is ventilated in a domain where the compliance is linear [21]. Otherwise, more complex models should be used instead of (1), like those proposed in [22, 23]. Under our assumptions (at least in the absence of ineffective efforts) the constants α and β can be estimated using linear regression, a topic widely discussed in the literature (see, e.g., [19], [13], and [24]). Therefore, we will assume hereafter that the estimation of P_{mus} is carried out over a cycle that does not present any ineffective effort, and that the constants α and β have already been estimated.

2.3. Muscle pressure identifiability

Our new respiratory mechanics estimation method builds upon the asymptotic model (4). We first exploit it to explain why, without further assumptions, the respiratory mechanics is not identifiable [12] even when α and β are known. The concept of identifiability refers to the fact that the unknown parameters explaining the data signals V , Q , and P_{ao} can be recovered unambiguously [25].

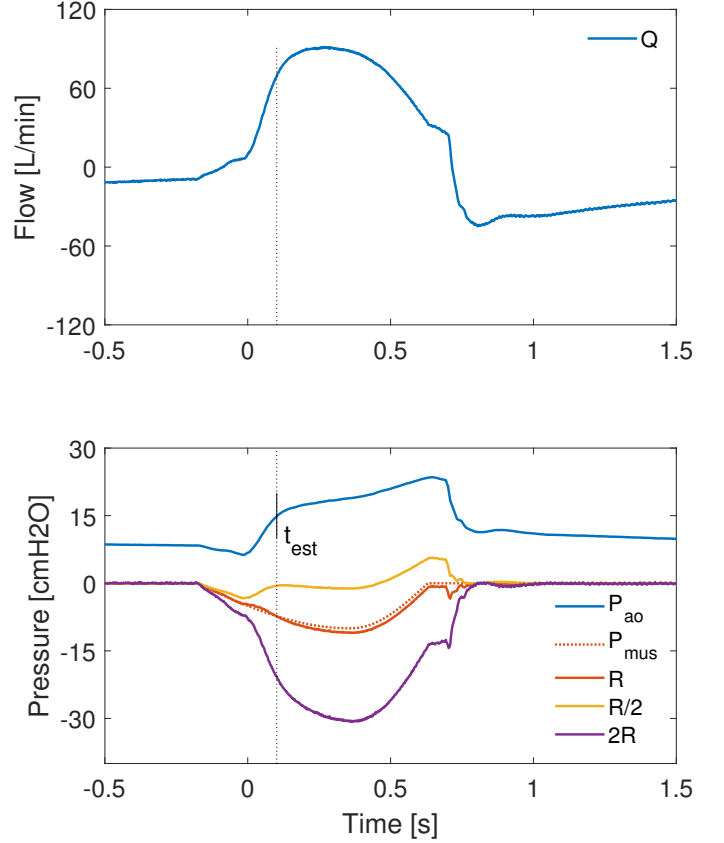


Figure 2: Three different reconstructions of the P_{mus} profile are computed from the same recording (in blue) of the flow Q and of the airway pressure P_{ao} , using different values of R in equation (6). The curve in red is obtained with the resistance estimation \hat{R} provided by the CDME procedure of Sect. 2.5, which maximizes the smoothness of the muscle pressure estimate. The yellow and magenta curves consider $\hat{R}/2$ and $2\hat{R}$, respectively, in (6). The estimation of \hat{R} provided by the CDME procedure clearly provides a smoother estimation of P_{mus} that is, moreover, closer to the real value of this signal.

FACT. Assume that α and β are known. For an arbitrary effort P_{mus} , the respiratory mechanics (1) are not identifiable. Indeed, for a given solution V , Q and P_{ao} of (1), there is a whole family of pressure profiles

$$\begin{aligned} P_{mus}(t, R) &= \frac{Q(t)}{K_{exp}} + P_{ao}(t) - P_{peep} \\ &\quad - \left(R + \frac{1}{K_{exp}} \right) (Q(t) - (\alpha V(t) + \beta)), \end{aligned} \quad (6)$$

parametrized by R , that generates identical evolutions of the measured variables V , Q , and P_{ao} .

To check this fact, observe that when α and β are known, one can retrieve the values of E and P_0 from (5):

$$E = -\alpha \left(R + \frac{1}{K_{exp}} \right) \quad \text{and} \quad P_0 = P_{peep} - \beta \left(R + \frac{1}{K_{exp}} \right). \quad (7)$$

Now, equation (1) yields

$$P_{ao} = RQ - \alpha \left(R + \frac{1}{K_{exp}} \right) V + P_{peep} - \beta \left(R + \frac{1}{K_{exp}} \right) + P_{mus}.$$

Adding Q/K_{exp} to both sides of this equation, we get

$$P_{mus} = P_{ao} + \frac{Q}{K_{exp}} - P_{peep} - \left(R + \frac{1}{K_{exp}}\right)(Q - (\alpha V + \beta)),$$

which coincides with (6). Consider now fixed signals V , Q , and P_{ao} that satisfy (1) with the ground truth parameters R , E , and P_0 . For an arbitrary choice of \hat{R} (different from R), one can generate the corresponding estimates of \hat{E} and \hat{P}_0 using (7) (in which R has been replaced by \hat{R}). Similarly, one can recover the pressure profile $P_{mus}(t, \hat{R})$ using (6). Since (1) is satisfied with \hat{R} and induced parameters \hat{E} and \hat{P}_0 , the parameter estimation problem is not mathematically identifiable. Indeed, the same set of signals are recovered with any arbitrary parameter \hat{R} , which does not make it possible to retrieve R without imposing extra assumptions.

