Controlled expiration in patients with chronic obstructive pulmonary disease on ventilatory support

Gecontroleerde uitademing bij patienten met chronisch obstructief longlijden tijdens ademhalingsondersteuning

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CONTENTS

CHAPTER 1

Introduction

Introduction

Chronic respiratory failure develops over the years in many patients with chronic obstructive pulmonary disease (COPD). During exacerbations of COPD the gas-exchange is known to deteriorate in these patients. This acute-on-chronic respiratory failure may ultimately lead to hypercapnic coma. Mechanical ventilation has to be applied to maintain gas-exchange. As this treatment does not affect the pathophysiological mechanisms leading to the respiratory failure, mechanical ventilation can only be considered as rescue therapy [1].

Altered respiratory mechanics associated with COPD may hamper ventilatory support. For the same reasons weaning from the ventilator is considered to be a cumbersome process, in many patients requiring long-term ventilatory support [2]. These altered respiratory mechanics can be elucidated in terms of elastic recoil of the lung and airways resistance. In this chapter these features will be described with emphasis on spontaneous breathing as well as mechanical ventilation. Adaptations of equipment used for ventilatory support and weaning purposes that may improve ventilation and gas-exchange in COPD, will be reviewed. Finally an outline of the investigations described in this thesis will be given.

The population of patients that is the subject of this thesis consists of those who are suffering from severe chronic airways obstruction in whom loss of elasticity of lung tissue may be present. Though COPD may not be the exactly right nomenclature for the condition present in all of those patients, it was applied to all patients because destruction of elastic tissue of a minor degree is difficult to demonstrate or exclude in a living person.

Airways compression

An important feature of COPD is the decrease of expiratory flow due to a reduction of driving pressure and an increase of resistance to airflow. The reduction in the driving pressure is caused by loss of elastic recoil of lung tissue. The increased airways resistance is amongst others related to loss of elastic support of airways that may lead to compression or even collapse of the airways during expiration.

Airways compression develops if the extramural pressure exceeds the intraluminal pressure in deformable airways [3]. Intraluminal pressure in an airway segment is equal to alveolar pressure minus the upstream pressure drop. Alveolar pressure is equal to the sum of the pressure exerted by elastic properties of the lung (elastic recoil pressure) and the intrapleural pressure. The

pressure at the outside of the airway is equal to intrapleural pressure which is determined by the pressure exerted by the thoracic wall and the respiratory muscles. Airways compression can only develop during mechanical ventilation if intrapleural pressure is positive. A positive intrapleural pressure can be encountered during forced and relaxed expirations. During forced expirations the force exerted by the respiratory muscles is directed inwards resulting in a positive pleural pressure. During relaxed expirations a positive pleural pressure can only be present if the thoracic wall exerts an inward force. This occurs during expiration at lung volumes in the range of the upper 40% of vital capacity [4], which is commonly observed in patients with severe COPD in case of hyperinflation. Airways compression is of clinical importance as it leads to a decrease in expiratory flow and can result in flow limitation.

Flow limitation

Flow limitation can be defined as the phenomenon of a constant flow at increasing driving pressure at a certain lung volume. Consequently, flow limitation can be detected by computing expiratory iso-volume pressure-flow relationships. These curves show, in case of flow limitation, that elevation of driving pressure at iso-volume above a certain critical level does not increase expiratory flow. This was demonstrated during forced expirations 30 years ago [5]. It has been suggested that increases of driving pressure and intrapleural pressure due to contraction of expiratory muscles coincide in such a way that, as a net result, expiratory flow remains unchanged. In agreement with this assumption is the observation that expiratory flow-volume curves obtained in healthy individuals during forced expirations are highly reproducible [6]. This finding can be explained by the presence of flow limitation: if the driving pressure varies in a range above the critical pressure-level, the iso-volume flows will not be affected. As these flows are only related to lung volume, the expiratory flow-volume curves will be reproducible and unaffected by the effort of the expiratory muscles. Although the mechanisms leading to airways compression are different in forced and relaxed expirations, flow limitation has also been established in patients with COPD during relaxed expirations. This also applies to patients with COPD who are mechanically ventilated.

Flow limitation during mechanical ventilation

When mechanical ventilation is compared to spontaneous breathing many similarities can be found with respect to expiration. At both conditions relaxed expiration occurs with only the elastic recoil pressure of the respiratory system as the driving pressure to overcome the passive expiratory flow resistance of the total system [7]. In mechanically ventilated patients with COPD flow limitation is well established [1, 8-10]. This can be elucidated by the hyperinflation encountered in these patients during the entire breathing cycle imposed by the ventilator.

Various methods using the expiratory flow pattern have been proposed to establish flow limitation in mechanically ventilated patients with COPD.

As during spontaneous breathing the computation of iso-volume pressure-flow relationships can be considered as the mainstay to establish flow limitation. In order to compute pressure-flow curves the driving pressures and flows have to be determined with the help of the interruptor technique [7]. By imposing an external resistor at the expiratory outlet of the ventilator, driving pressures can be reduced [1, 8-10]. When the corresponding flows are measured taking into account absolute lung volumes, iso-volume pressure-flow curves can be computed. Flow limitation is defined as a plateau in the iso-volume pressure-flow relationship [1, 8]. Reduction of driving pressure by application of the external resistor is not associated with a decrease of flow, until a certain critical level has been reached [8, 9].

A second method to detect flow limitation with the interruptor technique during relaxed expirations is by analysis of the expiratory flow signal after interruption. Flow limitation is suggested when a supramaximal flow transient is observed [7, 11].

From relaxed expiratory flow-volume relationships flow limitation has also been suggested when after the early peak flow, the curve is 'truncated' and a convexity in the curve is detected [1, 7, 10, 12]. This truncation is ascribed to the sudden collapse of airways causing a rapid fall in expiratory flow.

Flow limitation can also be estimated from the effect on the flow-volume curve of a negative pressure applied at the airway opening during expiration [10, 13]. When the increase in driving pressure due to the applied negative pressure has no effect on expiratory flow, flow limitation is assumed to be present [10, 13].

Dynamic hyperinflation

Dynamic hyperinflation is defined as the condition when expiration is terminated by the next inspiration at a lung volume above the static relaxation volume: the functional residual capacity (FRC) [14]. During quiet breathing a healthy subject expires to FRC. FRC is the lung volume at which the opposing forces of the elastic recoil pressures of lung and chest wall are equal. In COPD, FRC is known to be elevated as the elastic recoil pressure of the lung is decreased and the chest wall compliance is within normal limits (fig. 1) [15]. This condition has been referred to as static hyperinflation.

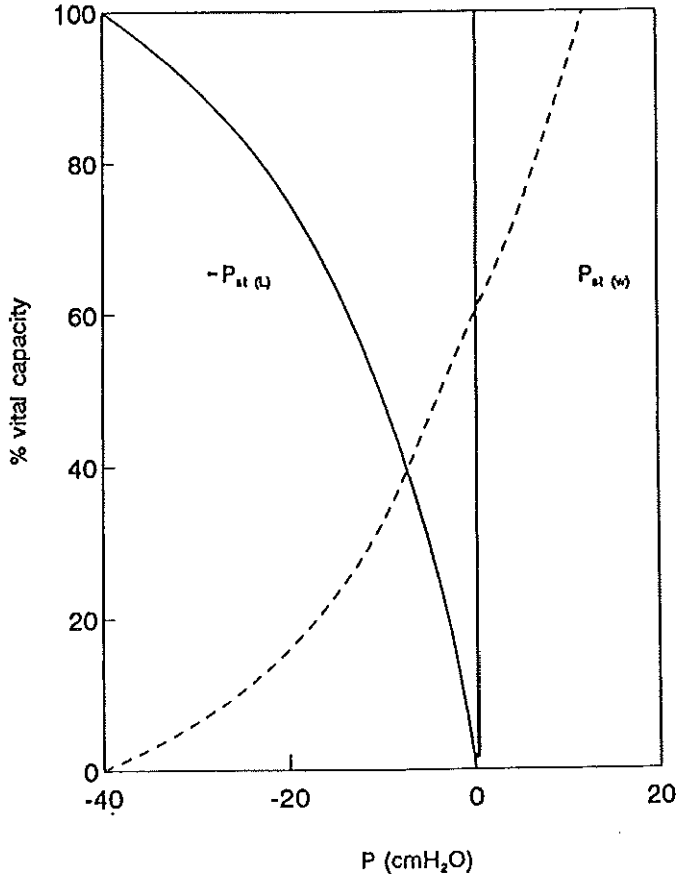

Figure 1 Campbell diagram.
$P_{st(L)}$ = volume-pressure curve of the lung, $P_{st(w)}$ = volume-pressure curve of the chest-wall

Several conditions have been described which are associated with dynamic hyperinflation. Amongst these are acute exacerbations in patients with COPD: at this condition the rate of lung emptying is decreased to such an extent that the expiration time precludes exhalation to the level of FRC [8, 16]. Dynamic hyperinflation is also often encountered in patients with COPD during mechanical ventilation [9, 17-21].

