ORIGINAL ARTICLE
MECHANICAL VENTILATION

Non-interventional monitoring of expiratory flow limitation during experimental mechanical ventilation

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ABSTRACT

Background: Expiratory flow limitation (EFL) is common among patients in the intensive care unit under mechanical ventilation (MV) and may have significant clinical consequences. In the present study, we examine the possibility of non-interventional detection of EFL during experimental MV.

Methods: Eight artificially ventilated New Zealand rabbits were included in the experiments. EFL was induced during MV by application of negative expiratory pressure (−5, −8 and −10 hPa) and detected by the negative expiratory pressure technique. Airway pressure (P_{aw}) and gas flow (V') were digitally recorded and processed off-line for the evaluation of respiratory mechanics. The method is based on the computation and monitoring of instantaneous respiratory resistance $R_{rs}(t)$. The resistive pressure ($P_{aw,res}(t)$) is calculated by subtracting from P_{aw} its elastic component and the end-expiratory pressure, as assessed by linear regression. Then, $R_{rs}(t)$ is computed as the instant ratio $P_{aw,res}(t)/V'(t)$.

Results: Two completely different patterns of expiratory $R_{rs}(t)$ separate the cases with EFL from those without EFL. Small and random fluctuations are noticed when EFL is absent, whereas the onset of EFL is accompanied by an abrupt and continuous rise in $R_{rs}(t)$, towards the end of expiration. Thus, EFL is not only detected but may also be quantified from the volume still to be expired at the time EFL occurs.

Conclusion: The proposed technique is a simple, accurate and non-interventional tool for EFL monitoring during MV.

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Respiratory system resistance in expiratory flow limitation during mechanical ventilation https://bit.ly/34hU6Bv

Cite this article as: Marinakis G, Paraschos M, Patrani M, *et al.* Non-interventional monitoring of expiratory flow limitation during experimental mechanical ventilation. *ERJ Open Res* 2021; 7: 00264-2020 [https://doi.org/10.1183/23120541.00264-2020].

Received: 12 May 2020 | Accepted after revision: 25 Sept 2020

Introduction

Detection of expiratory flow limitation (EFL) is crucial during mechanical ventilation (MV), because of its adverse effects on respiration and cardiovascular function [1–7]. Dynamic hyperinflation and increase of mean alveolar pressure are the net result of air trapping due to EFL. Increase of the necessary work of breathing to trigger assisted mode ventilation is also accompanying EFL. EFL may cause or aggravate uneven distribution of inspired gas. Therefore, EFL continuous detection may help for early and better adjustments of ventilatory setting and constants in order to confront its unpleasant side effects.

Previous studies proposed different techniques for detection of EFL during MV. Their common characteristic is the induction of variation of the expiratory pressure, such as the alteration of positive end-expiratory pressure (PEEP) [8, 9], the expiratory circuit resistance [10, 11] or the application of a negative expiratory pressure (NEP), which became the gold standard for EFL detection [12], with a wide applicability in most experimental and clinical research. The NEP technique does not require performance of forced vital capacity (FVC) manoeuvres, collaboration on the part of the patient or use of a body box [13, 14]. Comparison of expiratory flow under different driving expiratory pressures is the clue for the diagnosis of EFL. Such a manoeuvre is rather easy under conditions of spontaneous breathing, but it is hardly practical during MV. Furthermore, all these methods require some intervention in the regulation of ventilation, while they are not suitable for continuous monitoring [5].

We firstly proposed (Vassiliou *et al.* [15]) that strongly negative values of expiratory reactance, recognised with the aid of the forced oscillation technique method suggest the presence of EFL with high sensitivity and specificity during experimental MV. Since then, newer investigations confirmed the validity and usefulness of the proposed technique, which is easier to apply during spontaneous breathing than during mechanically assisted ventilation [13, 15–24].

Other studies have focused on respiratory system resistance (R_{rs}) and have shown that a pronounced negative volume dependence of resistance characterises the presence of EFL during MV [25, 37, 38]. These methods have been proved accurate for detecting EFL but none of them offers a quantitative measure of the disorder (*e.g.* the volume left to be expired), when EFL is established.

