Automatic detection of reverse-triggering related asynchronies during mechanical ventilation in ARDS patients using flow and pressure signals

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Abstract

Asynchrony due to reverse-triggering (RT) may appear in ARDS patients. The objective of this study is to validate an algo-rithm developed to detect these alterations in patient–ventilator interaction. We developed an algorithm that uses flow and airway pressure signals to classify breaths as normal, RT with or without breath stacking (BS) and patient initiated double-triggering (DT). The diagnostic performance of the algorithm was validated using two datasets of breaths, that are classified as stated above. The first dataset classification was based on visual inspection of esophageal pressure (Pes) signal from 699 breaths recorded from 11 ARDS patients. The other classification was obtained by vote of a group of 7 experts (2 physicians and 5 respiratory therapists, who were trained in ICU), who evaluated 1881 breaths gathered from recordings from 99 sub-jects. Experts used airway pressure and flow signals for breaths classification. The RT with or without BS represented 19% and 37% of breaths in Pes dataset while their frequency in the expert's dataset were 3% and 12%, respectively. The DT was very infrequent in both datasets. Algorithm classification accuracy was 0.92 (95% CI 0.89–0.94, $P < 0.001$) and 0.96 (95% CI 0.95–0.97, $P < 0.001$), in comparison with Pes and experts' opinion. Kappa statistics were 0.86 and 0.84, respectively. The algorithm precision, sensitivity and specificity for individual asynchronies were excellent. The algorithm yields an excellent accuracy for detecting clinically relevant asynchronies related to RT.

Keywords ARDS · Patient–ventilator interaction · Respiratory asynchrony · Reverse-triggering

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1 Introduction

Acute respiratory distress syndrome (ARDS) is a diffuse inflammatory injury of the lung, clinically characterized by marked gas exchange abnormalities and reduced respiratory system compliance [1]. Overall, ICU and hospital mortalities are around 35% and 40%, respectively. ARDS management requires the prompt identification and treatment of the primary causes of lung injury, while providing physiological support until recovery. Protective mechanical ventilation (MV) has been initially proposed in the nineties and has become the standard of care. The main points of this strategy include reducing tidal volume (Vt), using positive end-expiratory pressure (PEEP) to improve lung recruitment and avoiding high driving and end-inspiratory pressures [2–6].

Patient–ventilator asynchronies are frequently found during assisted MV, where subjects interact with the ventilator [7]. Following the widespread use of low Vt in ARDS MV, Pohlman et al. reported double triggering (DT) in patients heavily sedated, where asynchrony was unexpected [8]. This finding was called breath stacking (BS). During assisted ventilation, DT is observed when patient's inspiratory time exceeds ventilator set's inspiratory time. There, the subject effort triggers two (or even more) assisted breaths. However, the underlying mechanism in those ARDS cases is possibly related to the respiratory entrainment described in animal models and anesthetized humans [9–11]. In this setting, a controlled insufflation by the ventilator triggers a patient inspiratory effort. If ventilator triggering threshold is overcome, the latter may trigger an assisted breath (RT with BS). Otherwise, the patient's effort will fail to trigger the ventilator (RT without BS).

Our aim was to evaluate an algorithm for DT, RT with and without BS detection in signals previously recorded in ARDS patients during volume-controlled continuous mandatory ventilation (VC-CMV).

2 Materials and methods

A specific algorithm for asynchrony detection in respiratory data files was developed. Patient data was obtained with a FluxMed mechanical monitor and signals were acquired using FluxView software (MbMed, Buenos Aires, Argentina) at a sampling rate of 256 Hz. The output file from the monitor is a tab-delimited text file with variables name in the headings.

The scope of the algorithm is the detection of RT related asynchronies (with and without BS) and DT in signals from VC-CMV ventilated patients for a research purpose. VC-CMV is the most frequently used mode in ARDS patients in clinical settings or randomized trials mostly during the early phase of treatment [2, 12]. In this mode, the operator set a respiratory rate, a Vt, and a fixed inspiratory time and/or $\dot{V}$ are set by the operator. Constant inspiratory $\dot{V}$ is routinely used in our clinical practice.

