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Monitoring of total positive end-expiratory pressure during mechanical ventilation by artificial neural networks

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Abstract Ventilation treatment of acute lung injury (ALI) requires the application of positive airway pressure at the end of expiration ($PEEP_{app}$) to avoid lung collapse. However, the total pressure exerted on the alveolar walls ($PEEP_{tot}$) is the sum of $PEEP_{app}$ and intrinsic PEEP ($PEEP_i$), a hidden component. To measure $PEEP_{tot}$, ventilation must be discontinued with an end-expiratory hold maneuver (EEHM). We hypothesized that artificial neural networks (ANN) could estimate the $PEEP_{tot}$ from flow and pressure tracings during ongoing mechanical ventilation. Ten pigs were mechanically ventilated, and the time constant of their respiratory system (τ_{RS}) was measured. We shortened their expiratory time (TE) according to multiples of τ_{RS}, obtaining different respiratory patterns (R_{pat}). Pressure (P_{AW}) and flow (V'_{AW}) at the airway opening during ongoing mechanical ventilation were simultaneously recorded, with and without the addition of external resistance. The last breath of each R_{pat} included an EEHM, which was used to compute the reference $PEEP_{tot}$. The entire protocol was repeated after the induction of ALI with i.v. injection of oleic acid, and 382 tracings were obtained. The ANN had to extract the $PEEP_{tot}$, from the tracings without an EEHM. ANN agreement with reference $PEEP_{tot}$ was assessed with the Bland–Altman method. Bland Altman analysis of estimation error by ANN showed -0.40 ± 2.84 (expressed as bias $\pm$ precision) and ±5.58 as limits of agreement (data expressed as cmH_2O). The ANNs estimated the $PEEP_{tot}$ well at different levels of $PEEP_{app}$ under dynamic conditions, opening up new possibilities in monitoring $PEEP_i$ in critically ill patients who require ventilator treatment.

Keywords Artificial neural networks · Acute lung injury · Intrinsic positive end expiratory pressure · Animal model

The study was performed at the Hedenstierna Laboratory, University Hospital, Uppsala, Sweden.

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1 Introduction

Mechanical ventilation (MV) is currently used in patients with respiratory failure in the intensive care unit as well as during anesthesia in patients undergoing different surgical procedures. Caregivers, as part of respiratory therapy, may decide to maintain a certain amount of pressure in the lungs at the end of expiration in order to prevent end-expiratory lung collapse that may compromise oxygenation and gas exchange as well as make the lungs more prone to

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ventilation-induced lung injuries. This pressure is usually termed *applied positive end-expiratory pressure* (PEEP_app) and can be directly implemented on the control interface of the ventilator.
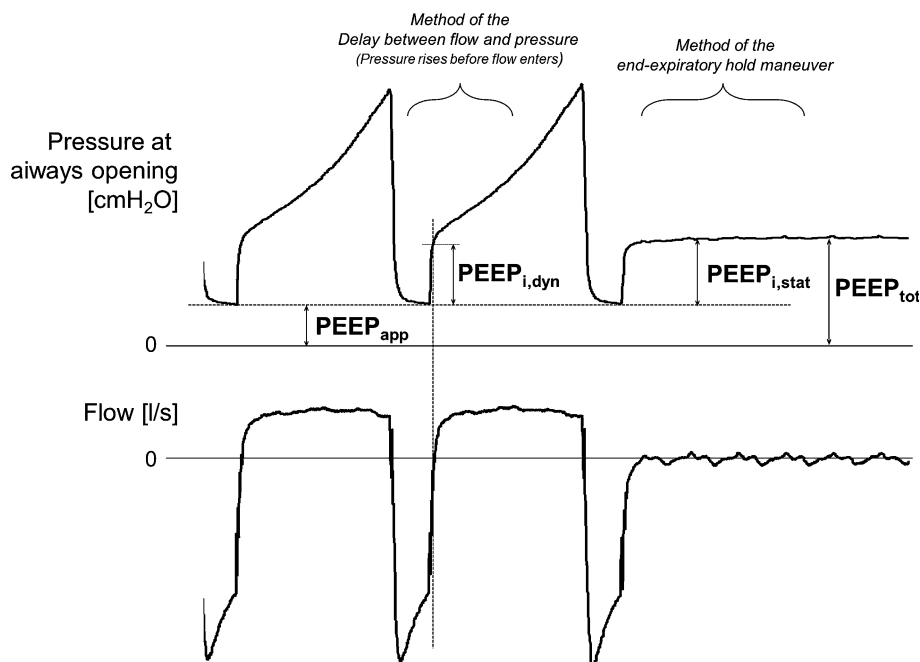
However, the *total* positive end-expiratory pressure (PEEP_tot) inside the lungs at the end of expiration is generated by the combination of ventilator settings and the respiratory mechanics of the connected patient. The component of PEEP_tot produced by incomplete expiration (Fig. 1) is termed intrinsic PEEP (PEEP_i) [1]:

$$PEEP_{tot} = PEEP_{app} + PEEP_{i} \qquad (1)$$

PEEP_i develops as a result of two possible conditions: (a) a discrepancy between the allowed expiratory time and the time needed to empty the lungs according to the time constant (compliance and resistance) of the respiratory system and (b) the expiratory flow limitation, typical of chronic obstructive pulmonary disease and other pulmonary diseases where airways narrow and even close during expiration, trapping air.

