To examine the relationship of expired capnograms and respiratory system resistance (Rrs) in intubated critically ill patients, we consecutively studied 41 mechanically ventilated patients to (1) analyze the association between expired CO₂ slope and auto-positive end-expiratory pressure (auto-PEEP), between Rrs and auto-PEEP, between Rrs and expired CO₂ slope, and between Rrs and arterial minus end-tidal PCO₂ gradient (PaCO₂-PetCO₂ gradient) and (2) to investigate the capacity of the expired CO₂ slope and PaCO₂-PetCO₂ gradient to predict Rrs during mechanical ventilation. Regression analysis found a close correlation between Rrs and expired CO₂ slope (r = 0.86; p < 0.001), between Rrs and auto-PEEP (r = 0.75; p < 0.001), and between auto-PEEP and expired CO₂ slope (r = 0.74; p < 0.001). Weak correlation was found between Rrs and PaCO₂-PetCO₂ gradient (r = 0.48; p < 0.01). Prediction interval limits at 95 percent confidence level for Rrs are approximately ± 7.39 cm H₂O/L/s from the predicted value obtained by the regression equation, where Rrs = 11.42 + 2.28 expired CO₂ slope. These observations suggest that CO₂ elimination in critically ill patients is strongly modulated by lung, airway, endotracheal tube, and ventilator equipment resistances. Although continuous capnogram waveform monitoring at the bedside might be useful to assess Rrs, very accurate predictions could be done only in determinate patients. (Chest 1994; 105:219-23)

Methods

Moderate ventilator monitoring includes the measurement of airway pressures and derived intermittent calculations such as respiratory system resistance (Rrs).¹ ² Patients in the ICU receiving mechanical ventilation often exhibit high Rrs due to bronchospasm,³ structural airway abnormalities,⁴ low lung volume,⁵ and retained bronchial secretions both attached to the airways or to the wall of the endotracheal tube.⁶ The measurement of Rrs is useful to assess the effects of bronchodilator drugs, to characterize the various diseases, to alert clinicians to the risk of barotrauma, and to improve patient treatment.³⁴⁷

Measurements of expired capnogram have been proposed as a continuous noninvasive method to determine end-tidal PCO₂ (PetCO₂) in order to assess alveolar ventilation in patients without pulmonary dynamic hyperinflation.⁸ The factors that influence the waveform of the expired capnogram are the ventilation perfusion mismatch of some lung zones, airway gas mixing, and CO₂ sequential expiration. Therefore, the increasing expired CO₂ slope observed in determinate patients may be a result of the serial mixing of gas flowing from units with different time constants.⁹ ¹⁰ In fact, during general anesthesia, the expired CO₂ slope has been associated with increased respiratory resistance in patients with normal lungs.¹¹

The purpose of the present study was to investigate the relationship between Rrs and expired capnogram in a population of critically ill patients receiving mechanical ventilation admitted in a general intensive care service. In addition, we assessed whether the expired CO₂ slope and arterial minus end-tidal PCO₂ gradient (PaCO₂-PetCO₂) gradient could be a sensitive parameter to predict Rrs during total ventilatory support.

Subjects

Forty-one consecutive patients aged between 23 and 89 years (mean ± SEM, 66.5 ± 2.34 years) who had been admitted to the general ICU of the Hospital of Sabadell (Spain) were studied. Mechanical ventilatory support had been initiated for a variety of medical and/or surgical processes. The diagnosis was COPD in 21, ischemic heart disease in 10, septic shock in 5, adult respiratory distress syndrome (ARDS) in 2, acute asthma in 2, and coma in 1. Informed consent was obtained from the patients' relatives according to the requirements of the Clinical Research Committee of the Hospital of Sabadell.