The method evaluated in this study does not require any change in the MV and enables cycle-by-cycle detection of EFL. It is based on the computation and monitoring of instantaneous respiratory resistance ($R_{rs}(t)$).

Methods

Experiments

Eight New Zealand rabbits (2.1–2.5 kg) were mechanically ventilated at 50 breaths·min^{-1} and tidal volume (V_T) of 25 mL. The animals were already anaesthetised with sodium thiopental (15–20 mg·kg^{-1}, intravenously (*i.v.*)), tracheostomised and muscle relaxed with vecuronium bromide (0.8 mg·kg^{-1}, followed by continuous *i.v.* infusion of 0.4 mg·kg^{-1}·h^{-1}) immediately after their connection to the ventilator. The same type of endotracheal tube (ET) was used in all experiments (55 mm in length and 3.8 mm in internal diameter) with an *in vitro* determined resistance of 7.41 hPa·s·L^{-1}. All experiments have been performed according to the Declaration of Helsinki conventions for the use and care of animals in biomedical research. Experimental data were recorded during previous studies of the last author [2] during his scientific stage in the Institut National de la Santé et de la Recherche Médicale, INSERM, France under the guidance of the late Resné Peslin.

Ventilator and measuring structure

A computer-driven ventilator, built in the laboratory, was used for the experimental MV [26]. Two rubber bellows were separately controlling inspiration and expiration, permitting the modification of expiratory driving pressure without interruption of ventilation. Expiratory pressure was randomly set at 0, −5, −8 and −10 hPa during measurements, while setting the expiratory pressure at 5 hPa permitted reinflation of the experimental animals between measurements in order to avoid and/or correct atelectasis.

Gas flow (V') was measured with a Fleisch no. 00 pneumotachograph connected to a piezoresistive differential pressure transducer (Honeywell 176/14), and airways pressure (P_{aw}) was measured with a similar transducer. The two transducers were matched for amplitude (±2%) and phase (±2°) up to 15 Hz. The signals were digitised at a sampling rate of 180 Hz using a computer equipped with 12-bit analogue-to-digital and digital-to-analogue conversion board (PCLab, Digimétrie, Perpignan, France). Simultaneously the computer was used to control the pressure and flow delivered by the ventilator [26]. A schematic representation of the experimental set-up is depicted in figure 1.

At each level of end-expiratory pressure (EEP) three consecutive recordings of P_{aw} and V' during six respiratory cycles were performed. In one of the six cycles of the first recording, the expiratory pressure