During artificial ventilation, PEEP_tot has positive and negative consequences for the respiratory and cardiovascular systems. The PEEP_tot affects oxygenation, gas exchange (redistributing blood flow and ventilation) and respiratory system mechanics (shifting the pressure/volume curve of the lung). Furthermore, the PEEP_tot has potential effects on the integrity of the lung parenchyma (increasing the potential for ventilator-induced lung injury) as well as cardiovascular dynamics (increasing the intra-thoracic pressure reduces venous return and cardiac output).

Thus, awareness of the PEEP_tot is very important during mechanical ventilation. Although the PEEP_app is known to the physician, PEEP_i is hidden and mostly unpredictable. Thus, it requires monitoring. Different methods have been proposed for estimating PEEP_i during controlled mechanical ventilation (CMV). A frequently used method for estimating PEEP_tot in paralyzed patients who are mechanically ventilated involves creating static conditions and applying an end-expiratory hold maneuver (EEHM), with cessation of gas flow at end-expiration from the airways. Once the PEEP_tot and PEEP_app are known, PEEP_i can be calculated (Eq. 1) [2, 3].

PEEP_tot assessed with an EEHM is the reference value for patient monitoring. However, it requires the discontinuation of the cyclic succession of inspiration and expiration for a varying number of seconds, and in patients with acute respiratory distress, these repetitive respiratory pauses can be dangerous. Therefore, a continuous non-invasive monitoring method for PEEP_tot would be advantageous.

We hypothesized that artificial neural networks (ANNs), fed by inspiratory airway pressure and flow, would enable the measurement of PEEP_tot and its components PEEP_i and PEEP_app during ongoing mechanical ventilation. The aim was to test this hypothesis in an animal model, training ANNs on examples of PEEP_i generated by the progressive shortening of the expiratory time (TE).

Therefore, the objectives of the present contribution were as follows: to train one ANN to assess PEEP_tot from dynamic respiratory tracings and to test the ANN performance, assessing any dependency of the estimation error by PEEP_app.

Fig. 1 Respiratory tracings depicting the methods for detecting the persistence of alveolar pressure at the end of expiration. *PEEP* positive end expiratory pressure, *PEEP_app* applied PEEP, *PEEP_i,dyn* intrinsic PEEP measured in dynamic conditions, i.e. without stopping inspiratory flow, *PEEP_i,stat* intrinsic PEEP measured in static conditions, i.e. during a breath-hold maneuver. Further explanation in the text

2 Materials and methods

2.1 Experimental design

This study was composed of two phases. During the first phase, a porcine model of pulmonary dynamic hyperinflation with the progressive reduction of the allowed expiratory time set on the ventilator was created. Pressure (P_{AW}) and flow (V'_{AW}) at the airway openings were recorded in different scenarios: with and without additional resistance, during healthy conditions and after acute lung injury. From these tracings, expiratory time constant (τ_{RS}), respiratory system resistance (R_{RS}) and compliance (C_{RS}), total static PEEP ($PEEP_{tot,stat}$) and total dynamic PEEP ($PEEP_{tot,dyn}$) were calculated. During the second phase, an artificial neural network was trained and tested to estimate $PEEP_{tot,stat}$ from the recorded signals.

2.2 Animal model

The present study was approved by the local institutional review board for the care of animal subjects; the care and the handling of the animals were in accordance with the regulations of the Swedish Board for Laboratory Animals and executed following the European Union Directive 2010/63/EU for animal experiments.

Ten healthy pigs (Hampshire, Yorkshire and Swedish mixed country breed; weight 30.0 ± 2.5 kg) were included in the study. They were premedicated with azaperone 40 mg im (Janssen, Wien, Austria) at the farm. Anesthesia was induced with intramuscular administration of atropine (0.04 mg/kg), tiletamine-zolazepam 5 mg/kg (Boehringer Ingelheim, Copenhagen, Denmark) and medetomidine 5 µg/kg (Orion Pharma AB, Sollentuna, Sweden). The trachea was intubated via tracheostomy, using a cuffed endotracheal tube (n. 5.5, Portex, Smiths Medical Inc, St Paul, USA). Then total intravenous anesthesia started, by the administration of ketamine 20 mg/kg/h (Vetpharma AB, Zurich, Switzerland), and fentanyl 5 µg/kg/h (Pharmalink, Spånga, Sweden). After adequate anesthesia was achieved (tested by lack of reaction to painful stimulation between the front hooves), i.v. infusion of pancuronium 0.24 mg/kg/h (Organon Teknika, Göteborg, Sweden) was added. During each experiment, the fluid replacement strategy, based on the constant infusion of Rehydrex® (Fresenius Kabi, Uppsala, Sweden) with glucose 25 mg/ml at a starting rate of 5 ml/kg/h, aimed at maintaining stable systemic arterial pressure. Instrumentation consisted of the insertion of an 18 gauge catheter into the left carotid artery for continuous invasive arterial pressure measurement and sampling of arterial blood gases. Another 18-gauge catheter was introduced into the right external jugular vein, together with a floating tip pulmonary artery (PA) catheter. The latter

catheter was inserted and positioned as guided by the pressure tracings on the connected bedside monitor (CS/3™, Datex Ohmeda, Helsinki, Finland). This set-up allowed the measurement of cardiac output, with injection of cold boluses of physiological saline (approximately 10 ml per bolus at a temperature of 3–5°C, in triplicate) randomly during the respiratory cycle and the continuous monitoring of blood temperature by using the sensor located in the PA catheter. Urinary output was measured with a surgically inserted suprapubic bladder catheter. Arterial and mixed venous samples were taken to measure pO_2, pCO_2 and pH with a blood gas machine (ABL 300, Radiometer, Copenhagen, Denmark) during various phases of the experiment.