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Para el artículo, por favor asegúrese de que el texto esté en inglés y cumpla con los requisitos de publicación.
Patients were orally intubated with a cuffed endotracheal tube (Hi-lo Evac Mallinckrodt, Athone, Ireland) with an inner diameter ranging from 8 to 9.5 mm. At the time of the study, the number of days with the same endotracheal tube in place ranged from 1 to 18 (mean ± SEM, 5.6 ± 0.76). Mechanical ventilation in assist/control mode was carried out with volume-cycled ventilators (Servo 900C and Servo 300, Siemens, Solna, Sweden). Inspired gas was humidified with disposable heat and moisture exchangers (Edith Flex, Gambro Engstr;auom, Bromma, Sweden) that were changed daily. Patients had indwelling radial or femoral artery catheters for blood gas collection and hemodynamic monitoring purposes. Samples of blood were drawn in heparin-rinsed plastic syringes and were immediately analyzed for oxygen and carbon dioxide tensions (ABL 500, Radiometer Copenhagen, Copenhagen, Denmark). An on-line infrared CO₂ analyzer (HP78556A, Palo Alto, Calif) was used to continuously monitor CO₂ partial pressure changes and was placed between the distal port of the disposable humidifier and the proximal port of the endotracheal tube. Before each study, the CO₂ analyzer was calibrated using certified gas with known concentrations of CO₂ (0 and 55.8 mm Hg). Capnograms were continuously recorded against time on a multichannel strip chart (HP7857A, Palo Alto, Calif) using a paper speed of 25 mm/s. The highest CO₂ concentration point at end-expiration was taken as PEEP. The slope of expired CO₂ (mm Hg/s) was calculated by linear regression during phase III of the expired capnogram. The initial 25 percent of the expired capnogram was rejected for calculation because it consisted of gas eliminated from two sequential compartments, instrumental and anatomic dead spaces, ie, not participating in gas exchange. The final PEEP and expired CO₂ slope were obtained averaging values from strip-recorded tracings over a 20-s period. Airway pressures, flow, and tidal volume were obtained from the ventilators that were provided with built-in sensors for flow and pressure. The calibration of the ventilators was periodically tested with a differential pressure transducer (MP45 Validyne Engineering Corp., Northridge, Calif) and a heated pneumotachograph Fleisch No. 2 (Metabo, Epalinges, Switzerland) in order to obtain tidal volume by electronic integration of the flow signal (13461570 Gould Integrator A, Cleveland, Ohio).

Protocol

Measurements of PaCO₂ and the expired capnograms were obtained during hemodynamically and ventilatory stable conditions and after a period of 20 min without variation in PEEP readings. Auto-positive end-expiratory pressure (auto-PEEP) or intrinsic PEEP was measured by pressing the end-expiratory hold knob on the ventilator during a standard respiratory cycle. Since external PEEP was used in some patients, the pressure measured by occluding the airway at end-expiration was the sum total of the external PEEP and auto-PEEP. We also used the end-inspiratory hold knob of the ventilators for brief (3 s) airway occlusions at end-inspiration. The pressure plateau observed on the display of the ventilators at the end of the occlusion was the elastic recoil pressure of the respiratory system. Total Rrs was calculated by dividing the difference between maximum airway peak inspiratory pressure (Pmax) and elastic recoil pressure of the respiratory system (Pelt,rs) by the inspiratory airflow. The gradient between PaCO₂ and PrsCO₂ was computed as a simple subtraction.

Data Analysis

The data were expressed as the mean ± SEM. Differences in expired CO₂ slope between patients with and without auto-PEEP were analyzed using Student's t test for unpaired data. Standard least-squares linear regression analysis was used for the following: (1) to study the relationship between the expired CO₂ slope and auto-PEEP, between Rrs and auto-PEEP, between Rrs and the expired CO₂ slope, and between Rrs and the PaCO₂-PtCO₂ gradient, and (2) to investigate the capacity of the expired CO₂ slope and PaCO₂-PtCO₂ gradient to predict the Rrs during mechanical ventilation.

Results

Our general population of patients had a variable degree of airflow obstruction, the Rrs ranging between 8.96 cm H₂O/L/s and 44.28 cm H₂O/L/s (19.66 ± 1.07 cm H₂O/L/s) and the expired CO₂ slope ranging between 0.69 mm Hg/s and 12.3 mm Hg/s (3.61 ± 0.40 mm Hg/s). The time set for expiration in the mechanical ventilator was 2.56 ± 0.09 s (range, 1.73 s to 3.75 s). Auto-PEEP was present in 25 of 41 patients (61 percent). All but four patients with COPD and the two asthmatic patients exhibited auto-PEEP during mechanical ventilation. Only 4 of these 25 patients with auto-PEEP had an expired CO₂ slope lower than 3 mm Hg/s. The mean value of expired CO₂ slope was 1.62 ± 0.13 mm Hg/s in patients without auto-PEEP and 4.88 ± 0.51 mm Hg/s in patients with auto-PEEP (p < 0.01), thus confirming our previous results that a very positive expired CO₂ slope identifies patients with auto-PEEP during mechanical ventilation.