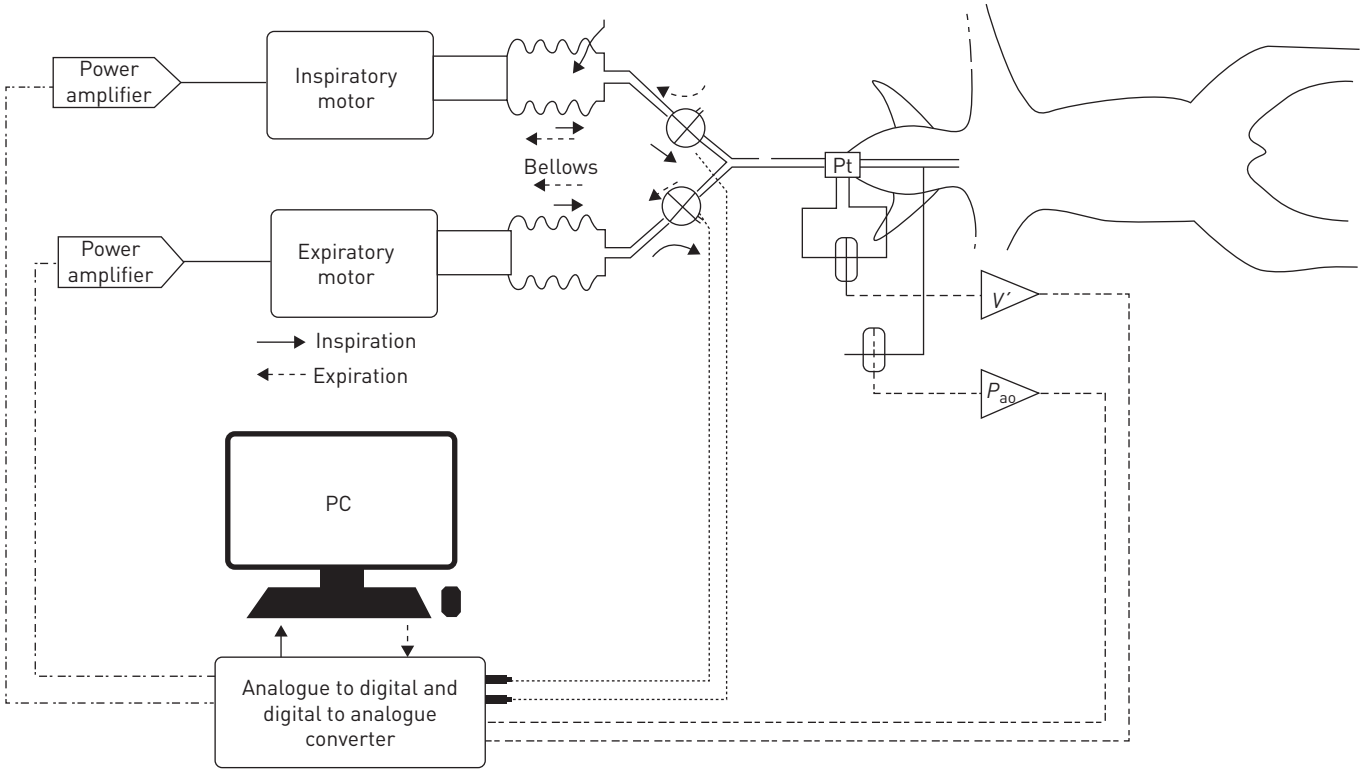

FIGURE 1 Diagrammatic illustration of the measuring, the recording and the driving the experimental artificial ventilation components. Pt: pneumotachograph; V': flow; P_{ao}: airways opening pressure.

was further lowered by 5 hPa (NEP cycle) in order to assess whether EFL was present [27] (figure 2). The presence of EFL at a given level of EEP was determined by comparing the flow–volume relationship of the NEP cycle to that of the preceding cycle. When EFL was present (V' unchanged by lowering EEP) the fraction of the V_T left to be expired at the onset of EFL (V_{EFL}) was measured.

Data analysis

The recorded data were processed and analysed off-line with the aid of specifically developed software. The flow signal was corrected for a 5% offset of the mean unsigned flow (Peslin *et al.* [28]), which was found satisfactory in order to correct the volume drift. Volume (V) was calculated by numerical integration of V', through the software and the pressure signal was corrected for the pressure drop along the ET. Data of P_{aw}, V', and V were analysed by multiple linear regression on a cycle-per-cycle basis according to the linear model equation:

$$P_{aw}(t) = E_{rs} \times V(t) + R_{rs} \times V'(t) + EEP \quad (1)$$

where E_{rs} and R_{rs} represent the respiratory system elastance and resistance respectively and EEP corresponds to the P_{aw} value at the end of the expiration (nil V and V').

E_{rs} and EEP values were averaged for the six consecutive cycles included in the same file because inter-cycle variation was found to be no higher than 4%.