2.3 Ventilation and creation of intrinsic PEEP

At the beginning of each experimental session, all pigs were ventilated using volume controlled - constant flow mechanical ventilation (VC-MV; Servo 300, Siemens Elema, Solna, Sweden). The tidal volume (V_T) was set between 8 and 9 ml/kg to obtain normocapnia ($PaCO_2$ 35–45 mm Hg). $PEEP_{app}$ was initially set to 5 cmH_2O. Inspiratory fraction of oxygen (F_IO_2) was maintained at 0.5. The inspiratory-to-expiratory ratio was set to 1:2 (s) and the respiratory rate 20 breaths/min. After a stabilization period of 45 min after instrumentation, the animals were randomized to receive an applied PEEP of 0, 5 or 10 cmH_2O, and a baseline recording of airway pressure and flow (P_{AW} and V'_{AW}) was obtained. A tracing of the inspired volume (V_{RS}) versus time was obtained from V'_{AW} by integration. Using the slope of the expiratory volume/flow curve, the expiratory time constant of the respiratory system, τ_{RS}, was determined. This was used to calculate the ventilation patterns in the second part of the experiment. During constant minute ventilation and respiratory cycle time (T_{TOT}), the expiratory time was progressively shortened in proportion to expiratory τ_{RS}. The experimental protocol was composed of different recording sessions of P_{AW} and V'_{AW}, characterized by an expiratory time equal to decreasing multiples of τ_{RS}, 3.0, 2.5, 2.0, 1.5, 1.0 times τ_{RS}. After the TE was set to a predefined multiple of τ_{RS}, ventilation was maintained until a steady state was reached (verified by observing a stable peak pressure) and never <5 min. Then P_{AW} and V'_{AW} were recorded for 10 or more consecutive cycles; the last breath had an end-inspiratory hold maneuver (EIHM) and an EEHM. This last breath was used to estimate $PEEP_{tot,dyn}$ and $PEEP_{tot,stat}$.

After the measurements at the different multiples of τ_{RS}, the TE was returned to three times τ_{RS}, and resistance (R_{ADD}) was added in series with the endotracheal tube. It consisted of a pediatric n.3 tube (Mallinckrodt Medical, Athlone, Ireland). The purpose of its application was to

increase tube resistance and to increase the time constant of the system connected to the ventilator. The same protocol of progressive reduction of the TE in multiples of τ_{RS} was applied in the presence of R_{ADD}. After the last recording, R_{ADD} was removed, and the TE was again returned to three times τ_{RS}.

Acute lung injury (ALI) was then induced by repeated injections of small boluses of oleic acid (OA; Apoteksbolaget, Göteborg, Sweden) into the central venous catheter, targeting a total dose of 0.1 ml/kg [4]. Administration of OA was suspended if SaO_2 fell to 80 %. After a period of 2–3 h, when stable circulation had been achieved, similar recording sessions with a progressive reduction of the TE in proportion to τ_{RS} were obtained. Then, as before, the measurements were repeated with the additional resistance (R_{ADD}).

From the 10 animals involved in the study, a total of 20 recording sessions per animal were acquired in duplicate, for a total of 400 tracings. Of these, 18 of the 400 were discarded due to technical reasons, and the final pool of data included the remaining 382 tracings.

2.4 Recording of the respiratory variables

During mechanical ventilation, V'_{AW} was recorded with a Fleisch pneumotachograph (Laminar Flow Element type PT, Special Instruments GmbH, Nördlingen, Germany) positioned between the endotracheal tube and the ventilator and connected to a differential pressure transducer (Diff-Cap Pressure Transducer, Special Instruments GmbH, Nördlingen, Germany). Calibration of the flow measurement device was performed by using a source of constant flow and a precision flow meter (Calibration Analyzer TS4121/P, Timeter Instrument Corporation, St. Louis, MO, USA) connected in series with the transducer to be calibrated.

P_{AW}, esophageal and gastric pressures were measured with pressure transducers (Digima Clic Pressure Transducers, Special Instruments GmbH, Nördlingen, Germany). Signals from the transducers were forwarded to an analog/ digital converter card (DAQ-card AI-16XE50, National Instruments Corp., Austin, TX, USA) and stored on a PC at a sampling frequency of 200 Hz, using BioBench software (ver. 1.0, National Instruments Corp.).

From the breath preceding the one used to feed the ANN, C_{RS} and R_{RS} were calculated by applying the interrupter technique, as described by Bates et al. [5].