As shown in Figures 1 and 2, there was a significant correlation between auto-PEEP and Rrs (r = 0.75; p < 0.001) and between auto-PEEP and the expired CO₂ slope...
slope \( r = 0.74; p < 0.001 \).

We considered whether expired capnogram monitoring might be used in an intensive care setting to assess \( Rrs \). To that end, linear regression analysis was used to compare direct measurements of \( Rrs \) with the expired \( CO_2 \) slope and \( PaCO_2 - PetCO_2 \) gradient in 41 mechanically ventilated patients. The results indicated a very good correlation between the expired \( CO_2 \) slope and \( Rrs \) over a wide range of values \( r = 0.86; p < 0.001 \). The relationship between \( Rrs \) (cm \( H_2O/L/s \)) and the expired \( CO_2 \) slope (mm Hg) was given by the following function:

\[
Rrs = 11.42 + 2.28 \text{ expired } CO_2 \text{ slope}
\]

Prediction interval limits at 95 percent confidence level for \( Rrs \) are approximately \( \pm 7.39 \text{ cm } H_2O/L/s \) (Fig 3).

The \( PaCO_2 - PetCO_2 \) gradients varied from \( \pm 3.8 \text{ mm Hg} \) to \( 28.7 \text{ mm Hg} \) \( (7.66 \pm 0.87 \text{ mm Hg}) \). A weak but significant association was found between \( Rrs \) and the \( PaCO_2 - PetCO_2 \) gradient \( r = 0.48; p < 0.01 \). The relationship between \( Rrs \) (cm \( H_2O/L/s \)) and the \( PaCO_2 - PetCO_2 \) gradient (mm Hg) was given by the following function:

\[
Rrs = 15.15 + 0.58 \text{ } PaCO_2 - PetCO_2 \text{ gradient}
\]

Prediction interval limits at 95 percent confidence level for \( Rrs \) are approximately \( \pm 12.72 \text{ cm } H_2O/L/s \) (Fig 4).

**Discussion**

Precise knowledge of \( Rrs \) in patients receiving mechanical ventilation is needed for adequate clinical management. In intubated patients with normal lungs, the value of \( Rrs \) is usually less than 4 cm \( H_2O/L/s \), excluding the flow-resistive properties of the endotracheal tube and equipment. The contribution of these later components to the \( Rrs \) could be as high as 12 cm \( H_2O/L/s \).\(^{15,15} \) The values of \( Rrs \) of the 41 patients studied amounted to \( 19.66 \pm 1.07 \text{ cm } H_2O/L/s \) and the \( Rrs \) values for patients with COPD \( (22.99 \pm 1.10 \text{ cm } H_2O/L/s) \), ARDS \( (13.33 \pm 3.09 \text{ cm } H_2O/L/s) \), or pulmonary edema \( (15.71 \pm 0.90 \text{ cm } H_2O/L/s) \) were similar to those results obtained by other investigators.\(^{16} \) Additionally, we found a high correlation between the degree of dynamic pulmonary hyperinflation (auto-PEEP) and \( Rrs \) as is shown in Figure 1, an association that has been found previously in nonintubated patients with COPD.\(^{17} \) Despite setting a long expiratory time in the ventilator \( (2.56 \pm 0.09 \text{ s}) \), auto-PEEP was present in 61 percent of patients. This should not be interpreted as an unusual finding since with this pattern of breathing, the factors that should have contributed mainly to the development of expiratory flow limitation are lung heterogeneity and airway morphologic abnormalities such as those observed in patients with COPD.\(^{4,18} \)

In a perfect homogeneous normal lung, the ventilation/perfusion (V/Q) ratio, the time constant, and the \( PCO_2 \) are the same for all respiratory units. However, in presence of regional inequalities of ventilation and perfusion, faster units empty more rapidly at first while gas from slower units, presumably with very low V/Q ratio and high \( PCO_2 \), form a proportionately greater part of the end expiratory gas. Therefore, sequential \( CO_2 \) elimination is the major contributor to the increasing expiratory \( CO_2 \) slope.\(^{6} \) In a previous study, we reported mean values of the expired \( CO_2 \) slope of 1.7 mm Hg/s in mechanically ventilated patients without auto-PEEP and 4.2 mm Hg/s in patients with auto-PEEP.\(^{6} \) These data are in accordance with the results of the present study and in line with other investigations that have shown a mean expired \( CO_2 \) slope value of 1.84 mm Hg/s in patients without chronic bronchitis.\(^{19} \)

In line with the results of Watson and coworkers\(^{11} \) in intubated patients with normal lungs, we found a strong correlation between the expired \( CO_2 \) slope and \( Rrs \). Given a uniform distribution of perfusion, slow hypercapnic units, and sequential emptying, the expired capnogram reflects V/Q abnormalities.\(^{10,11,20} \) In

**Figure 3.** Correlation between \( Rrs \) and the expired \( CO_2 \) slope in 41 intubated critically ill patients. Dotted lines represent 95 percent confidence intervals of the regression line. Long dashed lines represent 95 percent prediction intervals for a single observation.