The end-expiratory lung volume above FRC associated with dynamic hyperinflation can be determined by the technique of prolonged expiration [17]. With this technique a maximal passive exhalation into a spirometer is performed. The difference in expired volumes between tidal breathing and a prolonged passive expiration is referred to as the ΔEEV or dynamic hyperinflated volume [4, 17]. As this technique requires expiration times that cannot be imposed on spontaneously breathing patients in severe respiratory distress, ΔEEV can only be obtained in patients who are sedated and paralysed and mechanically ventilated.

Intrinsic Positive End-Expiratory Pressure

As at FRC the opposite forces exerted by the lung and the chest wall are equal, the static recoil pressure of the respiratory system is zero at this lung volume. When dynamic hyperinflation is present, the elastic recoil pressure of the lung and eventually the force exerted by the chest wall, will cause a positive recoil pressure of the respiratory system at end-expiration. The pressure is referred to as auto or intrinsic positive end-expiratory pressure (PEEP) [9, 22]. This term has been derived from ventilator terminology: the ventilator can apply a threshold during lung emptying in order to impose a positive pressure at airway-opening at end-expiration. This positive end-expiratory pressure or PEEP is used to prevent collapse of alveoli [23]. If at end-expiration a steady state is reached, the pressure in the alveoli is equal to the PEEP imposed at airway opening. In this condition the lung volume at end-expiration will exceed FRC.

When dynamic hyperinflation is present, a pressure gradient between alveoli and airway opening is encountered at end-expiration. This implies a positive alveolar pressure at a airway opening pressure equal to ambient pressure, when no ventilator PEEP is imposed. This also indicates that during uninterrupted breathing intrinsic PEEP cannot be detected at airway opening. Therefore intrinsic PEEP has been referred to as occult PEEP in contrast to the PEEP imposed by the ventilator [19].

The height of intrinsic PEEP is determined by three variables: rate of lung emptying, tidal volume and expiration time [24]. Although intrinsic PEEP can be encountered in spontaneously breathing patients, high levels of intrinsic PEEP are predominantly described during ventilatory support. This can be explained by the differences between spontaneous breathing and mechanical ventilation. During spontaneous breathing each patient with COPD will apply an expiration time associated with the lowest intrinsic PEEP-level, depending on his ventilatory needs and altered respiratory mechanics. Hypoventilation adds to a reduction of the level of intrinsic PEEP in these patients. During ventilatory support two of the three variables determining the level of intrinsic PEEP have to be set by the ventilator: tidal volume and expiration time. Mechanical ventilatory support aimed at restoring normoventilation in patients with COPD, will inevitably increase intrinsic PEEP. When controlled ventilation is applied with fixed tidal volumes and expiration times, the intrinsic PEEP-level detected is considered to be the result of an equilibrium between the respiratory variables governing the relaxed expiration. This can be illustrated in a patient with COPD under sedation and paralysis in whom mechanical ventilation is started at FRC-level. In figure 2 airway pressure, volume-displacement and flow during this manoeuvre are shown.

During the first breathing cycles the inflated volumes are not completely expired leading to dynamic hyperinflation and intrinsic PEEP. As the intrinsic PEEP-level determines the pressure in the alveoli at the start of inflation, end-inspiratory pressures will rise from the first inflation in accordance to the increasing intrinsic PEEP-levels. This increase in end-inspiratory pressure will elevate the rate of lung emptying to such an extent that eventually expired volume will be equal to inflated volume. At this point an equilibrium has come about between the respiratory variables, determining the rate of lung emptying.

Intrinsic PEEP is known to exert various deleterious effects in patients with COPD. In spontaneously breathing patients intrinsic PEEP acts as an inspiratory threshold as the alveolar pressure has to be reduced to the airway opening pressure-level, before the inspiratory flow is initiated [8, 16, 18, 22, 25]. This indicates that in the presence of intrinsic PEEP the elastic work of breathing is increased. The concomitant dynamic hyperinflation is known to lead to a less efficient action of the inspiratory muscles [26]. The effects of intrinsic PEEP during ventilatory support are predominantly related to the high intrathoracic pressures encountered in this condition. Amongst these are reduced venous return to the heart, impaired cardiac function and barotrauma [4, 17, 25, 27-30].

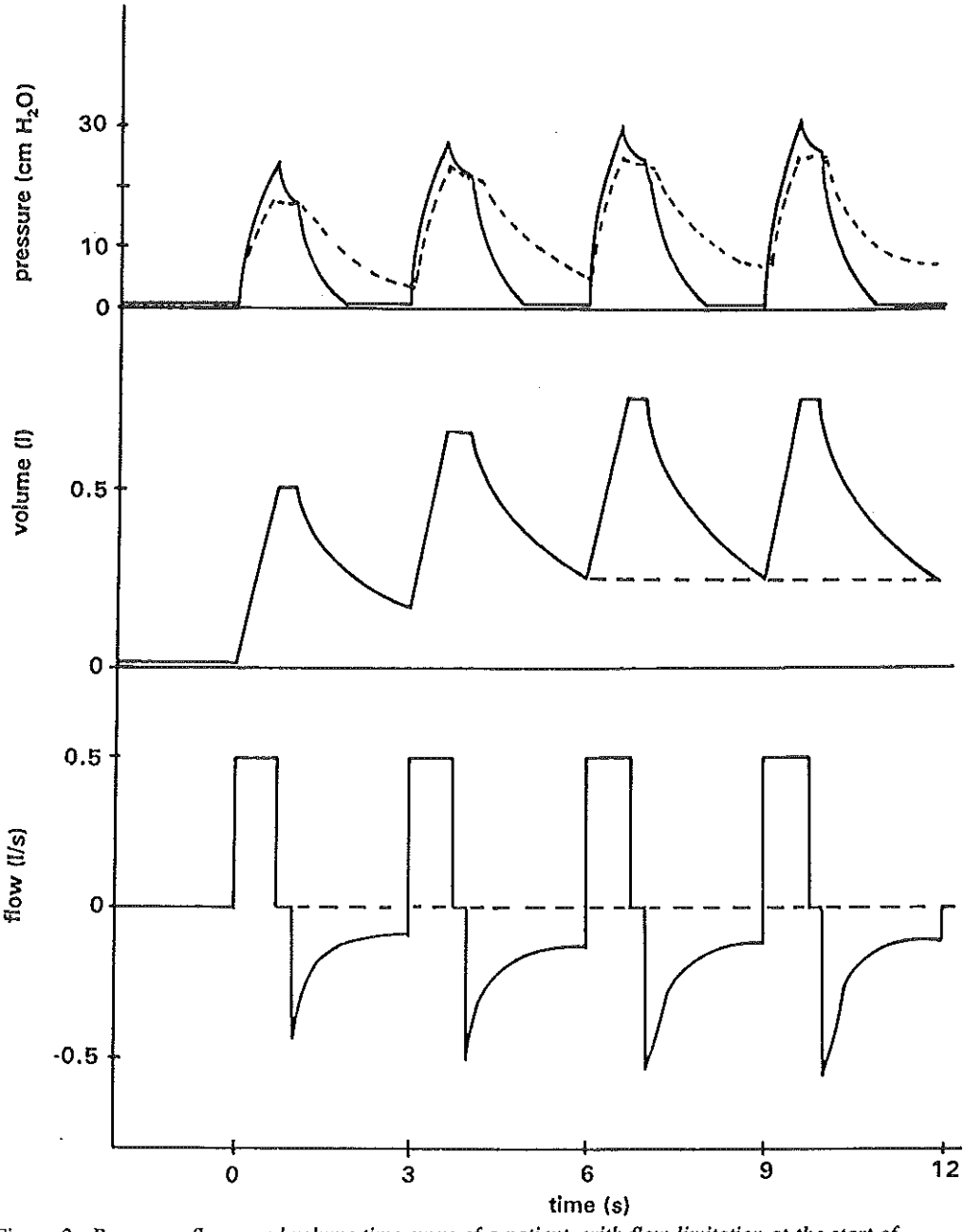

Figure 2 Pressure-, flow-, and volume-time curve of a patient with flow limitation at the start of mechanical ventilation starting from FRC. For further explanation see text.