2.5 Data analysis and the neural network

The tracings, after having been filtered in the range between 49.6 and 50.4 Hz, were downsampled at 100 Hz, in order to reduce redundancy among neighboring points. The onset of the inspiratory flow ($t_{INIFLOW}$) was identified with a computer
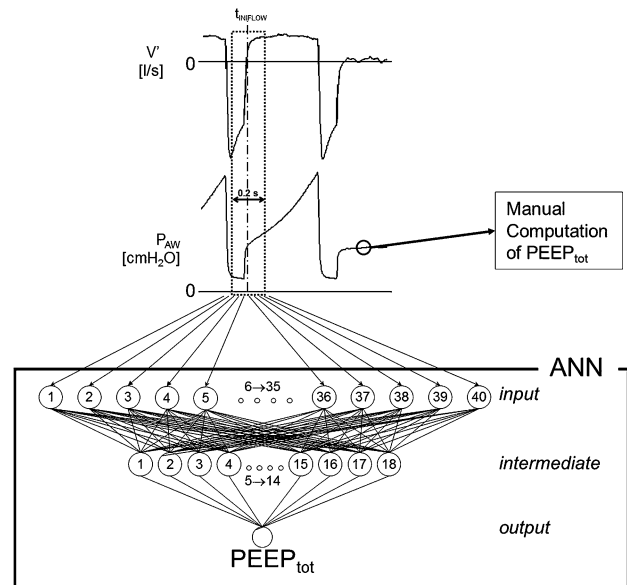

Fig. 2 Data used to feed the artificial neural network (ANN). The input pattern was formed by 20 synchronous samples of P_{AW} and V' around the onset of the inspiratory flow. P_{AW} pressure at the airway opening, V' flow at airway opening, s seconds, $t_{INIFLOW}$ time of the onset of the inspiratory flow, $PEEP_{tot}$ total positive end expiratory pressure

script: This was used to cut out from the tracing of V'_{AW} and P_{AW} the segments of curves extending from 0.1 s before $t_{INIFLOW}$ to 0.1 s after $t_{INIFLOW}$ (see Fig. 2). The segments (consisting of 20 V'_{AW} points and 20 P_{AW} points) formed an input pattern of 40 points that fed the neural network.

The ANN was implemented via software on a computer (Neural Networks Toolbox ver. 3.0 for MatLab ver. 5, The MathWorks Inc., Natick, MA, USA). The learning algorithm was *resilient backpropagation*. The ANNs consisted of three layers, whose *activating functions* were *log-sigmoids* for the input and the intermediate layer and *linear* for the output layer. The number of neurons in the input layer was 40 (determined by the dimensions of the input pattern). The output layer consisted of 1 neuron, yielding $PEEP_{tot,stat}$ calculated by the ANN. To determine the best architecture, that is, the number of intermediate neurons that provided the best performance for the required task, we used eight-fold cross-validation with early stopping. More details about this method can be found in the study by Haykin [6] and in our previous papers [7, 8]. The ANN architecture that showed the best performance had 18 intermediate neurons. The training data set included 305 input patterns out of 382 recordings; the remaining 77 were used as the data test set, to examine the performance of the ANN.

The ANN had to extract $PEEP_{tot,stat}$ from the input pattern described above. The ANN training consisted of giving at the same time for each input pattern the corresponding $PEEP_{tot,stat}$, estimated by the EEHM. After training, the test

phase consisted of feeding the ANN with input patterns not seen before and comparing the results it yielded to the $PEEP_{tot,stat}$ calculated separately.

We computed the linear regression between the results yielded by the ANN and the measure of $PEEP_{tot,stat}$ (by using the expiratory hold maneuver method) to assess the ANN's performance on this task. We also analyzed the measurement error according to Bland and Altman [9, 10]. Plotting the ANN measurement error versus the applied PEEP and drawing a linear regression, we aimed at checking whether there was dependency between the two variables. We also analyzed the relation between $PEEP_{tot,dyn}$ and $PEEP_{tot,stat}$ in order to disclose any possible interdependence between the two variables that might influence the ANN's performance.

3 Results

The time constant of the respiratory system in healthy conditions was 0.80 ± 0.13 s and was decreased to 0.74 ± 0.12 s after OA was administered. The mean R_{RS} ranged from 16.80 ± 11.37 [cmH$_2$O/(L/s)] (baseline) to 18.32 ± 18.27 [cmH$_2$O/(L/s)] (with a TE of 1 τ_{RS}). Decreasing the expiratory time in proportion to τ_{RS} did not noticeably change R_{RS}. The mean respiratory system compliance showed a tendency to decrease when the expiratory time was decreased. After ALI was induced with OA administration, at corresponding respiratory patterns, C_{RS} was reduced, as expected. The main hemodynamic, respiratory and gas exchange variables are reported in Table 1.

Total PEEP, measured in dynamic conditions, tended to increase when the expiratory time was decreased. When total PEEP was measured in static conditions (Fig. 3), a similar tendency toward higher values for short expiratory times was found. The Bland–Altman analysis of the ANN estimation error (Fig. 4) showed -0.40 ± 2.84 (expressed as bias $\pm$ precision); thus, ± 5.58 was the limit of agreement (data expressed as cmH$_2$O). The linear regression of estimation error by ANN versus $PEEP_{app}$ (Fig. 5) had an equation of y = 0.11 x $-$0.87 and the coefficient R = 0.1.