**Figure 4.** Correlation between \( Rrs \) and the \( PaCO_2 - PetCO_2 \) gradient in 41 intubated critically ill patients. Dotted lines represent 95 percent confidence intervals of the regression line. Long dashed lines represent 95 percent prediction intervals for a single observation.
fact, Rrs and increments in Rrs, which indicated increased time constant inequalities and maldistribution of fast and slow units within the lung, correlated very well with the expired CO₂ slope in our study. These observations suggest that CO₂ elimination is impaired by a flow-resistive mechanism and that the degree of airways obstruction modulates the PCO₂ rate of rising during expiration. However, despite the strong correlation found between Rrs and the expired CO₂ slope, wide prediction intervals were obtained for a given value of estimated Rrs using the regression equation. Therefore, the expired CO₂ slope has limited clinical applicability in order to predict Rrs with sufficient accuracy at the bedside as can be observed in Figure 3.

Respiratory system resistance, as it was measured in the present study, represented total airflow resistance of the respiratory system, also including the resistance of the endotracheal tube and ventilator equipment. At given values of lung and airways resistance, total Rrs may considerably vary breathing through different sized endotracheal tubes. Moreover, Wright and coworkers have demonstrated that endotracheal tubes contribute significantly to total airflow resistance and that the endotracheal tube resistance is often greater in vitro than indicated by studies in vitro because of secretions, head or neck position, tube deformation, or increased turbulence. Therefore, at a given airflow or endotracheal tube size, the relationship between Rrs and expired capnogram could vary due to the aforementioned physical factors. Although in our study Pmax was not measured in the proximal port of the endotracheal tube but with the pressure transducer built in the ventilator, a very strong association between the expired CO₂ slope and Rrs was found. Nevertheless, this association was not sufficiently accurate to predict Rrs from expired CO₂ tracings. This suggested that the resistive properties of the endotracheal tube, tubing, and ventilator equipment, which did not contribute to the exhaled CO₂, increased Rrs, thus possibly influencing our results.

In contrast, we found a weak correlation between PaCO₂-PetCO₂ gradients and Rrs. Because the PaCO₂-PetCO₂ gradient is not only influenced by structural airway abnormalities but also by high and low V/Q regions, it could explain why determinate patients may exhibit wide PaCO₂-PetCO₂ gradient together with both normal Rrs and expired CO₂ slope. Presumably, the patients included in this study suffered from a variety of diseases enabling the production of an increased physiologic dead space. In fact, the PaCO₂-PetCO₂ gradient in our patients amounted to 7.66 ± 0.87 mm Hg and similar values have been correlated with higher VO₂/VT in the literature. Patients receiving mechanical ventilation may develop lung areas with low V/Q ratios such as atelectasis with intrapulmonary shunt. As a result, PaCO₂ may increase with no change in PetCO₂ as mixed venous blood bypasses ventilated alveoli, thus increasing the calculated PaCO₂-PetCO₂ gradient. Moreover, the breathing pattern can alter the PaCO₂-PetCO₂ gradient by itself. Yamanaka and Sue reported that minute ventilation higher than 15 L/min produced a PaCO₂-PetCO₂ gradient of 18 mm Hg in critically ill patients. In line with this, Hoffman and coworkers showed an inconstant PaCO₂-PetCO₂ gradient with changes in the pattern of breathing in 20 patients receiving mechanical ventilatory support. Finally, low cardiac output states may widen the PaCO₂-PetCO₂ gradient as pulmonary perfusion decreases whereas lung mechanical properties remained unchanged.

In conclusion, these observations suggest that CO₂ elimination in critically ill patients receiving total ventilatory support is strongly modulated by lung, airway, endotracheal tube, and ventilator equipment resistances. Continuous capnogram waveform monitoring at the bedside might be useful to assess Rrs during mechanical ventilation. However, very accurate prediction of Rrs through expired CO₂ slope measurement could not be done in the light of the present results.

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