2.1 Description of the algorithm for asynchrony detection

A set of previously acquired raw respiratory data files containing Paw and $\dot{V}$ signals from patients suffering from ARDS and ventilated with protective MV using VC-CMV were used to derivate the algorithm. This data was only used for tuning functions parameters and not for diagnostic performance testing. The algorithm was embedded in a non-distributed R package [13]. Signals were processed as follows.

First, inspiratory and expiratory phases are established using $\dot{V}$ signal. The algorithm detects whether an inspiratory pause is used. Each breath is then classified as assisted or controlled, based on the finding of a Paw decrease larger than 1 cmH_2O within an 80 ms window before starting insufflation as a sign of subject effort.

RT without BS is searched during inspiration and expiration in controlled breaths (those triggered by the ventilator). In order to detect the latter, each cycle expiratory $\dot{V}$ signal is passed through a 4 Hz low-pass filter. Local maxima and minima from the filtered signal during expiration are located. The first local minimum corresponds to the $\dot{V}$ expiratory peak and is disregarded. Then, the difference between each filtered $\dot{V}$ local minimum and the preceding local maximum is computed. If this distance exceeds a threshold, an expiratory RT without BS is established (Fig. 1). For this purpose, a baseline threshold was empirically set at 3 L/min. This threshold is further adjusted based on the suspicion of cardiac activity and the proportion of volume that remains to be exhaled. Cardiac activity is suspected if more than 1 local maxima is found with a frequency exceeding 40 per minute. In that case, the threshold was doubled (Fig. 2). Finally, a correction based on the expiratory volume was included in the algorithm as it is expected that given a small patient effort related to this asynchrony, the observed increase in $\dot{V}$ will be larger at lower lung volumes due to an elastic recoil pressure of the lower respiratory system:

$$\text{Adjusted threshold} = \text{threshold} \times e^{\frac{-Volume}{Vt}}$$

Here, Vt denotes the expiratory Vt and volume accounts for the decreasing expiratory volume observed where the suspected asynchrony is detected.

Inspiratory RT without BS is defined as a patient inspiratory effort following the beginning of a constant

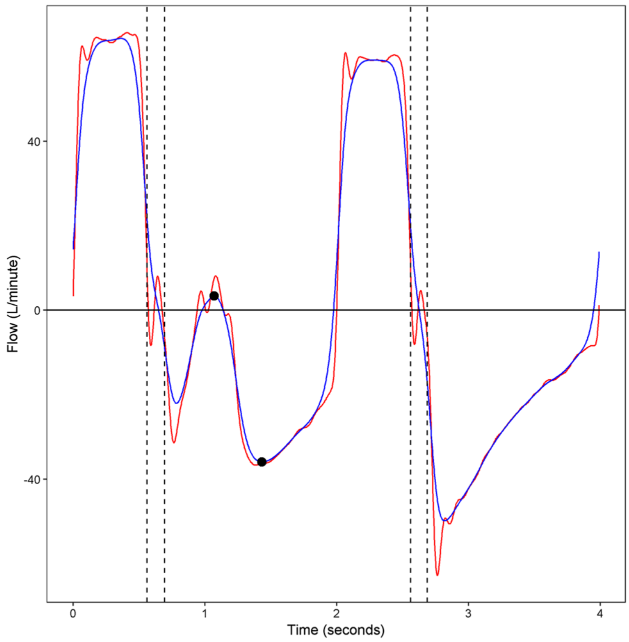

Fig. 1 Reverse-triggering without breath stacking detection during expiratory time. Flow-time and 4 Hz low-pass flow filtered signal are displayed in red and blue respectively. The dashed lines enclose the inspiratory pause. The black circles in the first breath represent local maximum and minimum during expiration. The flow difference between them is 14.8 L/min, while the adjusted threshold is 1.26. Thus, the algorithm classifies the local maximum as a reverse-triggering