2.4. Smoothness of muscle pressure estimates

In what follows, for an arbitrary nonsmooth (continuous but not differentiable) signal $h(t)$, the terms $\partial_-h(t_0)$ and $\partial_+h(t_0)$ denote the left and right derivatives of h at t_0 , namely

$$\partial_-h(t_0) = \lim_{t \rightarrow t_0^-} \frac{h(t) - h(t_0)}{t - t_0}$$

and

$$\partial_+h(t_0) = \lim_{t \rightarrow t_0^+} \frac{h(t) - h(t_0)}{t - t_0}.$$

Equation (6) can be rewritten in a more compact form

$$P_{mus}(t, R) = f(t) - \left(R + \frac{1}{K_{exp}}\right)g(t), \quad (8)$$

with

$$f(t) = \frac{Q(t)}{K_{exp}} + P_{ao} - P_{peep} \quad (9)$$

and

$$g(t) = Q(t) - (\alpha V(t) + \beta). \quad (10)$$

Note that the only unknown parameter in equation (8) is the airway resistance R . Indeed, all the parameters appearing in (9)-(10) are known. The following result constitutes the cornerstone of the paper. It states a condition under which one can unambiguously estimate the correct value of R , using equation (11) below. It is shown hereafter that this equation results from the equality $\partial_+P_{mus}(t_0, R) = \partial_-P_{mus}(t_0, R)$. A graphical representation of the underlying idea is proposed in Fig. 2.

CONTINUITY CONDITION. *If the flow is not differentiable at a time t_0 , then there exists a unique resistance value*

$$\hat{R} = \frac{\partial_+f(t_0) - \partial_-f(t_0)}{\partial_+g(t_0) - \partial_-g(t_0)} - \frac{1}{K_{exp}}, \quad (11)$$

for which the recovered signal $P_{mus}(t, R)$ in (6) is smooth (continuously differentiable) at t_0 .

The first-order continuity condition (11) results from the fact that the signals Q and P_{ao} are continuous but not smooth everywhere. On an interval where P_{mus} is smooth, the only points t_0

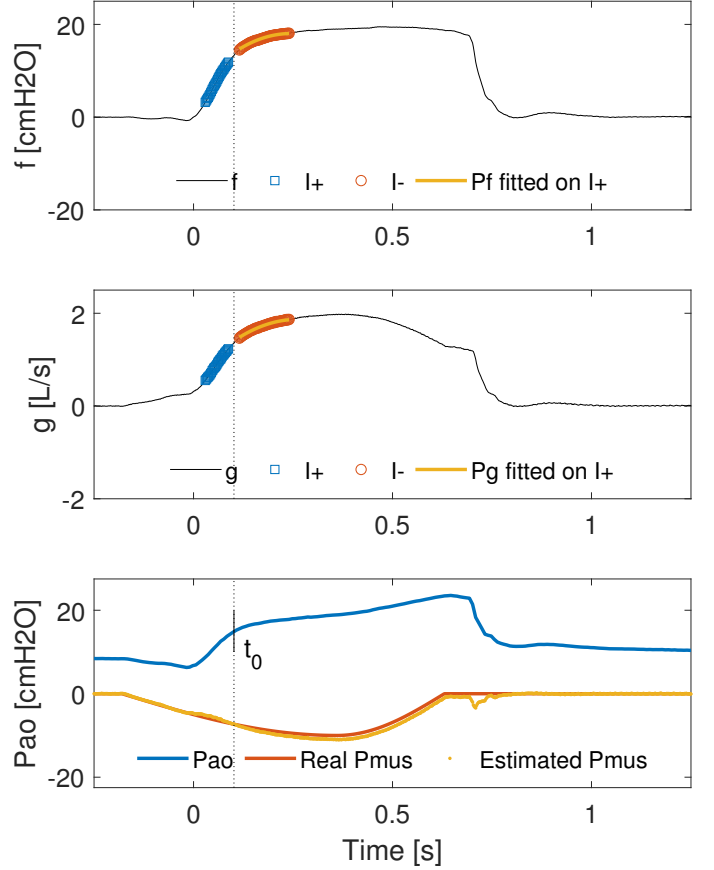


Figure 3: The functions f and g , defined by equations (9) and (10), are approximated by two parabolas P_f and P_g on a time interval I_+ , after $t_0 = t_{est}$. A typical estimate of P_{mus} is plotted (yellow dots) and compared to its real value (the ASL reference, in red). This estimate is obtained via the optimization procedure of Sect. 2.5, based on a cross-validation with the parabolas P_f and P_g , on a small interval I_- before t_0 .