If intrinsic PEEP is not taken into account during mechanical ventilation, errors are made in the calculation of respiratory system compliance and in the interpretation of central hemodynamic pressure measurements [21, 24].

The level of intrinsic PEEP can be determined during both static and dynamic conditions. When the airway opening is occluded at end-expiration, the static recoil of the total respiratory system can be measured at airway opening, with the prerequisite that inspiratory as well as expiratory muscle activity are absent. This pressure is referred to as static intrinsic PEEP [29, 31]. This method is based on the assumption that during occlusion of the airway, the pressure differences within the respiratory system will equilibrate and consequently the end-expiratory alveolar pressure can be estimated at the airway opening [16, 19]. Static intrinsic PEEP-levels can reliably be determined in mechanically ventilated patients under sedation and paralysis: in spontaneously breathing patients this technique requires the absence of respiratory muscle activity during both expiration and expiratory hold.

Intrinsic PEEP can also be estimated without interrupting respiration. With this technique, applied during mechanical ventilation, the pressure and the flow at airway opening are recorded against time. When intrinsic PEEP is present, the airway opening pressure will rise to a level equal to intrinsic PEEP before inspiratory flow starts [16, 29, 32]. The difference between the end-expiratory airway pressure and the pressure at the onset of the inspiratory flow is referred to as dynamic intrinsic PEEP. In spontaneously breathing patients a similar dynamic intrinsic PEEP measurement can be obtained if esophageal pressure and flow are recorded against time [16]. It is well known that in patients with COPD discrepancies between the measurements of dynamic and static intrinsic PEEP exist: these are attributed to regional differences in the mechanical properties of the lung [29]. As dynamic intrinsic PEEP represents the lowest regional end-expiratory alveolar pressure, static levels reflect a weighted mean value of alveolar pressure at end-expiration [14, 29].

Because dynamic hyperinflation is associated with deleterious cardiopulmonary effects, various adaptations of mechanical ventilation have been advocated to reduce the over-distension of the lungs. Reduction of resistance in external elements such as the endotracheal tube and the ventilator circuit have limited impact as the major part of the elevated resistance is found in the airways of the patient [24]. The ventilator settings can be adjusted to minimize dynamic hyperinflation. These include tidal volume, respiratory rate and the ratio between inspiration time and total breathing cycle time [24]. Adjustments of the ventilator settings will also have a

limited impact by the elevated ventilatory needs due to the high physiological dead space of the lungs in COPD.

Finally the ventilatory support can be adapted to control the expiration. In the majority of mechanically ventilated patients with COPD, in whom intrinsic PEEP is present, airways compression leading to expiratory flow limitation also occurs. Pursed lips breathing, a way of controlling expiratory flow, is advocated as a method to control expiratory flow in patients with COPD [33].

Pursed lips breathing

It is well known for years that some but not all patients with severe COPD get relief from dyspnea when they purse their lips during expiration [33]. Several studies on the working mechanism of pursed lips breathing have been published [34-43]. It is assumed that the beneficial effects of pursed lips breathing in patients with COPD comprise the combination of decreased airways compression, increased tidal volume and a decreased respiratory rate [42]. Less airways compression is assumed to result in less air trapping and a better emptying of highly compliant alveoli, and consequently a better ventilation-to-perfusion relationship in those lung units. Prevention of airways compression by pursed lips breathing can be explained by assuming that by imposing an external resistance at the airway opening the rapid fall of intraluminal pressure in the peripheral airways that causes airways compression is precluded [37]. An additional effect of pursed lips breathing is the reduction of the Bernouilli effect due to a high airflow by the initial peakflow thus reducing the tendency of poorly supported airways to collapse [43].

Adaptations to mechanical ventilatory support in COPD

Two adaptations to ventilatory support in patients with COPD will be described in this section: diminished expiratory flow and PEEP. The first adaptation, reducing the early fall of airway pressure at the onset of expiration had been incorporated in the Siemens Servo ventilator designed in the early seventies [44]. The concept resembling pursed lips breathing consisted of an adjustable reduction of the maximal expiratory flow. The effects of this diminished early expiratory flow or DEEF have been studied in pigs: DEEF was found to improve gas-exchange [42]. In patients with COPD ventilatory support with DEEF did not affect arterial blood-gases

[45]. In later versions of the Siemens ventilator this adaptation was abandoned. Recently, a French ventilator (César Taema) has been equipped with a controlled expiration mode. By this mode the fall in the expiratory airway opening pressure can be controlled. Preliminary studies indicate that the controlled expiration mode can improve gas-exchange in mechanically ventilated patients with COPD [46, 47].

PEEP imposed by the ventilator at the airway opening has been advocated to improve respiratory mechanics in patients with COPD. These effects of PEEP depend largely on the PEEP-devices used [3]. The early generations of "PEEP-devices" consisted of high resistance valves affecting the expiratory flow during the entire expiration. The new generation PEEP-devices operate as threshold resistor imposing minimal resistance until the preset pressure level is reached. The effect of external PEEP on respiratory mechanics in mechanically ventilated patients with COPD is related to the measure it counterbalances intrinsic PEEP. This applies to patients in whom expiratory flow limitation is encountered. The concept of flow limitation implicates a sharp fall in airway pressure over the flow-limiting segment. Analogous to a waterfall the pressure downstream can be elevated up to a critical level without affecting the pressure level upstream or the flow [9, 18, 20, 22, 48, 49]. It is well established that this critical pressure-level to which the airway opening pressure can be elevated during expiration, equals 75-85% of the static intrinsic PEEP [9, 20]. This implicates that a PEEP-level in the range of 75-85% of intrinsic PEEP can be imposed by the ventilator without affecting end-inspiratory pressure or expiratory flow [9, 12, 18, 20]. In agreement with these observations, end-expiratory lung volumes were found to be unchanged at such PEEP-levels [9]. As total PEEP-levels, being the sum of ventilator PEEP and intrinsic PEEP remained unchanged at this condition, intrinsic PEEP, the gradient between the end-expiratory alveolar and airway opening pressure was diminished. Imposing such levels of PEEP by the ventilator is considered useful in ventilatory modes that allow spontaneous breathing. In that case counterbalancing intrinsic PEEP by ventilator PEEP reduces the inspiratory effort of the respiratory muscles as the inspiratory threshold imposed by intrinsic PEEP is lowered [8]. Application of ventilator-PEEP below the intrinsic PEEP-level does not affect flow limitation. Although such levels of PEEP will reduce the driving pressure over the airways, this driving pressure will remain above the critical pressure-level below which flow will be reduced. In agreement with these findings it was established that such PEEP-levels did not affect gas-exchange in patients with COPD when controlled mechanical ventilation was applied [9, 20].

When levels of ventilator PEEP are imposed exceeding the intrinsic PEEP-level, respiratory mechanics are profoundly affected. At this condition airway pressures including total PEEP-levels are elevated associated with increased end-expiratory lung volumes [18]. Expiratory flows are as well affected by such PEEP-levels: iso-volume flows are reduced, indicating a decrease in driving pressure below the critical driving pressure.

Continuous Positive Airway Pressure

In the same way as ventilator-PEEP is imposed in partial ventilatory support, continuous positive airway pressure (CPAP) can be applied in spontaneously breathing patients with COPD [8, 16, 49]. CPAP can be described as a system imposing a continuous positive pressure at airway opening during spontaneous breathing. This positive pressure is maintained during the entire breathing cycle by a closed system, providing an airflow that is adjusted to the ventilatory needs of the patient. In patients with COPD, CPAP can be used to reduce the inspiratory work of breathing by counterbalancing the intrinsic PEEP present at end-expiration. As for the level of PEEP imposed during mechanical ventilation, the level of CPAP should be adjusted to the prevailing intrinsic PEEP-level. If a CPAP-level is chosen, lower than the intrinsic PEEP, work of breathing will be reduced without changes in lung emptying or end-expiratory lung volumes [8]. In order to affect lung emptying, CPAP-levels exceeding intrinsic PEEP should be applied. If such CPAP-levels are imposed lung volumes will inevitably be increased [16].