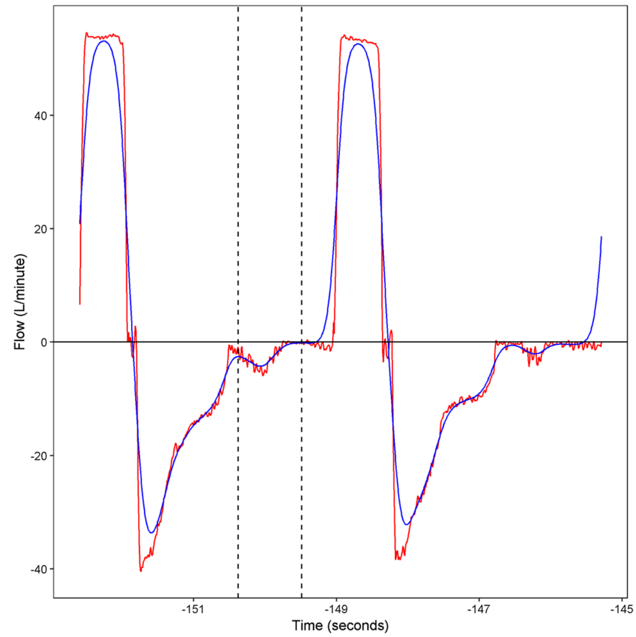

Fig. 2 Threshold adjustment for reverse-triggering without breath stacking adjustment during expiratory time. Flow-time and 4 Hz low-pass flow filtered signal are displayed in red and blue respectively. The dashed lines represent the local maxima time in the first breath. The difference between both local maxima is 0.886 s (rate 67.67/min). Thus, the algorithm assumes that this represents cardiac noise. The adjusted threshold are 4.92 and 5.24 L/min while local maxima to minima difference were 1.71 and 0.03 L/min, respectively

flow-controlled breath. If this occurs, an unexpected decrease in Paw before ventilator inspiratory time would be observed. In order to detect this, first Paw-time signal is low-filtered (4 Hz). Local maxima points are identified in the resulting filtered signal during inspiration. The time between the first local maxima and the end of insufflation is calculated. The asynchrony is recognized when this period is larger than 200 ms or 1/3 of the median insufflation time (in the case that insufflation time is lower than 600 ms) (Fig. 3).

DT and RT with BS are defined when an assisted breath follows an assisted or controlled ventilator breath with an expiratory Vt and time less than one half of the whole recording median values of these variables, or when 2 or more consecutive insufflations occur without expiration between them. The latter is detected when the insufflation time is larger than 1.5 times the median time of the whole recording. An assisted breath is established when a decrease larger than 1 cmH_2O in airway pressure is observed in a time window of 80 ms before insufflation. RT related asynchronies are established when the initial breath is not triggered by the patient, as stated above.

Datasets were processed with a x64-based PC (processor: Intel Core i3-5010U CPU 2.10 GHz, RAM memory: 12.0 GB) running R version 3.5.1 (2018-07-02) with

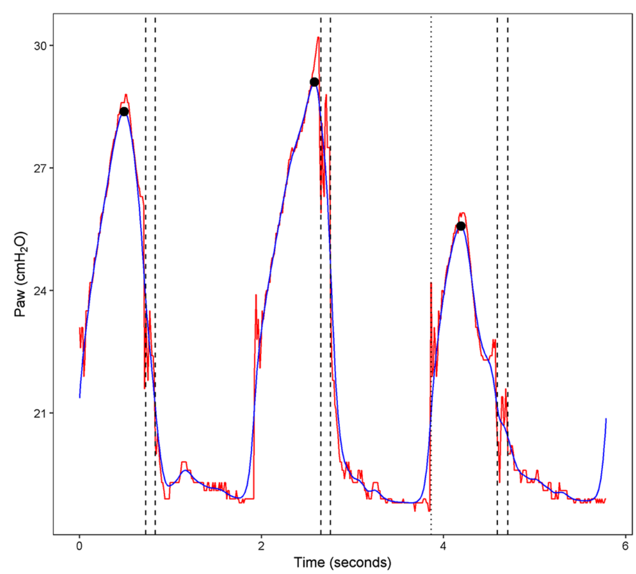

Fig. 3 Reverse-triggering without breath stacking detection during inspiratory time detection. Airway pressure–time and 4 Hz low-pass Paw filtered signal are displayed in red and blue respectively. The dashed lines enclose the inspiratory pause. The black circles represent local maximum of filtered Paw signal during inspiration. Each breath time between these points and plateau initiation is 0.234, 0.070 and 0.398 s. Insufflation time is 0.7 s. Therefore, breaths 1 and 3 are classified as reverse-triggering

RStudio desktop IDE version 1.1.456 in Windows 10. Average processing times were 8.97 ± 0.73 s per 30 min of respiratory signals or 10.09 ± 0.85 ms per breath.