where Q and P_{ao} are not differentiable are those where P_{flt} is not smooth. At these points, functions f and g are neither differentiable, so (11) is valid. Note that the signal $V(t)$ is smooth everywhere, since it reads as the anti-derivative of the continuous signal Q . Thus, (8), (9) and (10) can be used to compute

$$\partial_+P_{mus}(t_0, R) = \partial_+f(t_0) - (R + 1/K_{exp})\partial_+g(t_0)$$

and

$$\partial_-P_{mus}(t_0, R) = \partial_-f(t_0) - (R + 1/K_{exp})\partial_-g(t_0).$$

Imposing $\partial_+P_{mus}(t_0, R) = \partial_-P_{mus}(t_0, R)$, one can determine the unique value of the resistance

$$\hat{R} = \frac{\partial_+f(t_0) - \partial_-f(t_0)}{\partial_+g(t_0) - \partial_-g(t_0)} - \frac{1}{K_{exp}}, \quad (12)$$

for which $P_{mus}(t, \hat{R})$ is differentiable at t_0 . The discontinuity of the flow derivative and the smoothness of V at t_0 imply that $\partial_+g(t_0) \neq \partial_-g(t_0)$.

Respiratory effort:	Insufficient	Normal	Excessive
Number N of cycles	735	3651	4150
Simulated muscle pressure P_{mus} (cmH ₂ O)	4 (2 ; 4)	10 (8 ; 12)	22 (18 ; 26)
Simulated resistance R (cmH ₂ O/L/sec)	9 (6 ; 15)	15 (9 ; 24)	18 (12 ; 24)
Simulated compliance C (mL/cmH ₂ O)	55 (40 ; 75)	65 (45 ; 85)	55 (40 ; 75)
Simulated inspiratory time (msec)	800 (800 ; 1000)	1000 (800 ; 1000)	1000 (800 ; 1000)
Pressure support (cmH ₂ O)	10 (5 ; 15)	10 (5 ; 15)	10 (5 ; 15)
Tidal volume (mL)	356 (240 ; 522)	399 (301 ; 556)	574 (463 ; 732)
Estimated P_{mus} , CDME (cmH ₂ O)	4.5 (3.5 ; 5.4)	10.6 (8.2 ; 13.2)	22.5 (18.7 ; 26.9)
Estimated P_{mus} , Al-Rawas (cmH ₂ O)	2.8 (0 ; 3.9)	5.2 (3.5 ; 7.7)	6.6 (4.6 ; 9.7)
Estimated P_{mus} , Vicario (cmH ₂ O)	5.7 (4.2 ; 9.9)	10.4 (8 ; 13.4)	18.4 (15.2 ; 26.9)

Table 1: Description of the selected respiratory cycles (median and interquartile ranges). Insufficient respiratory effort was defined by muscle pressure < 5 cmH₂O. Excessive respiratory effort was defined by muscle pressure > 15 cmH₂O. CDME refers to Continuous Differentiability of Muscular Effort method.

2.5. CDME procedure for muscle pressure estimation

From a theoretical viewpoint, the one-sided derivatives appearing in (11) could be estimated using linear regression, applied to a Taylor expansion of the signals at t_0 . Indeed, for an arbitrary signal h , fixing $\epsilon > 0$ we can define on each interval $[t_0 - \epsilon, t_0]$ and $[t_0, t_0 + \epsilon]$ a Taylor expansion of the form

$$h(t) - h(t_0) = (t - t_0)(p_0 + p_1(t - t_0)). \quad (13)$$

Then, both unknown parameters p_0 and p_1 can be computed using ordinary least-squares. On each interval, the parameter p_0 provides the desired estimate of the one-sided derivative $\partial_{\pm} h(t_0)$. Nevertheless, the latter estimates are highly sensitive to estimation errors on t_0 . Back to the framework of condition (11), one can hardly estimate t_0 with high precision. Therefore, the resistance parameter cannot be recovered using (12), and more robust strategies must be envisioned.

Hereafter, we propose a robust method, named *Continuous-Differentiability of Muscular Effort* (CDME). Let us first assume that time t_0 is known. We then define two intervals $I_- = [t_0 - \epsilon - \eta_-, t_0 - \epsilon]$ and $I_+ = [t_0 + \epsilon, t_0 + \epsilon + \eta_+]$. The parameter $\epsilon > 0$ must be chosen sufficiently large to cope for the estimation errors on t_0 , while the parameters $\eta_- > 0$ and $\eta_+ > 0$ must be sufficiently small to ensure that P_{mus} is smooth on the whole interval $[t_0 - \epsilon - \eta_-, t_0 + \epsilon + \eta_+]$. Using linear regression, one can approximate the signals f and g on I_+ with second order polynomials P_f and P_g . Then, rewriting $P_{mus}(t)$ in (8) as $f(t) - \theta g(t)$ with

$$\theta = R + \frac{1}{K_{exp}}, \quad (14)$$

we get

$$P_{mus}(t) \approx P_f(t) - \theta P_g(t), \quad (15)$$

for $t \in I_+$. CDME is based on a cross-validation procedure, aiming to impose that (15) is also valid on I_- , since function $P_{mus}(t)$ has to be smooth around $t = t_0$. We propose to select the parameter θ for which the signal $P_{mus}(t)$ on I_- is as close

as possible to the one retrieved on I_+ . Thus, we address the following least squares problem:

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \sum_{t \in I_-} \left((f(t) - P_f(t)) - \theta(g(t) - P_g(t)) \right)^2, \quad (16)$$

which provides an estimate of the airway resistance

$$\hat{R} = \hat{\theta} - \frac{1}{K_{exp}}. \quad (17)$$

Criterion (16) quantifies that for $t \in I_-$, $P_{mus}(t) = f(t) - \theta g(t)$ should be as close as possible to the Taylor expansion of $P_{mus}(t)$ (obtained from data related to $t \in I_+$), evaluated for $t \in I_-$.