Summary

It is well established that in patients with COPD ventilatory support is hampered by the altered respiratory mechanics encountered in COPD. Adjustments to ventilatory support have been advocated to improve lung emptying in these patients. As the technology to assess respiratory mechanics in mechanically ventilated patients has not been well established, these adaptations until now have had limited impact. The aim of this thesis is to study respiratory mechanics in patients with COPD on ventilatory support and to assess the effects of various expiratory adaptations on the respiratory variables both during spontaneous breathing and mechanical ventilation.

Outline of the thesis

In chapter 2 the measuring equipment used to determine respiratory parameters in this thesis is described.

In chapter 3 and 4 the effects of continuous positive airway pressure (CPAP) on work of breathing in patients with COPD are described. Experimental results and a theoretical validation comparing breathing with and without CPAP with respect to the level of intrinsic PEEP are presented.

Chapter 5 describes the effect of the expiratory resistance of a ventilator CPAP system on the imposed work of breathing. The additional work imposed by the ventilator was related to the ventilatory needs of the patients and was compared to a continuous flow CPAP system.

In chapter 6 a validation of the interruptor method to establish airways compression is presented. The results obtained in spontaneously breathing patients with COPD with and without airways compression were compared to those of healthy volunteers. Body plethysmography was used as "golden standard" to establish airways compression. The same interruptor technique has been used in chapter 8 and 9.

In chapter 7 relaxed expiratory flow volume curves obtained in mechanically ventilated patients with COPD were analyzed to estimate the degree of airways obstruction. For this purpose, the slope of the second part of the flow-volume curve was compared to the forced expiratory volume in one second (FEV_1) obtained prior to the period of ventilatory support.

The effects of a mode of controlled expiration on airways compression in mechanically ventilated patients with COPD are described in chapter 8. Unimpeded expiration was compared to controlled expiration with respect to airway opening pressures, expiratory flow-volume curves and respiratory variables obtained with the interruptor technique.

In chapter 9 the effects of an alternative mode of controlled expiration on gas-exchange are presented. For this purpose, also mechanically ventilated patients with COPD were studied. Unimpeded expiration was compared to controlled expiration with respect to airway opening pressures, arterial blood gases and physiological dead space.

In chapter 10 the general discussion and a summary of the thesis are presented.

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CHAPTER 2

A Respiratory Mechanics monitoring system during artificial ventilation*

J.G.J.V. Aerts, B. van den Berg, H. Stam, A.F.M. Verbraak, P. Rijnbeek, J.M. Bogaard

Abstract

The ability to measure pressure, flow and volume and to calculate respiratory variables has been available for many years in the Intensive Care setting. Difficulties to determine and analyze the various parameters have limited the clinical use.

A Respiratory Mechanics Monitoring System (RMMS) has been developed, which allows determination of a series of respiratory variables. Data processing techniques incorporated in the system enable on-line signal analysis storage and retrieval. A general recording program is used which is adapted for the specific measurements. The various measurements and determinations in the establishment of respiratory mechanics are reviewed.

* This manuscript will be submitted for publication.

Introduction

In order to study respiratory mechanics during ventilatory support a monitoring system has been developed (Respiratory Mechanics Monitoring System RMMS), which is schematically presented in figure 1.

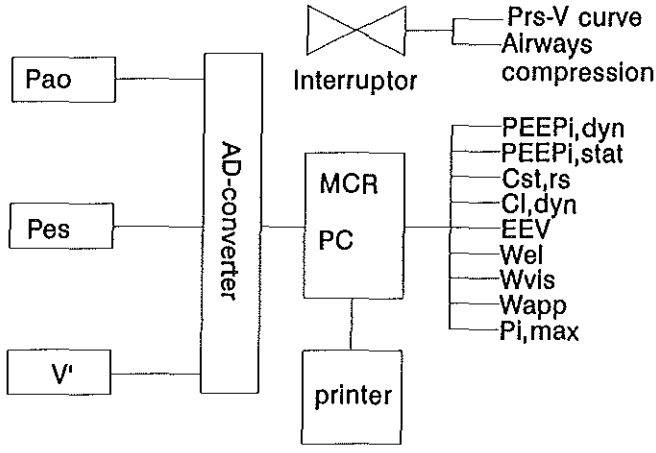

Figure 1 *Schematic representation of the RMMS. Pao = airway opening pressure, Pes = esophageal pressure, V' = airflow, AD-converter = analog to digital converter, MCR = multiple channel registration, PC = personal computer, Prs-V curve = curve representing the recoil pressure of the total respiratory system and lung volume, PEEPi,dyn = dynamic intrinsic PEEP-level, PEEPi,stat = static intrinsic PEEP-level, Cst,rs = static compliance of the total respiratory system, Cl-,dyn = dynamic lung compliance, EEV = end-expiratory lung volume, Wel = elastic work of breathing, Wvis = viscous work of breathing, Wapp = imposed work of breathing, Pi,max = maximal inspiratory pressure against an occlusion.*

The system input consists of basic variables as pressure and flow; volume is obtained by flow integration. Flow is the amount of gas that moves in and out of the airway over time. Pressures required for the assessment of respiratory mechanics include pleural pressure and airway opening pressure. Pleural pressure is usually not measured in humans but can be estimated by measuring the pressure in the distal esophagus [1]. Processing of these parameters provides derived variables as work of breathing and elasticity indices. Measured signals are displayed and stored in the RMMS by means of a personal computer. Derived signals are calculated on-

line. Incorporated in the RMMS are a closed circuit rebreathing system to determine absolute lung volumes and an interruptor device. Figure 2 shows an overview of the system.

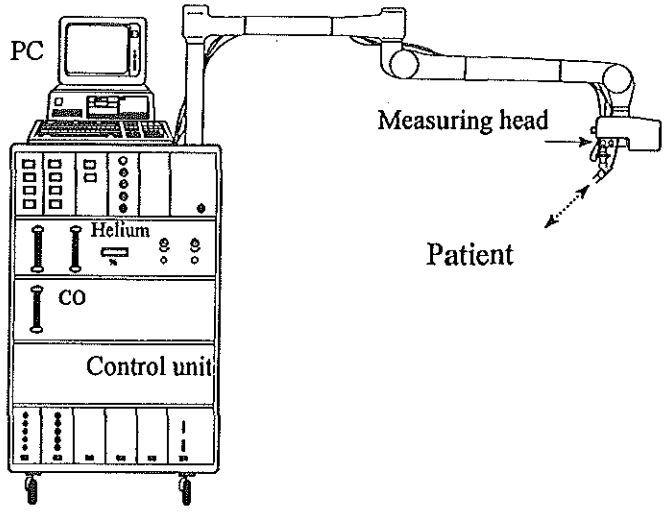

Figure 2 RMMS overview

In this chapter the RMMS and the respiratory variables determined by the system in this thesis are described. The set-up of the system to determine lung volume will be described briefly although this technique has not been used in the studies.

General Set-up

The RMMS (figure 2) incorporates a measuring head and a control unit. The measuring head is placed near the airway opening of the patient and is connected to the control unit via a movable arm. It consists of a heated pneumotachometer (Jaeger Würzburg Germany) and three pressure transducers (Validyne, Validyne CO, Northridge, USA). One pressure transducer is connected to the pneumotachometer, the other two are used to measure airway opening and esophageal pressure. Airway opening pressure is measured at the outlet of the endotracheal tube. Esophageal pressure is measured using a thin walled vinyl balloon incorporated in a double lumen nasogastric catheter (Mallinckrodt Inc., Argyle, NY, USA). The influence of noise is minimized by placement of the transducers in the measuring head.

Via an Analog/Digital converter signals are transferred, displayed and stored using the personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA). Software for display, storage and calculation of derived variables has been developed. The various signals are displayed using a multiple channel recording program (MCR, Medical Technical Section, University Hospital Dijkzigt, Rotterdam, the Netherlands). Adaptations of the software for the Intensive Care setting were programmed in Pascal (Borland International, Scotts Valley, USA) and Matlab (The Math Works Inc, Natick, USA). Signals are continuously sampled and stored at a chosen sample frequency. The variables displayed on the screen can easily be changed at the bed-side. Screen lay-out, time base and X-Y recordings can be added or changed.