The resistive component of P_{aw} was calculated according to:

$$P_{aw,\,res}(t) = P_{aw}(t) - E_{rs} \times V(t) - EEP \quad (2)$$

From equation (2) the instant values of resistance were calculated as:

$$R_{rs}(t) = P_{aw,\,res}(t)/V'(t) \quad (3)$$

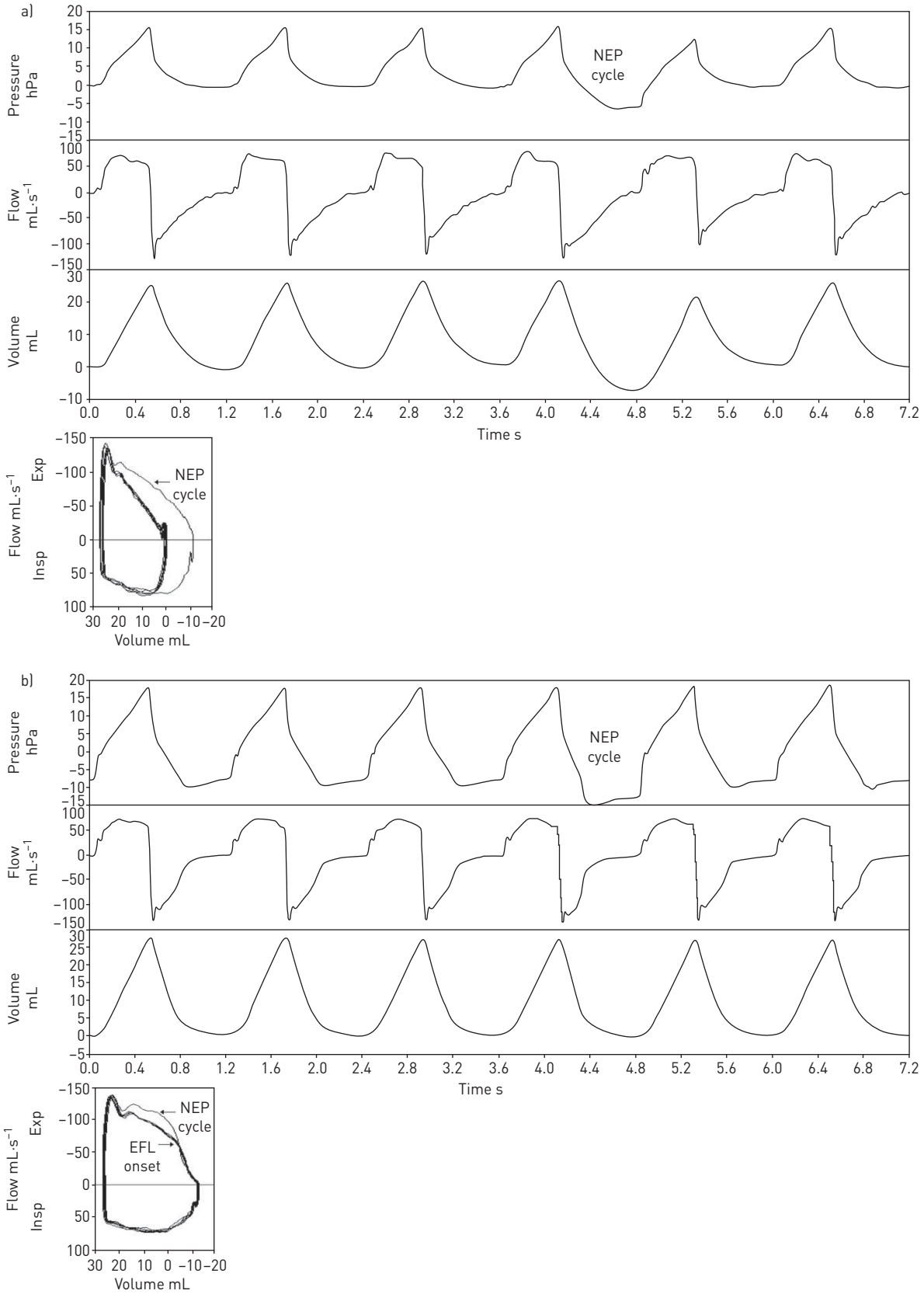

FIGURE 2 Records of pressure, flow, volume and flow–volume signals of five consecutive cycles. The records are used as reference for the recognition of expiratory flow limitation (EFL) with the negative expiratory pressure (NEP) method. The NEP cycles are indicated. a) no EFL is recognised. b) EFL is detected.