The relation between $PEEP_{tot,dyn}$ and $PEEP_{tot,stat}$ is presented in Fig. 6: The coordinates of the 382 samples (corresponding to the training and testing data pools) are the values of $PEEP_{tot,dyn}$ (y-axis) versus $PEEP_{tot,stat}$ (x-axis) measured on the same tracing. It was expressed with the linear regression y = 0.25 x $+$1.11 and a R^2 = 0.24.

4 Discussion

We trained and tested one ANN to estimate $PEEP_{tot,stat}$ from pressure and flow tracings at airway openings during ongoing mechanical ventilation in an experimental porcine

Table 1 Hemodynamic, respiratory and gas exchange variables

Variable	Baseline	After OA
HR (beats/min)	96 ± 15	108 ± 14*
MAP (mmHg)	92 ± 18	87 ± 14
CVP (mmHg)	9 ± 4	10 ± 4
MPAP (mmHg)	22 ± 7	38 ± 4*
PCWP (mmHg)	10 ± 2	13 ± 2*
CO (l/min)	3.2 ± 0.4	3.9 ± 0.5*
PaO$_2$ (kPa)	32 ± 5.1	15 ± 6.7*
PaCO$_2$ (kPa)	5.4 ± 0.9	7.1 ± 1.1*
R$_{RS}$ [cmH$_2$O/(L/s)]	16.8 ± 11.3	18.3 ± 18.2*
C$_{RS}$ (ml/cmH$_2$O)	28.8 ± 8.5	15.4 ± 6.9*

Data are presented as mean ± standard deviation

Reported measures of R$_{RS}$ and C$_{RS}$ after OA were sampled when the allowed expiratory time was equal to the time-constant of the respiratory system

OA oleic acid, HR heart rate, MAP mean (systemic) arterial pressure, CVP central venous pressure, MPAP mean pulmonary arterial pressure, PCWP pulmonary capillary wedge pressure, CO cardiac output, R$_{RS}$ resistance of the respiratory system, C$_{RS}$ compliance of the respiratory system

* Statistically significant difference between baseline and 1 h after the induction of lung injury by administration of oleic acid
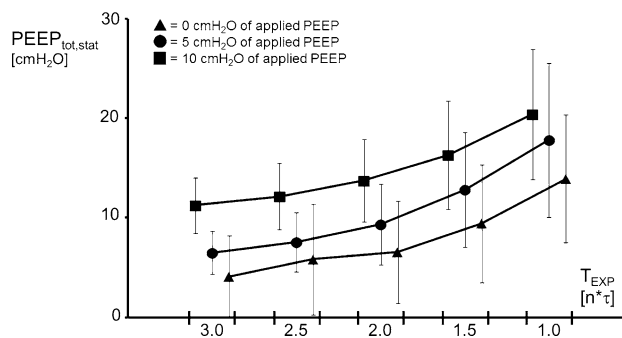

Fig. 3 Different examples of $PEEP_{tot,stat}$ were created by shortening the expiratory time. They were assessed with the expiratory hold maneuver, which represents the gold standard for PEEP measurement. They were generated starting from different applied PEEP levels. Bars represent standard deviation. T_{EXP} expiratory time expressed as multiple of expiratory time constants (τ), $PEEP_{tot,stat}$ total PEEP measured in static conditions, that is, during a breath-hold maneuver

model. To create a pool of data to train the ANN, we used an animal model of dynamic pulmonary hyperinflation obtained by decreasing the expiratory time during mechanical ventilation. In our model, the ANN performance was excellent with a close correlation and low bias between the ANN and the standard method for obtaining $PEEP_{tot,stat}$.

In a completely passive subject (i.e., muscle-paralyzed subject without spontaneous respiratory activity), expiration occurs passively because of the recoil of the elastic
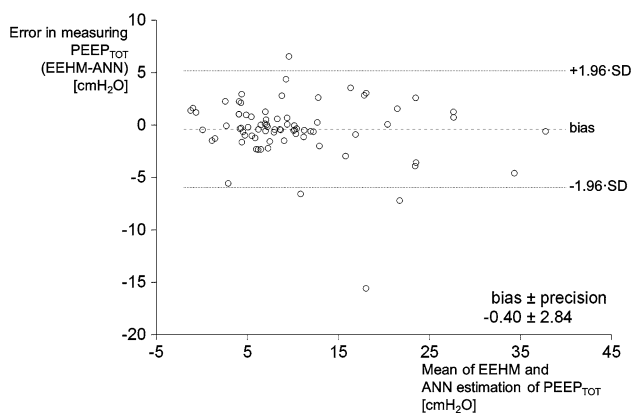
Fig. 4 PEEP$_{tot}$ estimation error with ANN, plotted versus the mean of ANN-based and reference measurements, according to the Bland–Altman test. *SD* standard deviation, *EEHM* end expiratory hold maneuver, $\pm 1.96 \times$ SD = limits of agreement, corresponding to ± 5.58 cmH$_2$O
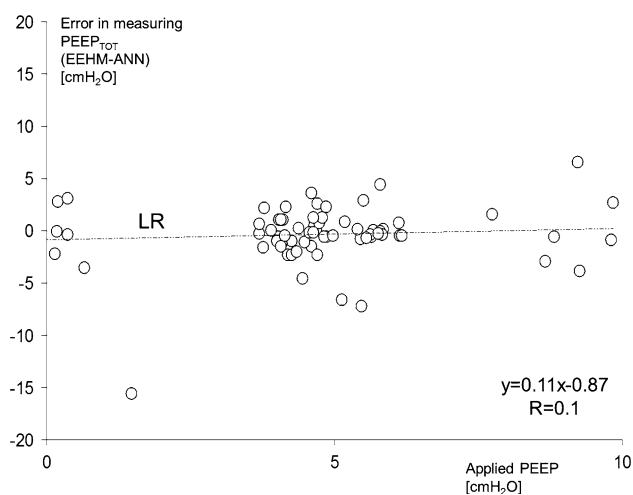