Measurements and signal processing

Intrinsic PEEP.

Intrinsic PEEP is defined as the presence of a pressure gradient between alveoli and airway opening at end-expiration [2]. Intrinsic PEEP can be estimated in various ways. The level of intrinsic PEEP can be determined in a direct way by occlusion of the airway opening at end-expiration. When respiratory muscle activity is absent during this occlusion, the pressure at the airway opening will equilibrate with alveolar pressure, and consequently the alveolar pressure can be estimated at airway opening. This technique can be applied in intubated subjects both during mechanical ventilation and spontaneous breathing. Absence of respiratory muscle activity is a prerequisite for these measurements. In the mechanically ventilated patient the expiratory line is occluded at end-expiration and the next ventilator breath is postponed. During the occlusion the pressure recorded outside of the airway opening will rapidly reach a plateau (figure 3), the intrinsic PEEP-level. In the presence of extrinsic PEEP, when a positive pressure is imposed by the ventilator at the airway opening during expiration, the abovementioned plateau equals the sum of extrinsic and intrinsic PEEP. This has been referred to as total PEEP. By subtracting the airway opening pressure just before the occlusion, the extrinsic PEEP-level, from total PEEP the intrinsic PEEP-level is calculated.

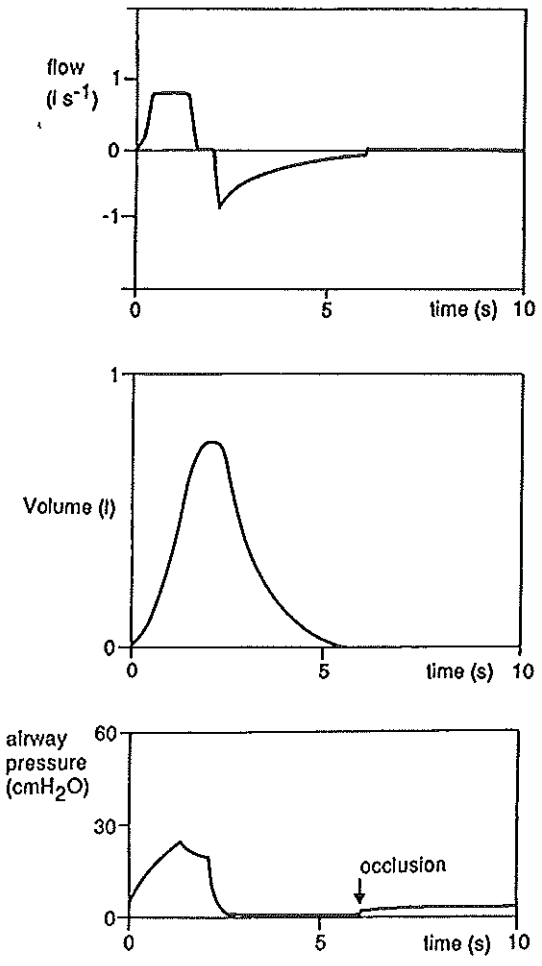

Figure 3 Determination of static intrinsic PEEP in ventilated patients. Occlusion applied at end-expiration.

During spontaneous breathing intrinsic PEEP can be estimated by occluding the airway at end-expiration, and maintaining the occlusion during two or more consecutive breaths. The expiratory plateau between the pressure drops, caused by inspiratory efforts, equals the static recoil pressure of the total respiratory system at end-expiration, in absence of respiratory muscle activity (figure 4).

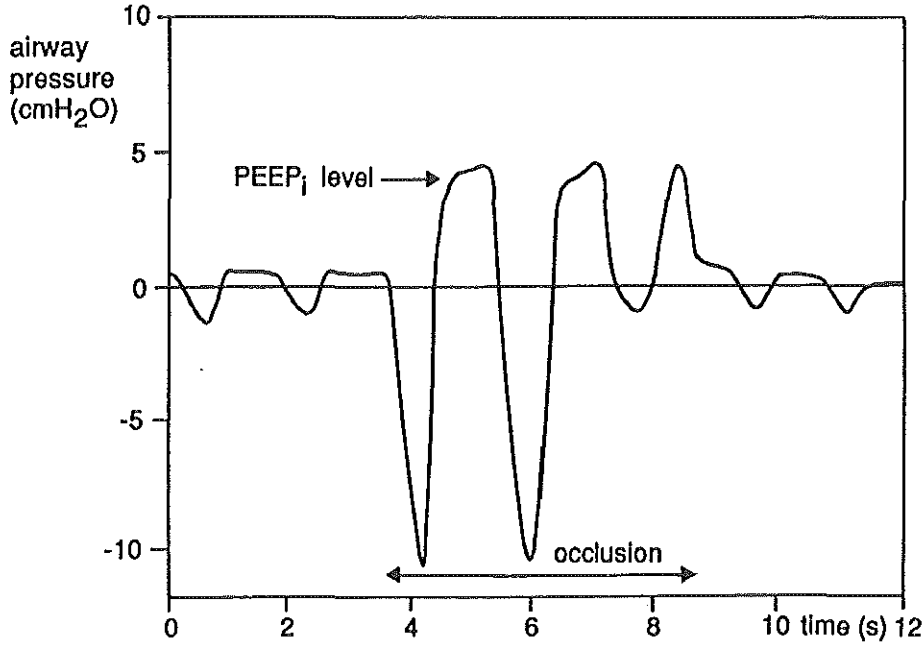

Figure 4 Determination of static intrinsic PEEP in intubated spontaneously breathing patients. Occlusion method.

A second, indirect, method to determine intrinsic PEEP is the measurement of the pressure needed to counterbalance the intrinsic PEEP before the start of inspiratory flow. Intrinsic PEEP determined in this way has been referred to as dynamic intrinsic PEEP. It can be obtained both during mechanical ventilation and spontaneous breathing.

In the mechanically ventilated patient this method requires simultaneous recording of inspiratory flow and airway pressure. When intrinsic PEEP is present, a positive pressure generated by the ventilator will be encountered at the onset of inflation before inspiratory flow starts [3] (figure 5).

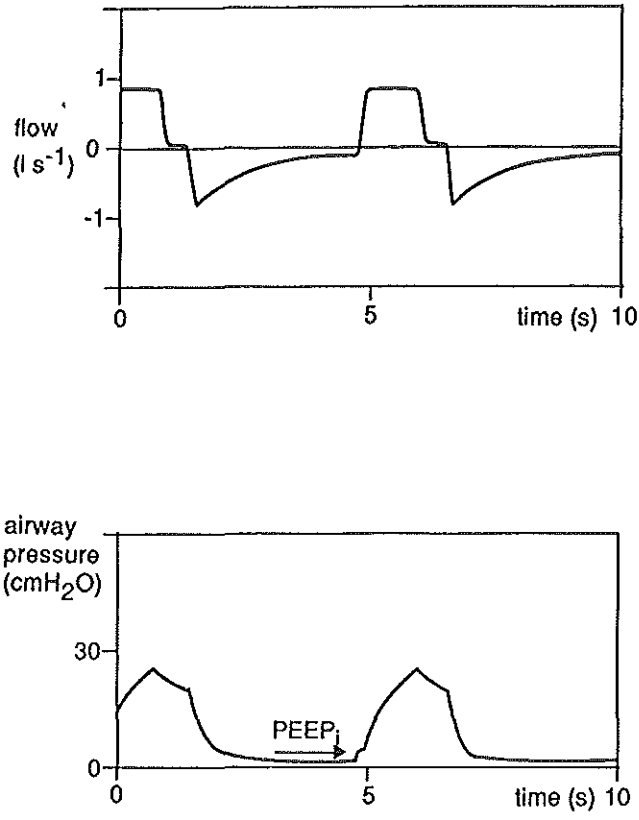

Figure 5 Determination of dynamic intrinsic PEEP in ventilated patients. Simultaneous recording of inspiratory flow and pressure.

During spontaneous breathing the negative deflection in esophageal pressure before the start of inspiratory flow is assumed to represent the inspiratory muscle force required to counterbalance the intrinsic PEEP [4] (figure 6). The intrinsic PEEP-level is equal to the esophageal pressure gradient between the onset of inspiratory effort and the start of inspiratory flow.