To be able to compute \hat{R} , a crucial issue is to detect both intervals I_- and I_+ surrounding the time t_0 where (i) the flow is non-smooth, that is, the flow derivative is discontinuous; and (ii) P_{mus} is smooth. Even if the flow is guaranteed to be non-smooth around t_{on} and t_{off} (the times when the phase of the ventilation mode changes), the degree of smoothness of P_{mus} at the same times is uncertain. Indeed, the start of the patient effort t_{str} is shortly followed by t_{on} , and the end of the patient effort t_{end} might coincide with t_{off} . For this reason, to estimate \hat{R} in the CDME method, we have chosen to set t_0 as the time t_{est} at which the second order derivative of P_{ao} reaches its minimal value (see Figs. 1 and 3). This corresponds to the time where the curvature of this signal reaches a maximum. This choice ensures the smoothness of P_{mus} . Indeed t_{est} is located between t_{on} and t_{off} . It is therefore reasonable to expect P_{mus} to be differentiable at this point. In the experimental validation of our method, described below, the parameters ϵ , η_- , and η_+ were chosen as multiples of the time $d = t_{est} - t_{on}$, with $\epsilon = d/8$, $\eta_- = 3d/5$, and $\eta_+ = 5d/4$.

2.6. Experimental setting

The respiratory cycles studied were simulated using an Active Servo Lung 5000 mechanical simulator (ASL5000; IngMar Medical, Pittsburgh, PA, USA), connected to a Puritan-Benett Covidien PB 980 intensive care ventilator (Medtronic, Minneapolis, MN, USA). A dedicated script was created, allowing the simulation of a large representative set of respiratory cycles, by systematically varying:

- Respiratory system compliance, from 30 to 100 mL/cmH₂O, in steps of 5 mL/cmH₂O;
- Respiratory system resistance from 3 to 30 cmH₂O/L/s, in steps of 3 cmH₂O/L/s;
- Inspiratory muscle pressure from 2 to 30 cmH₂O, in steps of 2 cmH₂O.

Two durations of respiratory effort were simulated: 800 and 1000 ms. The respiratory rate was set to 20 breaths/min. Expiration was passive. The ventilator was set in PSV mode, with a positive end-expiratory pressure of 8 cmH₂O. Three levels of pressure support were tested: 5, 10 and 15 cmH₂O. The inspiratory trigger was set to 1 L/min, the cycling-off threshold to 25 %, and the insufflation slope to 80 %. All possible combinations of these variables were simulated, except when the corresponding cycle exceeded the technical limitations of the ASL simulator. In particular, cycles that led to a total volume (including end-expiratory volume) greater than 1900 mL or to a flow greater than 120 L/min were excluded. Cycles corresponding to ineffective efforts were neither considered. Six cycles were simulated for each condition in order to reach a steady-state but only the last cycle was analyzed.

2.7. Assessment of experimental results

Flow, airway pressure and simulated muscle pressure were recorded by the ASL 5000 and sampled at 512 Hz. For each respiratory cycle selected for analysis, muscle pressure was calculated with three different methods: 1) The CDME method presented in Sect. 2.5; 2) The method derived from Al-Rawas *et al.* [13]; and 3) Vicario *et al.*'s method [12]. Agreement between simulated and estimated muscle pressure was studied for each method by a Spearman correlation and by a Bland-Altman analysis. The sensitivity and specificity of each method for diagnosing insufficient or excessive respiratory efforts were calculated. Insufficient or excessive efforts were defined as simulated muscle pressure below 5 cmH₂O or greater than 15 cmH₂O, respectively. In addition, the receiver operating characteristic (ROC) curves of each method for the diagnosis of insufficient efforts were computed. The comparison between the three methods was based on the areas under their ROC curves (AUROC) by DeLong's test for correlated ROC curves, with adjustment for multiple testing by the false discovery rate. The thresholds were chosen according to the most recent expert suggestions [26], and by analogy with the recent work [9]. While the threshold defining insufficient muscle pressure is consensual [27], the threshold defining excessive muscle pressure varies in the literature between 10 and 15 cmH₂O. We chose the highest threshold to define unquestionably excessive efforts. Nevertheless, in order to test the robustness of our results with respect to the muscle pressure threshold defining excessive effort, a second analysis was performed, where excessive muscle effort is defined by a muscle pressure greater than 11 cmH₂O.