Fig. 5 PEEP$_{tot}$ estimation error by the ANN plotted versus applied PEEP. *LR* linear regression line and its equation
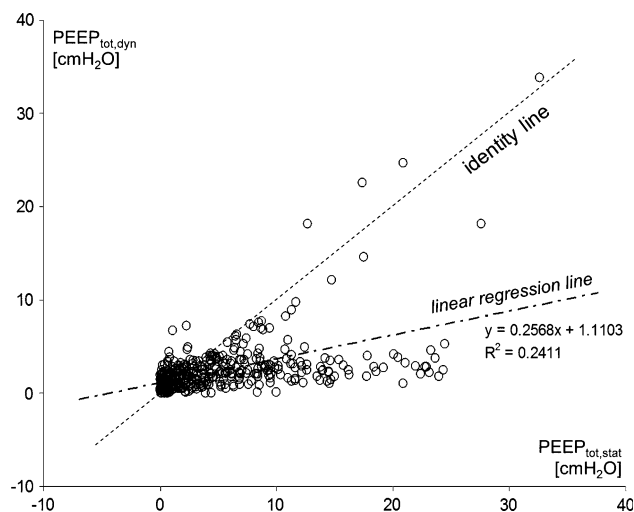

Fig. 6 Relation between PEEP$_{tot,dyn}$ (measured by the phase shift between the flow and pressure onsets) versus PEEP$_{tot,stat}$ (measured by the end-expiratory hold maneuver). The equation on the graph refers to the linear regression between the two variables. Of the 382 samples that are depicted in the figure, a minority of cases are positioned near the identity line. They represent conditions close to lung homogeneity, and have minimal PEEPi (measured as PEEP$_{tot,dyn}$) similar to the mean PEEPi (measured as PEEP$_{tot,stat}$) values

structures of the lung, previously stretched by the inspired volume of air. The proportion of the volume exhaled at the end of the expiration obeys the rules of compartmental kinetics:

$$V_t = V_0 \cdot e^{-\frac{t}{\tau_{RS}}} \tag{2}$$

where V_t is the volume contained in the lung at time t from the onset of expiration, V_0 is the volume at the beginning of expiration and τ_{RS} is the time constant of the respiratory system. Although based on a simple mono-compartmental system, this model accounts for the rise in PEEPi when the expiration time is decreased, indicating an increase in the trapped volume. At the beginning of the experiment after instrumentation and after OA damage, we measured expiratory τ_{RS}. We chose to measure it during expiration because apparent τ_{RS} can be different during inspiration

and expiration, due to variations in R_{RS} and C_{RS} at different lung volumes.

We aimed at generating PEEPi by decreasing the expiratory time in order to generate examples to train the ANN. We measured τ_{RS} from the slope of the expiratory volume/flow curve as described by McIlroy et al. [11]. This kind of analysis, based on a mono-compartmental model, cannot detect the mechanical behavior generated by additional compartments (in lung inhomogeneity) or by mechanical nonlinearities as in the presence of marked "flow limitation" typical of patients with chronic obstructive lung disease [12]. However, for our purposes, we considered the following method adequate: if the respiratory system subtended "longer" time constants (because of neglected obstructive or viscoelastic components), generation of PEEP$_i$ by shortening the expiratory time could have been enhanced. Moreover, the mono-compartmental model was not transferred to the ANN, which had to learn how to estimate PEEP$_{tot}$ through examples.

We decided to study ANNs during lung injury due to the need to estimate their performances in non-healthy conditions. Several models of lung injury have been described in the literature, and each model has its own peculiarities in terms of hemodynamics and respiratory mechanics [4]. We arbitrarily chose to use a model based on the intravenous administration of oleic acid that mimics the early phase of adult respiratory distress syndrome (ARDS) by developing important alterations of lung permeability and by releasing inflammatory mediators. In principle, the study of a single,

specific kind of lung injury can represent a limit to the general applicability of the ANN method. Thus, in the near future, it may be advisable to test the ANN performance on other models of lung disease.