2.2 Algorithm performance

Two types of comparisons were made in order to evaluate the performance of the algorithm. Two sets of respiratory data files, acquired from different subjects and not previously employed for developing the algorithm, were used. These recordings were obtained from ARDS ventilated adult patients, according to Berlin's definition, without infusion neuromuscular blocking agents [1]. In both cases, Google Forms with figures containing ten breaths linked to tables with options for each cycle were offered to the raters for its classification.

First, a set of files containing respiratory data including esophageal pressure (Pes) recordings was evaluated by an expert (POR) and each breath was classified as normal, RT with or without BS or DT and compared against the algorithm diagnosis. Pes was used as surrogate of subject respiratory muscle activity. Second, other set of randomly selected strips of 20 consecutive breaths gathered from recordings of a multicenter study of ARDS patients was classified in the same categories by experts using $\dot{V}$ and Paw signals [14, 15]. The first breath of each strip was disregarded because it could be difficult for the experts to classify it without the previous breathing history. Then, each breath class was assigned by expert's vote and compared with the algorithm output.

For both comparisons, different classification metrics such as accuracy, Cohen's kappa coefficient (κ), sensitivity, specificity and positive and negative predictive values were calculated using confusionMatrix function from caret package. These performance statistics were calculated on a breath by breath basis. Additionally, the median (25th to 75th range) of accuracy and κ assessed by subject were also obtained. All statistical analysis and graphics were performed with R software.

3 Results

3.1 Pes dataset

Respiratory data from 11 patients, including 710 breaths with Pes signal, was used for the first evaluation. Clinical data from these patients is included in Table 1. Ventilatory parameters were in accordance with protective ARDS MV, including low Vt, high respiratory rate and moderate to high PEEP levels. Patients were deeply sedated (low RASS value). Breath classification is shown in Fig. 4. As expected, DT frequency was low. Overall algorithm classification accuracy was 0.92 (95% CI 0.89–0.94, $P < 0.001$). κ statistic was 0.86. When these parameters were assessed by subject, the median (25th to 75th range) values were 0.95 (0.9–0.97) and 0.91 (0.82–0.95) respectively. Specific classes detection performance was highly accurate (Table 2).

Table 1 Clinical data expressed as median (range) or median (25–75 quartile) from patients of Pes and experts' datasets

Variables	Pes	Experts
Vt (mL/kg)	6.19 (5.86–6.48)	6.06 (5.88–6.53)
RR (bpm)	27 (25.5–29)	26 (23–30)
PEEP (cmH_2O)	12.1 (9.5–13)	13 (10–16)
Pplat (cmH_2O)	23 (18.75–23.5)	25 (22–27.6)
pH	7.36 (7.34–7.4)	7.35 (7.3–7.41)
PaO_2/FiO_2 (mmHg)	212.5 (156.87–263.33)	183.51 (146.67–230)
RASS	− 5 (− 5 to 4)	− 5 (− 5 to 4)

Pes esophageal pressure classification, *Vt* tidal volume, *RR* respiratory rate, *PEEP* positive end-expiratory pressure, *Pplat* inspiratory plateau pressure, *RASS* Richmond Agitation and Sedation Scale [29]

3.2 Experts' dataset

A random sample of 1881 breaths was gathered from signals obtained from 99 patients with ARDS and they were evaluated by 7 experts (2 physicians and 5 respiratory therapists). These patients were also treated with protective MV parameters and were heavily sedated (Table 1). The frequency of asynchronies in these breaths was lower compared with the Pes dataset (Fig. 4) and, again, DT was very infrequently found. Between experts, complete agreement in breaths classification was attained in 72.88%. Disagreements were more frequent in RT without BS and DT classes (median probability [P25–P75]): 0.14 [0–0.2] and 0.44 [0.36–0.52] respectively).