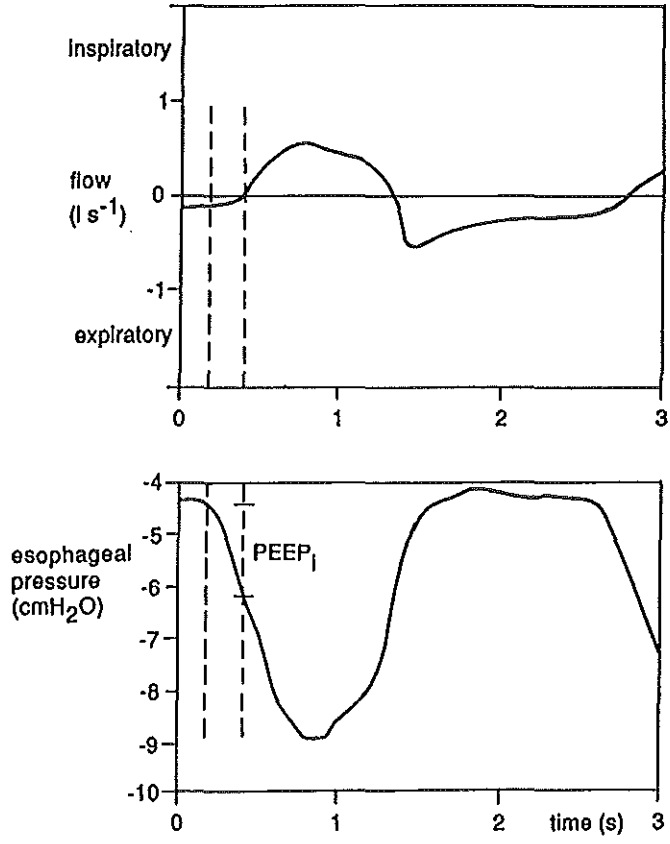

Figure 6 Determination of dynamic intrinsic PEEP in spontaneously breathing patients. Simultaneous recording of airflow and esophageal pressure.

Static compliance

Compliance is a measure of distensibility of the respiratory system. The static compliance of the total respiratory system, Cst,rs, can be computed by dividing the change in lung volume by the change in recoil pressure of the total respiratory system. In order to obtain the static recoil pressures, end-inspiratory and end-expiratory holds are obligatory. In mechanically ventilated patients these holds can be applied when the respiratory muscles are paralysed.

Dynamic hyperinflation

Dynamic hyperinflation is defined as the condition when the expiration is terminated by the next inspiration at a lung volume above FRC. The degree of dynamic hyperinflation can be assessed by measuring the end-expiratory lung volume above FRC. In mechanically ventilated patients this volume can be measured by imposing a prolonged expiration time. For this manoeuvre paralysis of the patient is necessary. At steady state, inspiratory volume equals expired volume. At the start of expiration the patient is disconnected from the ventilator. The total exhaled volume determined by means of the pneumotachometer represents the lung volume above FRC at end-inspiration. Subtracting inspired volume from this volume-level reveals the end-expiratory volume above FRC (ΔEEV) (figure 7).

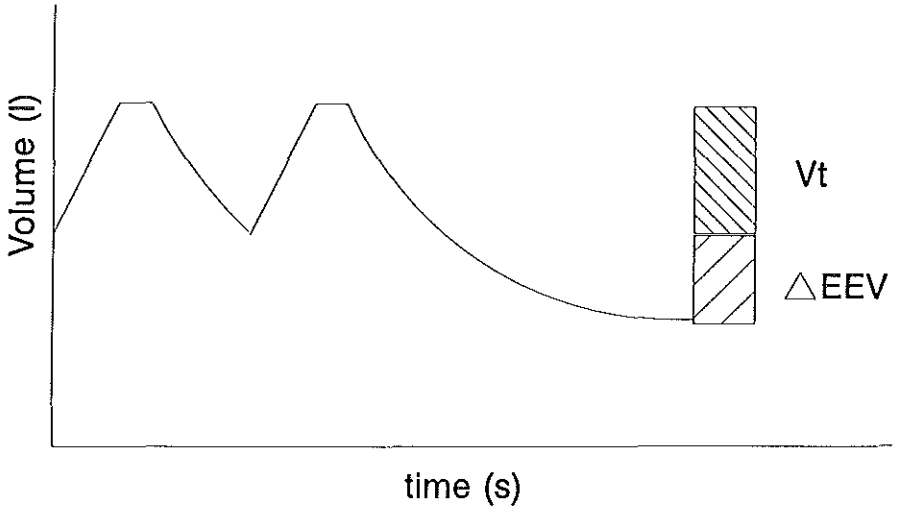

Figure 7 Determination of end-expiratory lung volume above FRC, obtained during prolonged expiration. Vt = tidal volume, ΔEEV = end-expiratory lung volume above FRC.

Work of breathing

Campbell Diagram

The elastic and resistive work done by the respiratory muscles during spontaneous breathing can be computed by using Campbell's diagram [5]. The elastic work is determined taking into account 4 components: level of volume displacement, dynamic lung compliance, chest-wall compliance and intrinsic PEEP. Resistive work of breathing is an estimate of the work performed to overcome resistive elements. In order to determine elastic and resistive work, pressure volume loops are used: volume displacement is plotted against esophageal pressure relative to atmospheric pressure. In figure 8 an esophageal pressure volume curve of a patient is shown and Campbell's analysis is indicated.

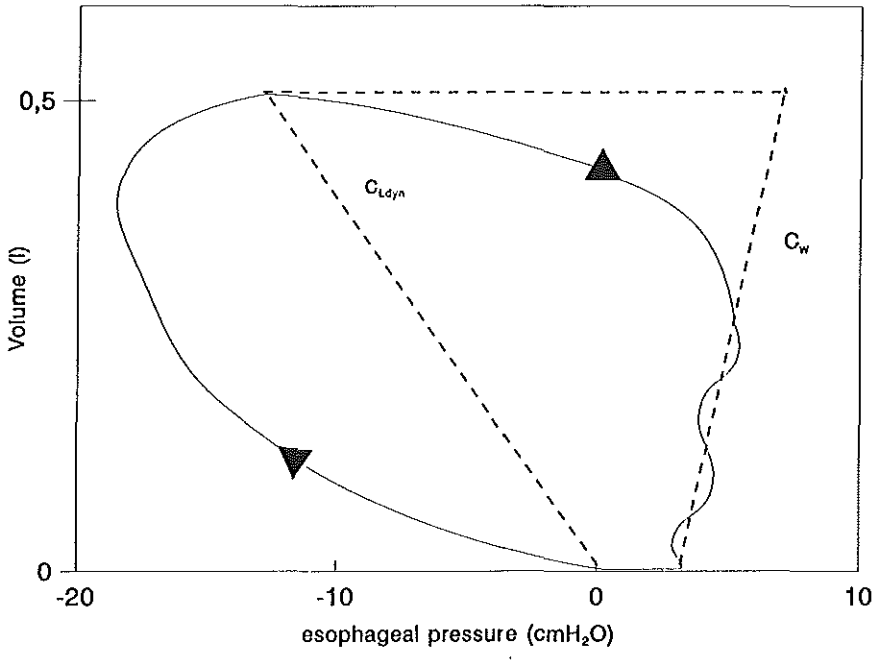

Figure 8 Pressure-volume diagram of a spontaneously breathing patient with COPD. CL,dyn = dynamic lung compliance, Cw = chest-wall compliance.

At first the line representing dynamic lung compliance (CL,dyn) has to be estimated by drawing a line between the values of the esophageal pressures at the start and the end of inspiration. Secondly, the line representing the pressure exerted by the chest-wall at the prevalent lung volumes has to be drawn. As this last pressure can only be determined during paralysis standard values are commonly used. In both healthy individuals and in patients the compliance of the chest-wall is assumed to be 4% of the predicted vital capacity in l per cm H_2O [6]. The line representing the compliance of the chest-wall is fitted in the esophageal pressure volume loop assuming the recoil pressure of the chest-wall at end-expiration to correspond to the negative deflection that indicates the onset of inspiratory effort. In the presence of intrinsic PEEP the lines of lung- and chest wall compliance do not intersect, but are separated by a pressure-level equal to the dynamic intrinsic PEEP-level.
The inspiratory resistive work is obtained by integration of the area subtended by the dynamic changes in esophageal pressure and lung volume during inspiration and the line of CL,dyn. Flow resistive work done on the chest-wall cannot be separated from total resistive work. The inspiratory elastic work is obtained by integration of the area subtended by the CL,dyn and the Cw during inspiration.