Intrinsic PEEP can be measured in static or dynamic conditions. Static measurements require an EEHM. The different mechanical compartments of the lung can retain a variable amount of gas at the end of the expiration, in relation to the expiratory time constant [13]. EEHM allows the equilibration of pressures between these compartments and the airway conduction system up to the pressure transducer. This value represents the weighted mean of the pressures inside the lung compartments at end expiration (regional $PEEP_i$) and may include the contribution of the elasticity of the tubing system.

Dynamic measurement of $PEEP_i$ in completely passive mechanically ventilated subjects does not involve an end-expiratory pause. In the presence of $PEEP_i$, the rise in airway pressure precedes the rise of flow. At the end of the preceding expiration, the lungs have retained a volume of gas that generates $PEEP_i$. To force the gas flow to enter the lung during the following inspiration, a gradient of pressure must be created between the airways and the peripheral compartments. Therefore, the flow starts only when the pressure applied to the airways exceeds $PEEP_i$ [3].

If the lung has compartments that have different time constants, $PEEP_i$ measured with this method represents the minimum regional $PEEP_i$, that is, the minimum pressure the ventilator has to generate in order to make air enter the lung [2, 13]. If the lung is perfectly homogenous, $PEEP_i$ measured with the static and dynamic methods is the same. However, this homogeneity cannot be observed even in physiological conditions. These two measurements reflect the relation between the minimum and average $PEEP_i$ so closely that the ratio between dynamic and static $PEEP_i$ has been used as a measure of lung homogeneity [14] and defined as the inequality index. According to Maltais and coworkers, the fewer the obstructive components of the lungs (a sign of inhomogeneous pathology), the closer the $PEEP_{i,dyn}$ and $PEEP_{i,stat}$ values.

When external PEEP is applied, measurement in either static or dynamic conditions yields $PEEP_{tot}$, that is, the sum of the effects of $PEEP_i$ and $PEEP_{app}$. To separate these effects, Eq. 1 can be applied.

The ANN used in this paper was trained and tested according to accepted standards and based on our previous studies [6–8, 15]. As confirmed by the computer science literature, ANNs are universal function approximators [16, 17]. We decided to test their application to the estimation of $PEEP_{tot}$ during mechanical ventilation. Other studies have addressed the problem of monitoring $PEEP_i$ online. Eberhard et al. [18] applied a technique based on the least squares fitting method on a breath-by-breath basis, tested in patients who presented with acute respiratory distress syndrome. Nucci et al. [19] studied in a group of eight patients the performance of the recursive least squares method to obtain $PEEP_i$ online and stable and repeatable results. More recently, Mayaud et al. [20] developed an expert system for calculating a series of respiratory parameters that included $PEEP_i$. However, they analyzed 23 tracings from patients who were breathing spontaneously, and not all presented a detectable $PEEP_i$. Although the researchers found good agreement between their algorithm and the manual computation of $PEEP_i$, only one case had a $PEEP_i$ higher than 5 cmH_2O. Thus, the performance of their method must be validated in a wider range of conditions.

The ANN described in the present paper shares with other multilayer perceptrons the limitation derived from the choice of the pool of training examples. Although having the capacity of generalizing its knowledge, if the ANN has to face completely different patterns during use, similar to the patterns derived from other ventilation modalities or different pathologies, the ANN must be retrained on tracings that contain the new examples. The same limitations apply to the mechanical implications of muscle relaxation used in the present protocol. If the ANN has to face tracings derived from a spontaneously breathing subject, it must be retrained. Artificial neural networks process data using a complex matrix of connections between the artificial neurons. This implies that ANNs act similarly to a black box in which identification of the algorithm behind their performance is very difficult. From the clinical point of view, this will not show whether the calculation of $PEEP_{tot,\ stat}$ is based on an estimate of the inhomogeneity in $PEEP_i$ or the elastic components of the respiratory system.

In the first step, the experimental model was used to produce a pool of examples of $PEEP_{tot}$, necessary for training the ANN. The shape of $PEEP_{tot,stat}$ plotted versus TE (Fig. 3) showed an exponential pattern, as expected by the respiratory dynamics. The increase in PEEP and in the subsequently trapped volume increased exponentially at linear decreases in the TE.

A Bland–Altman test showed low bias and scatter of the ANN estimate of $PEEP_{tot,stat}$. Moreover, evaluation of the dependency of the estimation error by the ANN and applied PEEP demonstrated the absence of such a correlation. Thus, we concluded that the ANN could estimate $PEEP_{tot,stat}$ reliably, without any influence from the level of $PEEP_{app}$. To obtain $PEEP_i$ from $PEEP_{tot}$, it is sufficient to subtract $PEEP_{app}$ (which can be easily read on the ventilator display). Another issue we wanted to disclose was the possibility that the ANN would have approximated $PEEP_{tot,stat}$ (by using dynamic tracings) because of a potential strict correlation between $PEEP_{tot,dyn}$ and $PEEP_{tot,stat}$. Our data showed that it was not the case,
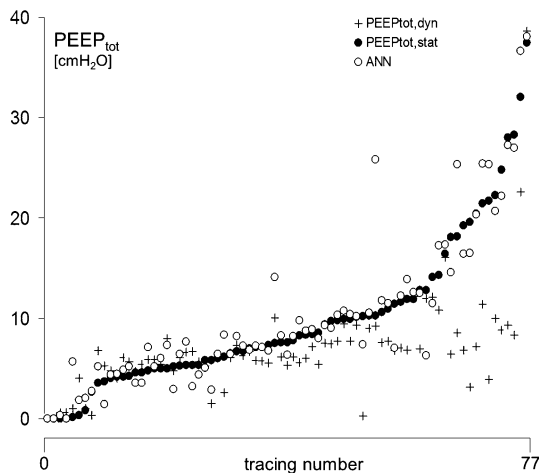
Fig. 7 Plot comparing the manual measurements of $PEEP_{tot,stat}$ and $PEEP_{tot,dyn}$ with the measurement of $PEEP_{tot}$ made by the ANN on the same tracing. On the y-axis: estimation of $PEEP_{tot}$ with the three methods. Tracings (on the x-axis) are ordered according to increasing values of $PEEP_{tot,stat}$, from data set 1 to 77. $PEEP_{tot,stat}$ (reference measure) was assessed with the end-expiratory hold maneuver; $PEEP_{tot,dyn}$ was calculated by the shift between the onset of inspiratory flow and pressure. The ANN estimate follows the $PEEP_{tot,stat}$ more closely than the $PEEP_{tot,dyn}$