Correlation	CMDE	Al-Rawas	Vicario
r_s (95% CI)	0.94 (0.94; 0.95)	0.4 (0.39; 0.42)	0.72 (0.71; 0.73)
p	<0.0001	<0.0001	<0.0001

B&A Plots	CMDE	Al-Rawas	Vicario
Bias (SD)	0.7 (2.9)	-9.1 (7.2)	-0.4 (6)
Lower AL	-5	-23.3	-12
Upper AL	6.4	5.1	11.3

Table 2: Spearman correlation coefficient r_s and Bland-Altman analysis results. CI: confidence interval. SD: standard deviation. AL: Agreement limit.

3. Results

Using the experimental protocol described in Sect. 2.6, a set of 9896 different conditions were simulated. Among them, 1360 were excluded: 1036 cycles corresponding to ineffective efforts and 324 cycles related to inspiratory flows strictly greater than 2 L/s. The remaining 8536 cycles were analyzed: 735 with muscle pressure strictly lower than 5 cmH₂O, 3651 with muscle pressure between 5 and 15 cmH₂O, and 4150 with muscle pressure strictly greater than 15 cmH₂O (see Table 1). The muscle pressure estimates calculated by each of the three methods were significantly correlated with the simulated muscle pressure values (Table 1). On the contrary, Spearman's coefficients provided by the three methods were significantly different. The Bland-Altman analysis showed narrower limits of agreement with CDME than with the two competing methods (Table 2). Correlation plots and Bland-Altman plots corresponding to each muscle pressure estimation method are available in Fig. 4.

3.1. Diagnosis of insufficient effort

The area under the ROC curve of the proposed CDME method (Fig. 5) for diagnosing insufficient respiratory effort was 0.97 (95% confidence interval [CI], 0.97–0.98). At a threshold of 5 cmH₂O, CDME predicted insufficient effort (muscle pressure lower than 5 cmH₂O) with a sensitivity of 65% (95% CI, 61–68%) and a specificity of 99% (95% CI, 99–99%). The area under the ROC curve of the method derived from Al-Rawas *et al.* for diagnosing insufficient respiratory effort was 0.88 (95% CI, 0.87–0.89). At the same threshold of 5 cmH₂O, this method predicted insufficient effort with a sensitivity of 100% (95% CI, 99–100%) and a specificity of 61% (95% CI, 60–62%). The area under the ROC curve of Vicario *et al.*'s method for diagnosing insufficient respiratory effort was 0.82 (95% CI, 0.80–0.84). At the same threshold of 5 cmH₂O, Vicario *et al.*'s method predicted insufficient effort with a sensitivity of 44% (95% CI, 40–47%) and specificity of 99% (95% CI, 99–99). These results are summarized on top of Table 3. The AUROC of the CDME method was statistically higher than for competing methods.

3.2. Diagnosis of excessive effort

The area under the ROC curve of the CDME method for diagnosing excessive respiratory effort was 0.97 (95% CI, 0.97–