Imposed work of breathing

In order to wean patients from mechanical ventilation, ventilatory circuits providing an airflow through wide-bore tubes can be attached to the endotracheal tube. Alternatively, the ventilator can be used to allow spontaneous breathing via the ventilator tubes attached to the patient's airway opening. Although these circuits warrant a continuous flow of inspiratory gas, as a drawback they impose additional work to the patient. This work imposed by the ventilatory circuit can be computed by plotting the area of the changes in airway opening pressure and volume during spontaneous breathing. Assessment of additional work imposed by ventilatory circuit is important in clinical practice as high levels of imposed work may hamper the weaning process.

Pi,max

The maximal inspiratory pressure generated against an occluded airway has been referred to as Pi,max [8]. This pressure is considered a measure of the strength of the inspiratory muscles. Pi,max can be measured both in intubated and in non-intubated patients. In intubated patients

equal Pi,max values are obtained, measured at airway opening and in the esophagus. In non-intubated subjects differences between airway opening and esophageal pressures are encountered due to the physical properties of the upper airway. For the procedure a two-way valve is used separating inspiratory and expiratory flow. This valve is attached to the airway opening: after occluding the inspiratory line during expiration, the patient is asked to make a maximal inspiratory effort after complete expiration. Maximal negative pressures will be established at residual volume: however, in clinical practice Pi,max is commonly determined at FRC.

Respiratory measurements obtained with the interruptor method

The interruptor-technique allows the physician to determine the elastic and flow-resistive properties of the respiratory system during passive exhalation [9]. For this technique a valve is placed in the expiratory line that can be opened and closed at high velocities. The analysis is based on the assumption that a rapid pressure equilibration between the alveoli and the airway opening occurs during an occlusion. The alveolar pressure obtained by this technique, is considered to be only minimally disturbed by the movement of lung and chest-wall. The RMMS has been equipped with a pneumatic interruptor valve (4200 series, Type TM7/8 Hans Rudolph Inc., Kansas City, MO, USA). It consists of a sliding piston placed in series with the pneumotachometer. Airway opening pressure was measured proximal to the interruptor valve. The opening and closure of the piston was computer controlled. The switching speed, from complete closure to complete opening, was 65-110 ms.

Dynamic properties of interruptor device and measuring equipment were analyzed, using a constant flow generator. The system was critically damped based on this analysis. Ninety percent rise time was less than 25 ms, which was considered accurate. Quasi static alveolar pressure-volume loops can be obtained by plotting the plateau pressures during occlusion versus the respective volume levels above FRC. These curves yield the elastic behaviour of the respiratory system over a large volume range.

The presence of airways compression can be established by analysis of the expiratory flow pattern after opening of the interruptor valve. Supramaximal flow transients (flow spikes) post-interruption are observed in the expiratory flow signal whenever airways compression is present [10].

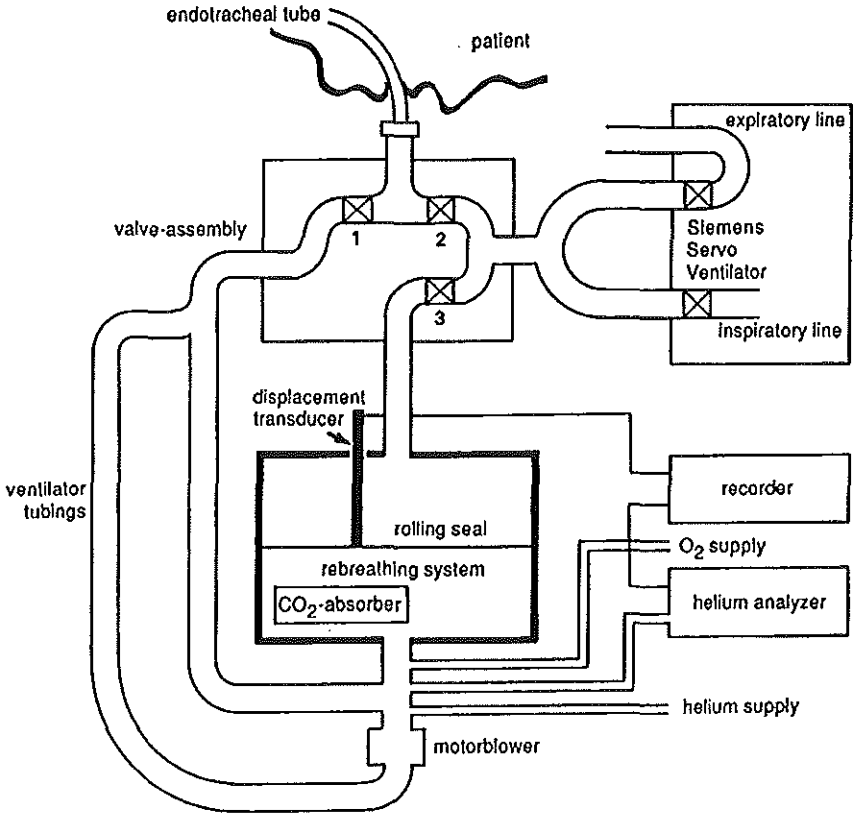

Figure 9 *Set up of closed circuit helium dilution technique. The valve assembly is shown with three valves numbered 1-3.*
Normal ventilation: ventilator-patient: valve 2 open, 1 and 3 closed.
EEV-determination: ventilator-rolling seal spirometer-patient: valve 2 closed, 1 and 3 open.

End-expiratory lung volume

EEV is determined by a closed circuit inert gas dilution technique designed for mechanically ventilated patients (figure 9). This system has been adapted from a measuring device described elsewhere [11]. As rebreathing system a box is used with a bellows built inside. During the procedure the box is ventilated by the ventilator and the bellows acts as rebreathing system. By inflating the box the bellows is compressed and its contents are emptied in the patient's lungs. A displacement transducer measures the volume-changes in the bellows. Carbon dioxide absorption is ensured by a canister with sodalime placed in the bellows. In order to compensate for

the oxygen uptake of the patient, oxygen is supplied to the rebreathing system automatically. As indicator gas helium is used: a heat conductivity helium-analyzer (Mijnhardt type UG45) is built in the RMMS.

The equipment to determine EEV includes the bellows-in-box unit and a valve-assembly. The latter, incorporated in the measuring head of the RMMS is used to switch from direct ventilation of the patient by the ventilator to ventilation through the rebreathing system.

Conclusion

The ability to measure pressure, flow and volume and to analyze respiratory variables has been available for many years. The difficulties to determine the various parameters has limited the clinical use in the Intensive Care setting. In recent years intensive care ventilators have been equipped to determine respiratory parameters. Progress in data processing techniques now enables on-line signal analysis, storage and retrieval in integrated and compact systems.

We consider a respiratory mechanics monitoring system to be indispensable in diagnosis and treatment of patients on ventilatory support.

Acknowledgement

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CHAPTER 3

Continuous positive airway pressure (CPAP) in dependence on static intrinsic PEEP-levels in patients with COPD*

B. van den Berg, J.G.J.V. Aerts, J.M. Bogaard

Abstract

The application of continuous positive airway pressure (CPAP) is known to reduce inspiratory work of breathing in intubated patients with chronic obstructive pulmonary disease (COPD). This effect is caused by a decrease in elastic work related to a reduction in intrinsic PEEP. The aim of this study was to relate the decrease in inspiratory work due to CPAP to the intrinsic PEEP-levels obtained during spontaneous breathing without positive pressure.

Ten intubated patients with COPD who had been ventilated for acute respiratory failure were studied. Intrinsic PEEP was determined during tracheal occlusions performed at end-expiration when the patient was breathing without positive airway pressure. Inspiratory work was computed during breathing through a circuit with a CPAP of 0.5 kPa and the same circuit without positive pressure.

Intrinsic PEEP-levels ranged from 0.26 to 1.31 kPa. Compared to spontaneous breathing without positive pressure, CPAP reduced the total inspiratory work per liter of ventilation (Witot) from 1.42 ± .48 to 1.24 ± .50 J.l^{-1} (means ± SD $p < 0.01$). This decrease was found to be related to the intrinsic PEEP-levels: the largest reductions were found in the patients with an intrinsic PEEP-level close to the CPAP-level applied.