because, in our pool of data, only the 24 % of the $PEEP_{tot,dyn}$ values could be inferred by the corresponding $PEEP_{tot,stat}$ (see Fig. 6). This is in line with the concept that $PEEP_{tot,dyn}$ approximates $PEEP_{tot,stat}$ more closely in situations of pulmonary homogeneity [21], and we observed this in our experiments in a healthy lung before we administered the oleic acid. Comparison of the $PEEP_{tot}$ estimate by the ANN with the manually computed $PEEP_{tot,stat}$ and $PEEP_{tot,dyn}$ (see Fig. 7) supported the finding that the ANN yielded results that were directly related to $PEEP_{tot,stat}$.

The ANN that had been taught with $PEEP_{tot,stat}$ showed good agreement with the manually calculated $PEEP_{tot,stat}$, although the flow and pressure recordings in the selected regions are commonly used to calculate $PEEP_{tot,dyn}$. This suggests that more information is available in the P_{AW} and V' curves than in the phase shift between them that is used for the manual calculation of $PEEP_{tot,dyn}$.

To measure $PEEP_{tot,stat}$ for research purposes, application of EEHM remains the gold standard of reference, and for precision. However, when the purpose is the continuous monitoring of a variable, the measurement property of measure that should be aimed is robustness. In this respect, although this paper was not designed to assess the robustness of ANNs in continuous monitoring of $PEEP_{tot,stat}$, this property of multilayer perceptrons is well demonstrated in the literature of this field [22].

Whether the reported limit of agreement (where 95 % of the measurement errors are positioned) is acceptable for a monitoring method should be discussed. In the present

experiment, we measured the direct estimation of total $PEEP_{tot,stat}$ on single tracings, "not seen before" by the ANN and without any averaging of the computation over the presentation of different tracings on the same condition. We can expect that an ANN that faces recursively different breaths of the same tracing during ongoing ventilation would minimize the random error, because the estimation error is averaged over the elaboration of different tracings. Nevertheless, these theoretical speculations require a purposely designed study, in which the limits of precision of routine use are assessed including repetitive presentation of the same trace and adding a comparison with other accepted standards of monitoring $PEEP_i$, such as the multilinear fitting and the use of phase shift between pressure and flow.

Intrinsic PEEP has been a frequently debated topic of critical care for many years [23]. The importance of $PEEP_i$ derives from the physiological consequences of its presence, spanning from alteration of hemodynamics (mainly the reduction of cardiac output due to a decrease in cardiac filling caused by the positive intrathoracic pressure) [24] to the potential risk of barotrauma (due to the possible high alveolar pressures) [2].

Moreover, as first reported by Jonson et al. [25], if $PEEP_i$ is not considered, a significant error can affect the measurement of static C_{RS}. This finding led researchers to introduce this correction factor when estimating respiratory mechanics [26–28]. In previous studies, we demonstrated the capability of an ANN to extract information from respiratory signals [7, 8, 29]. Another mechanical consequence of $PEEP_i$ is the generation of higher levels of lung strain [30, 31], which, as result of pulmonary inhomogeneity, may induce a ventilator-induced lung injury [32]. The possibility of estimated $PEEP_{tot,stat}$ during ongoing mechanical ventilation is an important achievement. $PEEP_i$ measured by applying an end-expiratory pause requires a breath hold that must be prolonged by more than 1 s, and often more than 3 s in order to display a stable $PEEP_i$ value [33]. Moreover, in conditions of pulmonary inhomogeneity, occlusion of up to 5 s may be required [34].

The potential for hemodynamic and gas exchange impairment that these conditions present may not allow frequent and prolonged alterations of the breathing pattern. The estimation of $PEEP_{tot}$ by ANNs does not require the cessation of the breath series. This opens up a perspective in the field of respiratory mechanics monitoring, because of the possibility of estimating $PEEP_i$ in safer conditions. Further studies are necessary to ascertain that the performance shown by the ANN in the assessment of $PEEP_i$ in this experimental setting can be reproduced in different models of lung pathology and during different ventilatory strategies.

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