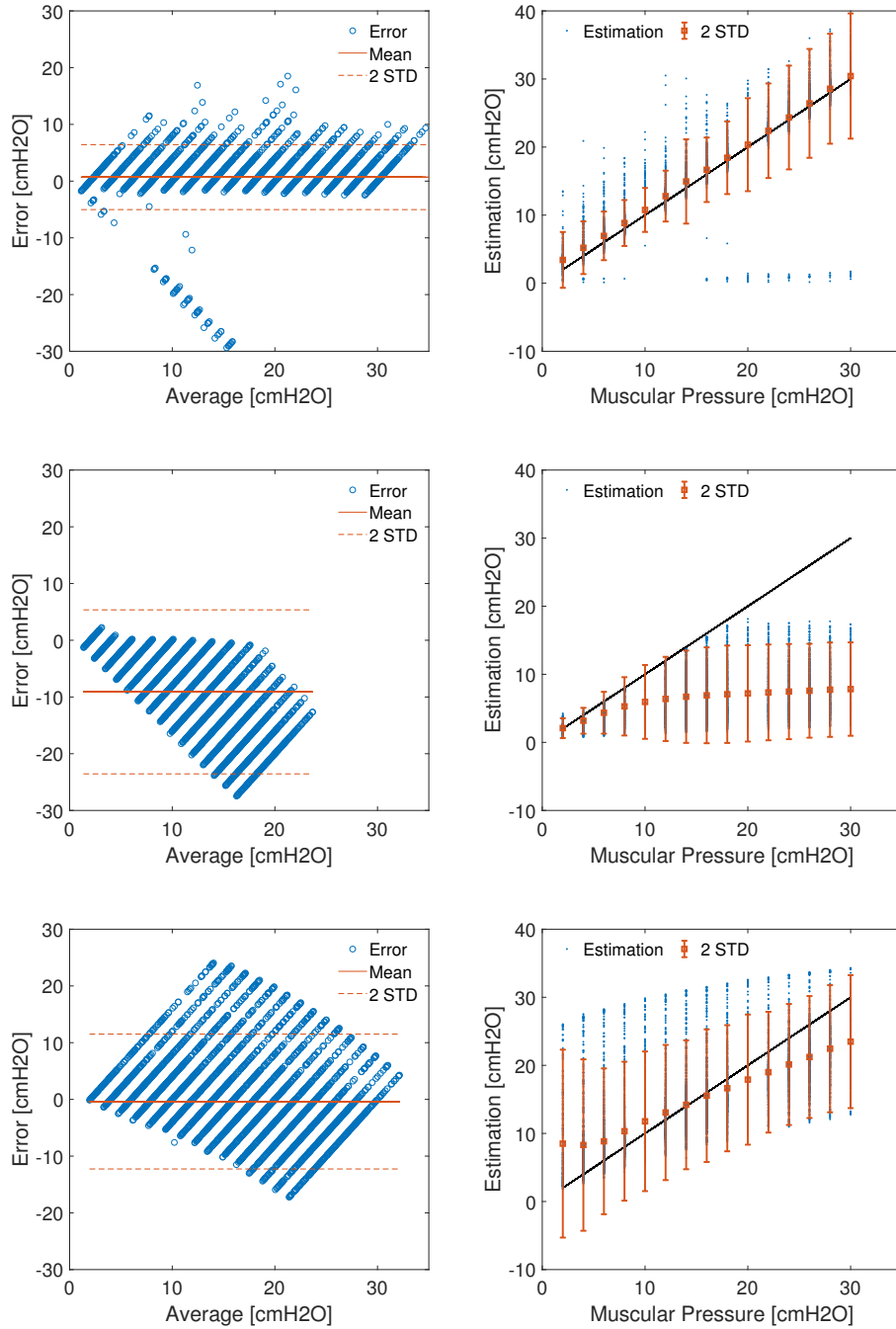


Figure 4: Bland-Altman (LEFT) and Correlation (RIGHT) plots including 95% limits of agreement (2STD) for the three tested methods: The proposed CDME method (TOP), Al-Rawas *et al.* (MIDDLE) and Vicario *et al.* (BOTTOM). Cycles with an ineffective breath or with $Q_{max} > 2 L/s$ have been excluded.

0.98). At the threshold of 15 cmH₂O, this method predicted excessive effort (muscle pressure greater than 15 cmH₂O) with a sensitivity of 98% (95% CI, 97–98%) and a specificity of 93% (95% CI, 92–94%). The area under the ROC curve of the method derived from Al-Rawas *et al.* for diagnosing excessive respiratory effort was 0.68 (95% CI, 0.67, 0.69). At the same threshold of 15 cmH₂O, this method predicted excessive effort with a sensitivity of 4% (95% CI, 3–4%) and a specificity of 100% (95% CI, 100–100%). The area under the ROC curve of

Vicario *et al.*'s method for diagnosing excessive respiratory effort was 0.87 (95% CI, 0.86–0.88). At the same threshold of 15 cmH₂O, Vicario *et al.*'s method predicted excessive effort with a sensitivity of 76% (95% CI, 75–78%) and a specificity of 83% (95% CI, 82–84%). These results are summarized in the middle of Table 3. The AUROC of the CDME method was statistically higher than those of competing methods. Analysis by defining excessive effort as muscle pressure higher than 11 cmH₂O led to similar results (see the bottom of Table 3).

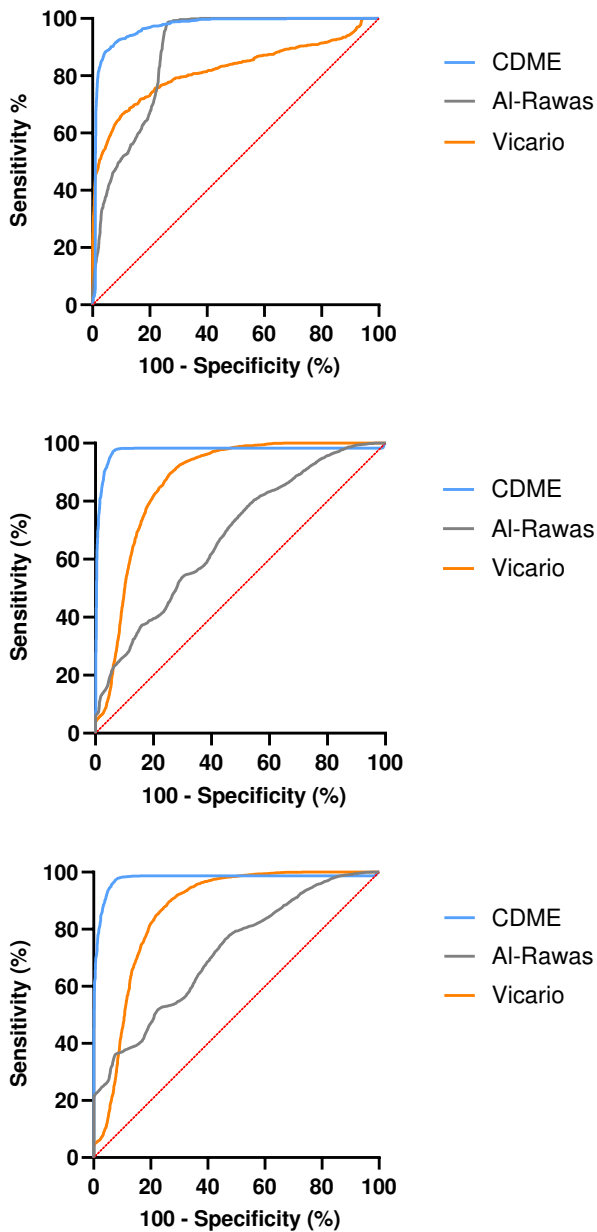


Figure 5: Receiver operating characteristic (ROC) curves of the three tested methods. TOP: Insufficient respiratory effort ($P_{mus} < 5 \text{ cmH}_2\text{O}$). MIDDLE: Excessive respiratory effort ($P_{mus} > 15 \text{ cmH}_2\text{O}$). BOTTOM: Excessive respiratory effort ($P_{mus} > 11 \text{ cmH}_2\text{O}$).