The algorithm classification compared with the experts' opinion disclosed an overall accuracy of 0.96 (95% CI 0.95–0.97, $P < 0.001$) and a κ statistic of 0.84. Moreover, the medians (25th to 75th range) of these parameters calculated by subject were 1 (0.95–1) and 0.78 (0.6–0.97). Table 3 summarizes the diagnostic performance of the algorithm compared with experts by asynchrony class. Disregarding DT specific diagnostic performance due to their low prevalence, individual asynchrony detection was very accurate. It is noteworthy that while sensitivity for RT without BS detection in this analysis was lower (0.76) than the same parameter when Pes dataset classification was used (0.86), the specificity was extremely high (0.99).

3.3 Detection of RT without BT

Pes and experts' datasets included 2580 breaths. The algorithm counted 443 RT without BS. Among them, 324

Fig. 4 Distribution of breath classes in the datasets percentage of breaths classes in Pes and experts' datasets. *RT* reverse-triggering, *BS* breath stacking, *DT* patient initiated double-triggering

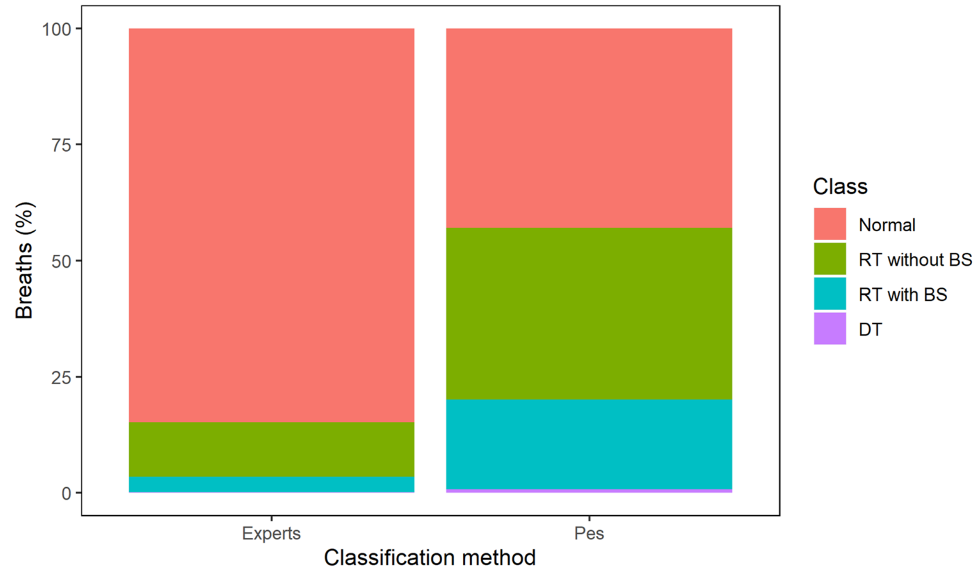

Table 2 Diagnostic performance of breaths by the algorithm against Pes classification

Metric	Normal	RT	
		Without BS	With BS
Sensitivity	0.97	0.86	0.90
Specificity	0.91	0.98	1.00
PPV	0.89	0.96	1.00
NPV	0.97	0.92	0.98
Prevalence	0.43	0.37	0.19

Patient initiated double-triggering class was not included in the table because its prevalence was too low (<0.01)

RT reverse-triggering, *BS* breath stacking, *PPV* positive predictive value, *NPV* negative predictive value

Table 3 Diagnostic performance of breaths by the algorithm against experts' classification

Metric	Normal	RT	
		Without BS	With BS
Sensitivity	0.99	0.74	0.89
Specificity	0.80	0.99	1.00
PPV	0.96	0.94	0.93
NPV	0.95	0.97	1.00
Prevalence	0.85	0.12	0.03

Patient initiated double-triggering class was not included in the table because its prevalence was too low (<0.01)

RT reverse-triggering, *BS* breath stacking, *PPV* positive predictive value, *NPV* negative predictive value

(71.14%) were exclusively detected during expiration, 63 (14.22%) on inspiration and the remaining 56 (12.63%) on both phases of the respiratory cycle.