Results

Graphical presentation of recorded and calculated physical quantities of MV are actually depicted in figure 2. Calculation of R_{rs} on each data sample permitted the construction of the resistance–time (R_{rs}–t) curve. Our results concerning experimental data are graphically depicted in figure 3. Signals on the upper part refer to a case without EFL, while signals on the lower part correspond to a case with EFL provoked with the application of a NEP of −8 hPa. Measurements in both cases are those including the NEP cycle to assess whether EFL was present or not. The EFL issue is supported by the partial overlapping of the expiratory V'–V curves.

Careful observation of the R_{rs}–t signals reveals that:

1) The R_{rs}–t signal is rather constant during the major part of both the inspiratory and the expiratory phases in the case without EFL. The only actual fluctuation of R_{rs}–t corresponds to the metaptosis from inspiration to expiration, as logically expected. Some "irregular" variations of very short duration can also be observed at the late expiratory phase corresponding to very low values of V'. A similar configuration of R_{rs}–t signal was observed in all cases without EFL.
2) An abrupt rise of expiratory R_{rs}(t) is observed whenever EFL was present. This expiratory R_{rs}(t) increase coincides with the onset of EFL as detected on the V'–V diagram with the aid of a cursor indicator. The onset of EFL was synchronously detected by the NEP technique as well as by the R_{rs}–t inflexion point and this observation was always confirmed with the aid of a digital point cursor moving along curves and signals. This was a facility incorporated in the analysis software, developed by the last author.

According to our results, the distinct and characteristic configuration of the expiratory R_{rs}–t signal permitted the recognition of EFL with a 100% sensitivity and specificity and the accurate quantification of EFL, through V_{EFL}, according to the NEP technique. Table 1 presents the noted values of $\%V_{EFL}$ as percentage of the applied VT in every experimental case and at all levels of applied expiratory pressure.

Discussion

Monitoring of EFL during MV is particularly important. EFL does not simply mean increased respiratory system resistance. It is a specific respiratory disorder with serious impact on respiratory and circulatory functions [1–7]. Furthermore, EFL monitoring confronts certain difficulties during MV, which underlines the severity of the "EFL issue".

A large number of previous studies have focused their interest on EFL detection in experimental and clinical MV [5]. The proposed methods are actual tests of airflow variability under different techniques of varying expiratory pressure. Changing the level of applied PEEP, adding or removing external resistance to the expiratory circuit, by-passing the expiratory circuit of the ventilator to the atmosphere and using negative expiratory pressure are some of the already proposed techniques with the latter (NEP method) being established as the gold standard for EFL detection during MV or even spontaneous respiration, as it is proven independent of body position without additional demands for patient cooperation [5, 8–12]. The diagnostic cornerstone of all the above-mentioned techniques is the comparison of two consecutive expiratory flow signals: one ordinary and one specifically devised for the EFL detection test. Therefore, they require transient alteration of the ventilatory settings and are not suitable for continuous monitoring.

The forced oscillation technique has been proven suitable for EFL monitoring without any intervention to ventilator settings and circuits [37]. Large negative variations of respiratory system reactance during expiration are a highly sensitive and specific index of EFL presence during experimental and clinical ventilation [29, 37]. The method is highly sensitive and specific, and its applications have become more popular in clinical practice, especially during spontaneous breathing [30–36].

A strongly negative volume dependence of resistance estimated with the aid of non linear regression analysis is also indicative of EFL during artificial ventilation [38–40]. The method is easily applicable with the aid of applied informatics and is suitable for continuous EFL detection, but does not offer a quantitative EFL diagnosis. Therefore, changes of EFL severity expressed as an increased or decreased part of V_T under EFL cannot be recognised by these methods, which offer partial monitoring for EFL.

The presently proposed method for the detection of EFL during experimental MV is based on the assumption of "constant" elastance throughout the respiratory cycle, permitting thus, the construction of the resistance–time signal. Of course, this assumption is arbitrary, as volume dependence of elastance is recognised during MV even in subjects without any underlying respiratory disorder and much more, in COPD or acute respiratory distress syndrome [27, 41–46]. We used linear regression analysis to calculate constant elastance and EEP. The method is widely used during MV [27, 29, 43, 47] and one of its important advantages is the synchronous calculation of both E_{rs} and EEP.