3.3. Classification accuracy

Classification accuracy was significantly different for each method ($p < 0.0001$ by global χ^2 test). Overall, our method allowed to correctly classify 92% of respiratory cycles, versus 33% for the method derived from Al-Rawas *et al.* ($p < 0.0001$ versus CDME) and 64% for Vicario *et al.*'s method ($p < 0.0001$ versus both CDME and the method derived from Al-Rawas *et al.*).

In order to test the robustness of this result towards the magnitude of simulated muscular pressure, we conducted in the ap-

pendix a sensitivity analysis that excludes cycles with simulated muscular pressure larger than $25 \text{ cmH}_2\text{O}$. The results of this analysis (7257 cycles) are provided in Table 5. The result obtained is similar to the one presented in the main analysis, with a classification accuracy of 38%, 91%, and 72% for the method derived from Al-Rawas *et al.*, CDME, and Vicario's method, respectively ($p < 0.001$ for all comparisons).

3.4. Computational load

The computation cost of the method derived from Al-Rawas *et al.* and of the CDME method are similar, in the sense that they are both linearly proportional to the sampling frequency. Their computational load is associated to the resolution of several standard least squares problems: two for the former against four for the latter. The dimension of these optimization problems is bounded by the number of signal samples measured during a ventilator cycle. In contrast, the computation cost of Vicario *et al.*'s method is significantly higher. Indeed, it requires to solve a least squares problem for each possible value of t_m (see [12]). Moreover, the cost of each least squares problem is large, since it includes inequality constraints, and no closed-form solution is available (unlike the standard unconstrained least squares problems involved in the other two methods).

Since the complexity of the three methods is increasing with the sampling frequency, all of them can be implemented in real time provided that the sampling frequency is small enough. In this study, each method was implemented with the highest sampling rate that was compatible with real-time execution. That is, with an execution time smaller than the period of the shortest respiratory cycle (arbitrarily set to 1.5 second). The estimation methods were implemented in the form of a Matlab script running on an Intel Core i7-10850H CPU, with a clock frequency of 2.70 GHz.

4. Discussion

We herein report an innovative method for estimating respiratory muscle pressure in patients invasively ventilated in PSV. Similar to [12], our approach does not require any interruption of the flow delivered to the patient (see, *e.g.*, [9]). The benefit of our estimation method is twofold. From a theoretical perspective, our work clarifies the identifiability issues associated with respiratory mechanics parameter estimation, completing the discussion outlined in [12]. From a numerical viewpoint, in contrast with [12], the proposed method does not require to solve a computationally expensive constrained least-squares optimization problem.

The main results of this study are the following:

- the proposed method can be applied to all respiratory cycles generated with a mechanical simulator (provided that ineffective efforts are excluded);
- the computational load for analyzing each cycle is short, allowing for real-time implementation;

Method:	CMDE	Al-Rawas	Vicario
AUROC	0.97 (0.97,0.98)	0.88 (0.87,0.89)	0.82 (0.80,0.84)
Sensitivity (%)	65 (61,68)	100 (99,100)	44 (40,47)
Specificity (%)	99 (99,99)	61 (60,62)	99 (99,99)

Insufficient respiratory effort (defined by muscle pressure < 5 cmH₂O). Average and 95 % CIs. AUROC: Area Under the Receiver Operating Curve.

Method:	CMDE	Al-Rawas	Vicario
AUROC	0.97 (0.97,0.98)	0.68 (0.67,0.69)	0.87 (0.86,0.88)
Sensitivity (%)	98 (97,98)	4 (3,4)	76 (75,78)
Specificity (%)	93 (92,94)	100 (100,100)	83 (82,84)

Excessive respiratory effort (muscle pressure > 15 cmH₂O).

Method:	CMDE	Al-Rawas	Vicario
AUROC	0.98 (0.97,0.98)	0.71 (0.71,0.73)	0.86 (0.86,0.87)
Sensitivity (%)	98 (98,99)	16 (15,17)	90 (89,91)
Specificity (%)	89 (88,90)	100 (100,100)	73 (71,75)

Excessive respiratory effort (muscle pressure > 11 cmH₂O).

Table 3: Accuracy of three methods for diagnosing insufficient or excessive respiratory efforts (two different thresholds are used to define excessive effort).

- the performance in diagnosing insufficient effort is good, similar to that of the method derived from Al-Rawas *et al.*'s;
- the performance in diagnosing excessive effort is excellent, and substantially better than previously published methods.