4 Discussion

The main finding of this study is that an automatic algorithm could accurately detect asynchronies related to RT in VC-CMV ventilated ARDS patients using flow and airway pressure signals. Accuracy was very high for both RT with and without BS. Nevertheless, RT without BS detection sensitivity was slightly lower while keeping a high specificity. Genuine patients' DT (one patient effort triggers two respiratory cycles) diagnostic performance could not be evaluated because these asynchronies were very infrequent in both datasets.

Patient–ventilator asynchronies have been related to clinical outcomes in studies including patients under spontaneous or assisted MV [7, 16]. During spontaneous MV, patients interact with the machine and the ventilator response is dictated by a set of rules. Thus, according to the mode of MV, certain asynchronies can be expected. Modes that react in proportion to patients' effort show the better results in terms of patient–ventilator interaction [17]. These modes are currently used in patients recovering from acute respiratory failure. During the acute phase of the disease, most clinicians choose VC-CMV in order to accurately limit Vt. Patients are usually sedated, so patient–ventilator interaction is not expected. Additionally, the use of neuromuscular blocking agents in the early phase of ARDS is frequent, as this treatment improved the adjusted 90-day survival and increased the time off the ventilator [18]. Thus, asynchrony is not expected in these patients. However, BS have been reported in ARDS patients, exposing them to injurious ventilatory conditions [8]. Akoumianaki et al. reported RT in a small series of heavily sedated ARDS patients in 12 to 100% of the recording time [9]. RT was detected with esophageal pressure recordings and different patterns of entrainment were described. Respiratory entrainment is a puzzling reflex that has been reported in different settings, both in humans and animal models. Although its physiological significance remains unrevealed, its clinical consequences on the ventilatory pattern can be easily understood. As stated above, if patient's triggered effort overcomes the ventilator trigger, the machine will start an insufflation (RT with BS). RT with BS may induce large changes in lungs volume and potentially high driving pressures, which have been linked to prognosis in ARDS [6]. On the other hand, RT without BS may induce plyometric diaphragmatic contractions, which in turns may induce muscle injury. RT in ARDS patients requires further study and accurate algorithm for its detection is desirable.

Most clinical studies of patient–ventilator interaction have used expert's visual inspection of respiratory signals as the main classification tool. This is time consuming, susceptible to reproducibility issues and not practical in evaluating large datasets. Ancient studies have mainly used flow and airway pressure signals for breath classification [7, 19]. With this approach, we found a complete classification agreement between our experts in 73% of the breaths of the dataset. This moderate result may be related to the reasons stated above. Other authors have used esophageal pressure as patient's effort surrogate [20]. It has suggested that detection of Ineffective Efforts (IE) and other asynchronies, such as auto-triggering, could be improved with the use of electrical activity of the diaphragm (EAdi) signal [21, 22]. However, both esophageal pressure monitoring and EAdi are invasive, require specific hardware and are not widely available. Esophageal pressure may be affected by cardiac noise and tracing interpretation could be challenging. EAdi appears very sensitive, but it could miss IE when accessory inspiratory muscles are the main source of the work of breathing [22].

DT can be easily detected by the visual inspection of flow and airway pressure curves. Pohlman et al. described frequent DT (breath stacking) in ARDS patients under protective MV that produced large Vt which increased lung injury [8]. They defined these DT as two breaths occurring in close proximity, that appeared to represent a single respiratory effort. Although this definition may be good enough for the human visual inspection of curves, it is not useful as a rule for developing an algorithm. In a different setting, Thille et al. proposed that a DT should be defined as two cycles where the first expiratory time is less than one half of the mean inspiratory time [7]. Mulqueeny et al. proposed that DT could be defined if the expiratory time between these inspirations was less than 500 ms [23]. More recently, the BREATH criteria proved that the inclusion of rules based on both inspiratory and expiratory time and Vt may improve the detection of high-volume injurious breath stacking [24]. Our algorithm proposed a DT and RT definition based both on the historic expiratory Vt and time. DT was defined when the first breath was assisted, while RT was classified when the initial breath was not triggered by the patient. As is shown in Tables 2 and 3, this definition of RT was highly sensitive and extremely specific according to diagnostic performance evaluation.