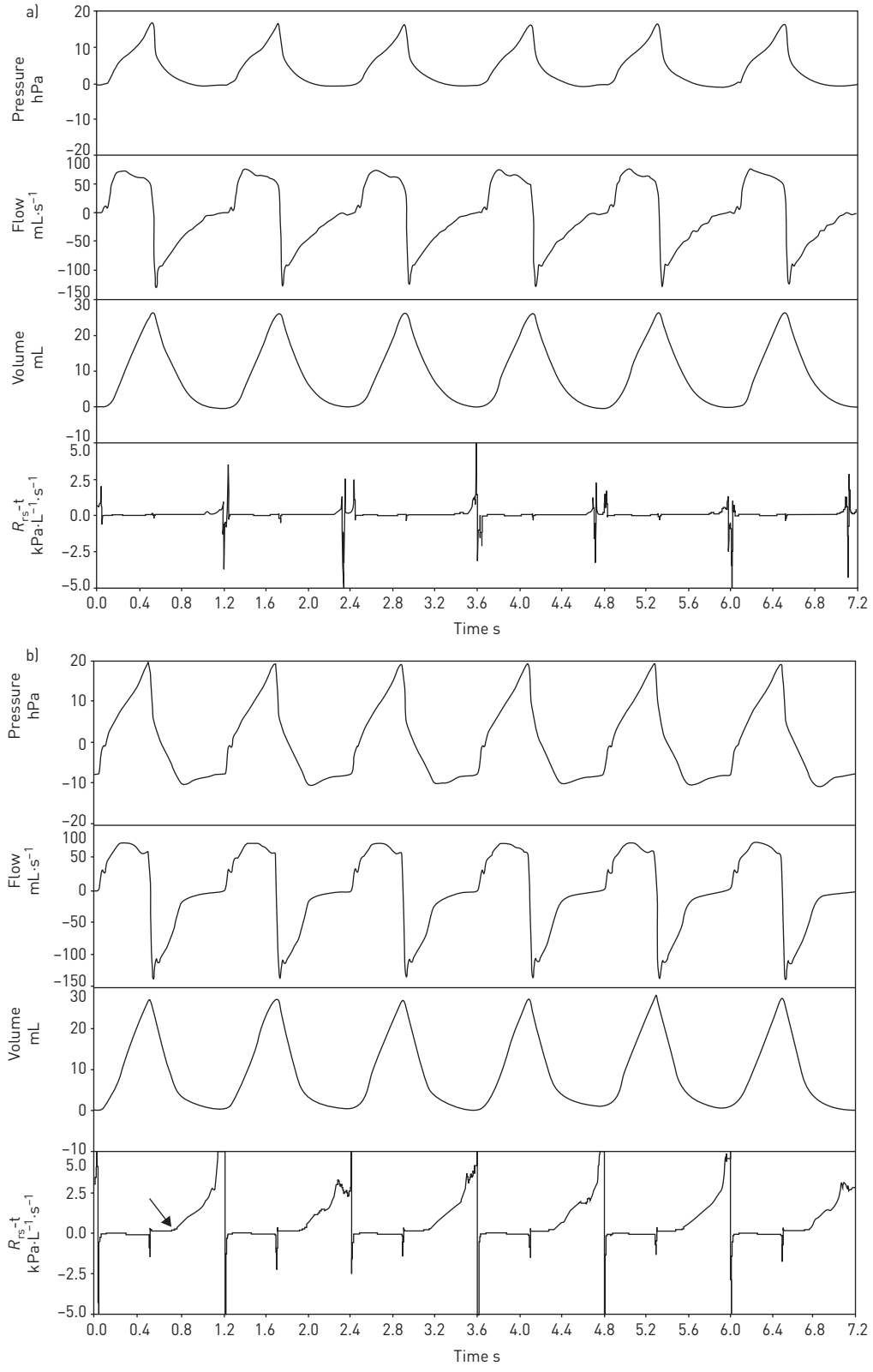

FIGURE 3 Airway pressure, flow, volume and R_{rs}–t signals of a record without expiratory flow limitation (a) and another where expiratory flow limitation was diagnosed by the negative expiratory pressure (NEP) method (b). The arrow in the first cycle below indicates the onset of R_{rs}(t) increase. R_{rs}: respiratory resistance: t: time.