The rest of this section provides a more detailed discussion on these points.

4.1. Performance in diagnosing insufficient effort

The proposed CDME method makes it possible to diagnose insufficient effort with a high specificity at the cost of an intermediate sensitivity. Thus, the risk associated with CDME is to under-diagnose insufficient efforts. CDME should therefore be combined with other techniques to improve the detection of insufficient effort: clinical examination, P0.1, dynamic analysis of the consequences of a change in the level of pressure support. Conversely, the method derived from Al-Rawas *et al.* [13] exhibits a high sensitivity but a lower specificity, causing risk of overdiagnosing inadequate effort. This method uses the expiratory part of the cycle to estimate the time constant of the respiratory system, and the terminal part of the insufflation to estimate the compliance and resistance. In the related mathematical model, it appears that the inspiratory muscle pressure is not taken into account, which means that the (implicit) conditions of validity of Al-Rawas *et al.*'s method are a passive expiration, and a passive end-insufflation. It is thus expected that the latter method yields better results for diagnosing weak efforts, a situation in which the end of insufflation is more likely to be passive, or at least the muscle pressure at end-insufflation is negligible compared to the level of pressure support. Finally and importantly, insufficient efforts are substantially less frequent than excessive efforts in recent studies (see, *e.g.*, [9] and

Method:	CMDE	Al-Rawas	Vicario
Insufficient	474 (64%)	735 (100%)	320 (44%)
Normal	3336 (91%)	1943 (53%)	1941 (53%)
Excessive	4053 (98%)	151 (4%)	3165 (76%)
Total	7863 (92%)*	2829 (33%)*	5426 (64%)*

Table 4: Classification accuracy, for detecting insufficient, normal, or excessive respiratory effort. * denotes $p < 0.0001$ versus other methods by exact Fisher test.

[8]). While this does not negate the potential toxicity of insufficient effort, this highlights the priority of detecting excessive respiratory effort.

4.2. Performance in diagnosing excessive effort

The performance of the CDME method in diagnosing excessive respiratory effort is excellent, and significantly better than the two previously published methods. Importantly, our results are robust with respect to the threshold defining excessive respiratory effort, which is controversial in the literature. As discussed in the previous section, the method derived from Al-Rawas *et al.* neglects the presence of significant inspiratory effort at the end of insufflation. This situation is likely to occur [27] and, even in some cases, with a respiratory effort exceeding twice the duration of insufflation, defining a short cycle. In case of significant respiratory effort at the end-insufflation, the respiratory system resistance is then strongly underestimated. Thus, the respiratory effort responsible for the generation of the tidal volume is underestimated. Similarly, Vicario *et al.* [12] reported that their method provided disappointing results when the end-inspiratory muscle pressure was not zero. The authors stated that this situation was exceptional. However, physiological studies on patient-ventilator asynchronies revealed that these situations are actually frequent and difficult to detect by simple visual inspection of the ventilator waveforms [27].

4.3. Limitations

While this paper provides a proof of concept of the underlying mathematical method, validated via a large set of experimental data, our work has several limitations. First, this work was carried out on cycles created on a high-fidelity ventilation simulator, not on patients. Thus, analyzed data were not subject to errors caused by other phenomena, such as cardiac activity. Compliance was considered constant, and flow was considered laminar. Ineffective efforts were excluded. Nevertheless, both premature and delayed cycling were analyzed. Whether our results can be transposed to real patient data is unknown. Second, the simulated patients were passive during expiration. Third, only one ventilator was tested, and no endotracheal tube was used. Last, data were recorded with the simulator rather than with the ventilator, implying a different sampling rate. Our objective was to generate a method applicable to a wide range of clinical situations, and thus to the full range of possible combinations of respiratory mechanics and effort, which is possible to test only using a simulator.

Appendix A - Sensitivity analysis

In our main data set, the values of P_{mus} are limited to 30 cmH₂O. This limit has been taken relatively high in order to cover all possible situations. Nevertheless, we verify in Tab. 5 that considering a smaller limit of 25 cmH₂O provides similar results for the classification of insufficient or excessive respiratory effort.

Method:	CMDE	Al-Rawas	Vicario
AUROC	0.97 (0.96,0.97)	0.87 (0.86,0.88)	0.80 (0.78,0.82)
Sensitivity (%)	65 (61,68)	100 (99,100)	44 (40,47)
Specificity (%)	99 (99,99)	59 (57,60)	99 (99,99)

Insufficient respiratory effort (defined by muscle pressure < 5 cmH₂O). Average and 95 % CIs. AUROC: Area Under the Receiver Operating Curve.

Method:	CMDE	Al-Rawas	Vicario
AUROC	0.97 (0.97,0.98)	0.66 (0.65,0.68)	0.85 (0.84,0.85)
Sensitivity (%)	98 (97,98)	4 (3,4)	69 (67,70)
Specificity (%)	93 (92,94)	100 (100,100)	83 (82,84)

Excessive respiratory effort (muscle pressure > 15 cmH₂O).

Table 5: Accuracy of three methods for diagnosing insufficient or excessive respiratory efforts (on a data set limited to the cycles for which $P_{mus} \leq 25$ cmH₂O).

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