Automatic asynchrony detection algorithms have been developed and validated mostly in spontaneous or assisted mechanical ventilation settings. In this setting, IE is one of the most challenging asynchronies for detection. RT without BS produces the same distortion in flow and airway pressure waveforms as IE during expiratory time. Several algorithms have been proposed for IE detection during the use of flow and pressure signals as raw data. Mulqueeny et al. used the first and second derivatives of flow signal to detect perturbations in expirations after its first 600 ms [23]. They studied patients in conventional ventilation and in non-invasive ventilation, and reported a sensitivity of 91% and a specificity of 97% for IE using transdiaphragmatic pressure as gold standard. Chen et al. developed an algorithm based on peak to peak difference of both expiratory flow and airway pressure during IE [25]. A flow difference of 5.45 L/min was associated with a sensitivity of 0.91 and a specificity of 0.96 for IE detection, while the optimal pressure difference was 0.45 cmH_2O (sensitivity of 0.93 and a specificity 0.92). They acknowledged a significant variation in optimal values between patients, and misclassification problems when small inspiratory Vt or noise (cardiac activity or respiratory secretions) were present. Our algorithm, while using some of the principles of these two previous studies for detecting RT without BS during the expiratory phase, adjusts the flow difference threshold (starting at 3 L/min) based on two variables: cardiac noise detection and instant expiratory volume at the flow local maximum time (Fig. 2). These two rules possibly increase precision, yielding a sensitivity of 0.86, a specificity of 0.98 and an excellent value of κ statistic when Pes dataset was used ($\kappa = 0.86$). Blanch et al. reported the diagnostic performance of Better Care® system for IE detection against expert visual inspection (8 patients) and Edi recordings (8 patients) [26]. This system fits a theoretical ideal mono-exponential expiratory flow curve and compares it with the actual expiratory flow curve. Then, it calculates the percentage deviation. IE class is defined by a deviation greater or equal than 42%. Compared with expert visual inspection, Better Care achieved sensitivity of 0.91, specificity of 0.91 and κ statistic of 0.79, whereas comparison with EAdi classification yielded sensitivity of 0.65, specificity of 0.99 and κ statistic of 0.73. Cuvelier et al. using a phase portrait of flow over a time window, showed different patterns between normal and IE breaths, and built an algorithm based on that principle [27]. However, IE were very rare in their validation dataset, precluding any diagnostic performance calculation. Finally, Gutierrez et al. showed some interesting results with spectral analysis of expiratory flow [28]. They found good correlation between the ratio of the first and the fundamental harmonic with the asynchrony index. So far, all the methods stated above detect IE during expiration in assisted or spontaneous mechanical ventilation. However, RT without BS may be observed during ventilator inspiration (Fig. 3). These represented 26.8% of them in our datasets. Thus, these inspiratory asynchronies could be missed without a specific rule.

The current study has some limitations. First, the algorithm, experts and Pes evaluations may miss RT when patient's effort is small. A more sensitive tool, such as EAdi, may overcome this situation, but this technique has its own limitations and it is not available for us. Second, the algorithm has been developed and proved useful only in VC-CMV with constant flow (square shape). This responds to our need to develop a tool for research. Nevertheless, if some rules are modified, the algorithm spectrum might be enlarged. Third, it is possible to misclassify RT occurring during a large inspiratory pause, which is usually not used in clinical practice. This was not tested. The main strength of the study is that the diagnostic performance of the algorithm was proved against Pes and expert opinion from a dataset obtained from a large number of ARDS patients admitted to different hospitals.

In conclusion, the algorithm accurately detects clinically relevant asynchronies that can be related to RT in VC-CMV ventilated ARDS patients. Further development is required to enlarge the spectrum of modes of MV.

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Compliance with ethical standards

Conflict of interest Matías Madorno is a partner and manager of MBMED S.A. The other authors declare that there is no conflict of interest.

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