TABLE 1 Quantification of EFL as % of V_T left to be expired at the moment of its onset as equivalently detected by the NEP technique and the specifically noted inflexion point on the R_{rs}–t graph at each level of applied EP in hPa

EP	1	2	3	4	5	6	7	8
0	-	-	-	-	-	-	-	-
−5	15	-	11	20	10	11	11	10
−8	21	18	23	30	18	12	22	15
−10	22	21	24	31	25	17	26	23

The numbered columns present the $\%V_{EFL}$ findings of the eight experimental animals. (-) denotes the absence of EFL. EFL: expiratory flow limitation; EP: expiratory pressure; NEP: negative expiratory pressure; R_{rs}: respiratory resistance: t: time; V_{EFL}: the fraction of the V_T left to be expired at the onset of EFL; V_T: tidal volume.

An important advantage of linear regression analysis (LRA) is the synchronous evaluation of its reliability according to the SE of estimation, corresponding to the root mean square difference. In most cases of MV the root mean square difference has been proven satisfactory, according to previous studies [28, 47] Therefore, the use of LRA may disregard important dependences of respiratory mechanics on volume and flow. These nonlinearities have been recognised in previous studies. Nevertheless, the clinically acceptable applicability of LRA as a very informative tool is also recognised [26, 27, 41–47]. Linear regression has been proven satisfactory even in cases of unsedated patients under MV [48].

Any other methodological approach for the evaluation of these mechanical parameters (end-inspiratory pause, Fourier analysis (FA)) is also acceptable [28, 42, 49–52]. LRA is preferable as more robust technique as it is not based on a few points (moments) of the respiratory cycle, as with the EEP method, but on a large number of points, according to the relatively high data acquisition frequency (180 Hz) of our experiments. Furthermore, LRA as a method applied on the time domain incorporates the influence of higher harmonic terms of the airways opening pressure and V', which is omitted during FA applied on the ventilatory frequency [28, 51]. In any case, the use of a single stable value of elastance during the whole respiratory cycle is very common in experimental and clinical MV and this is the clue of our algorithm. Indeed, under these conditions, the expiratory limb of the resistance–time curve (R_{rs}–t) offers the possibility not only of EFL detection, but most importantly, of EFL quantification, as it describes its pathophysiological sequence. The onset of EFL is easily recognised by an inflection point on the R_{rs}–t followed by a continuous rise, which reflects a further increase of resistance after EFL installation. A progressive airway collapse is responsible for a much higher resistance increase when EFL is present, than in its absence [53–55]. The increasing resistance from EFL onset towards the end of expiration was previously recognised as negative volume dependence of resistance [38]. Now, this severe nonlinearity of resistance appears directly on the R_{rs}–t and permits complete EFL detection.

The accuracy of the proposed technique is confirmed by the well-established NEP technique, while its nonintervention with ventilator settings and circuits renders it quite suitable for EFL monitoring during MV. It is based on a simple computational algorithm, with modest requirements of infrastructure. Actually, the possibility of data acquisition and analysis appears more often in modern ventilators and the required software adaptation for monitoring R_{rs}(t) are really the minimum. Further study, during clinical MV is necessary to establish the validity of the proposed technique and its usefulness in clinical practice, where rapid therapeutic interventions (*e.g.* altering inspiration and expiration ratio, application of PEEP, administration of bronchodilators) are necessary and crucial in patients with COPD and acute respiratory distress syndrome in order to obtain relief from detrimental consequences of EFL.

Conflict of interest: None declared.

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