In intubated patients with COPD, the decrease in Witot due to a CPAP of 0.5 kPa was found to be related to the intrinsic PEEP-levels present when no positive airway pressure was applied. The intrinsic PEEP measured during tracheal occlusions could be used to estimate the effect of CPAP in these patients.

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Introduction

Dynamic hyperinflation is frequently observed in patients with chronic obstructive pulmonary disease (COPD) and respiratory failure. This phenomenon occurs in severe airway obstruction, when the rate of lung emptying is decreased and the expiration is terminated by the next inspiration before the functional residual capacity i.e. the relaxed static equilibrium of the respiratory system has been reached [1]. This condition also leads to the presence of a positive alveolar pressure at end-expiration, a pressure known as "intrinsic" or "auto" PEEP [1].

The presence of intrinsic PEEP is associated with an increased work of breathing as the pressure gradient between alveoli and mouth acts as an inspiratory threshold to the respiratory muscles [2]. This pressure gradient can be reduced by application of a positive pressure at the mouth [1]. It has been shown that continuous positive airway pressure (CPAP) can reduce the level of intrinsic PEEP and consequently the inspiratory work of breathing in patients with COPD [3]. Therefore, CPAP is commonly applied as a weaning mode in patients with COPD, who had been ventilated for respiratory failure.

When CPAP is applied as a weaning mode, a certain level of CPAP should be chosen for the individual patient. It has been suggested that the level of positive pressure applied at the mouth should not exceed the intrinsic PEEP-level in order to avoid increases in alveolar pressure and end-expiratory lung volume [4, 5]. On the other hand, when a low CPAP-level is applied in a patient with a high intrinsic PEEP-level, only a slight reduction of inspiratory work can be expected. In clinical practice low levels of CPAP, not exceeding 0.5 kPa, are commonly used [6].

We studied the effects of CPAP on work of breathing in intubated patients with COPD in relation to the intrinsic PEEP-levels obtained during tracheal occlusions. In order to estimate the effects of application of a positive pressure, an experimental circuit with a CPAP-level of 0.5 kPa was compared to a circuit without positive pressure.

Patients and Methods

Patients

Ten patients with COPD, aged 65 - 81 yrs, were studied. Patient data are shown in table 1. In seven patients vital capacity and forced expiratory volume in 1 s (FEV_1) were obtained before

the period of mechanical ventilation when the patients were breathing spontaneously without an endotracheal tube. Exacerbations of chronic bronchitis leading to acute respiratory failure with severe hypercapnia, prompted the institution of mechanical ventilation in eight patients. In patient no.6 a cardiac arrest and in patient no.7 an atelectasis due to bronchial secretions prompted endotracheal intubation and ventilatory support. All patients were alert during the study and informed consent was obtained.

Table 1

Patient data

Patient	Age	Sex	BH	BW	VC	FEV_1	$PaCO_2$ at start of mechanical ventilation
no	yrs	m/f	m	kg	l	l	kPa
1	78	m	1.80	50	3.30	0.98	9.1
2	78	m	1.67	70	2.79	0.58	11.8
3	80	f	1.60	80	n.d.	n.d.	12.0
4	70	m	1.75	58	3.77	0.72	9.9
5	76	f	1.66	65	n.d.	n.d.	9.1
6	73	f	1.60	53	1.37	0.55	10.4
7	66	m	1.77	61	3.34	0.89	6.2
8	81	m	1.75	75	n.d.	n.d.	6.7
9	65	f	1.67	72	1.70	0.80	n.d.
10	73	m	1.83	71	2.44	0.54	11.5

BH = body height; BW = body weight; VC = vital capacity; FEV_1 = forced expiratory volume in 1 s.; n.d. = not done.

Respiratory measurements

Flow (V') was measured with a heated pneumotachometer (Lilly) positioned at the endotracheal tube. Volume displacement was obtained by integration of the flow signal (Jaeger, Würzburg, Germany). Airway opening pressure (Pao) was recorded proximal to the pneumotachometer using a differential pressure transducer (Validyne). Esophageal pressure (Pes) was measured using another differential pressure transducer connected to an esophageal balloon attached to a nasogastric catheter. The esophageal balloon was filled with 0.5 - 1.0 ml of air and properly positioned using the "occlusion test" as previously described [7]. In order to perform the occlusion test the patients were breathing through a two-way valve connected to the endotracheal tube, with the facility to occlude the inspiratory and expiratory line separately.

Using the same two-way valve, tracheal occlusions at end-expiration were performed and maintained for 3 inspiratory efforts. For this manoeuvre the inspiratory line is closed during the expiration of the patient and subsequently the expiratory line is closed during the first occluded inspiratory effort. By measuring the plateau in Pao between the occluded efforts, the elastic recoil pressure of the total respiratory system at end-expiration was estimated (Figure 1). This static elastic recoil pressure is assumed to equal the level of intrinsic PEEP during spontaneous breathing and is called "static" intrinsic PEEP (PEEPi,stat) [8].

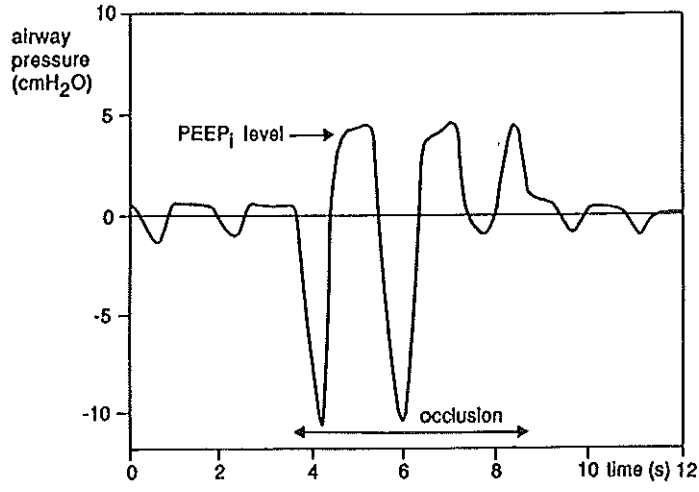

Figure 1 Determination of 'static' intrinsic PEEP-level in intubated spontaneusly breathing patients.
Occlusion method using a two-way valve at the endotracheal tube.

Study protocol

The patients were studied in semirecumbent position. Mechanical ventilation was discontinued and patients were allowed to breath spontaneously. Intrinsic PEEP-levels were obtained during tracheal occlusions. Subsequently, the patients were breathing through an experimental circuit consisting of a continuous high flow (approximately 1.6 l.s-1) generator (Downs Flow generator # 9250 Vital Signs Inc., Totowa, USA). The inspiratory oxygen fraction (F_{I,O_2}) was monitored (Oxygen Monitor 404, Instrumental Laboratory) and kept constant at 0.4 throughout the study. The flow resistance of the experimental circuit including the pneumotachometer, amounted to 0.023 $kPa.l^{-1}.s$ at a flow of 1 $l.s^{-1}$. A spring-loaded PEEP-valve of 0.5 kPa (Vital Signs) was added to the circuit in order to apply CPAP. This PEEP-valve is known to have a minimal resistance above its threshold, which is considered of critical importance in high flow, non-reservoir circuits [9].

The patients were allowed to breath spontaneously through the experimental circuit for approximately 10 minutes after which the respiratory measurements were obtained. Subsequently the PEEP-valve was added to or removed from the circuit and after a control period of 10 minutes the measurements were repeated.

Data analysis

Respiratory measurements were obtained from 6 to 8 breaths for each condition. The tidal excursions of Pao were determined during both conditions in order to establish the performance of the experimental circuit with and without the PEEP-valve.

Graphical analysis of the esophageal pressure-volume diagrams of the breaths was used to calculate work of breathing (figure 2). Between the values of the Pes at the start of inspiration and expiration a line was drawn, the slope of which represented the dynamic lung compliance ($C_{L,dyn}$). The start of inspiration was defined as the Pes at the start of inspiratory volume-displacement. The inspiratory resistive work was obtained by integration of the area subtended by the dynamic changes in Pes and lung volume during inspiration and the $C_{L,dyn}$ line. The resistive work thus obtained, included work done in overcoming the resistance of the respiratory system, endotracheal tube and experimental circuit.

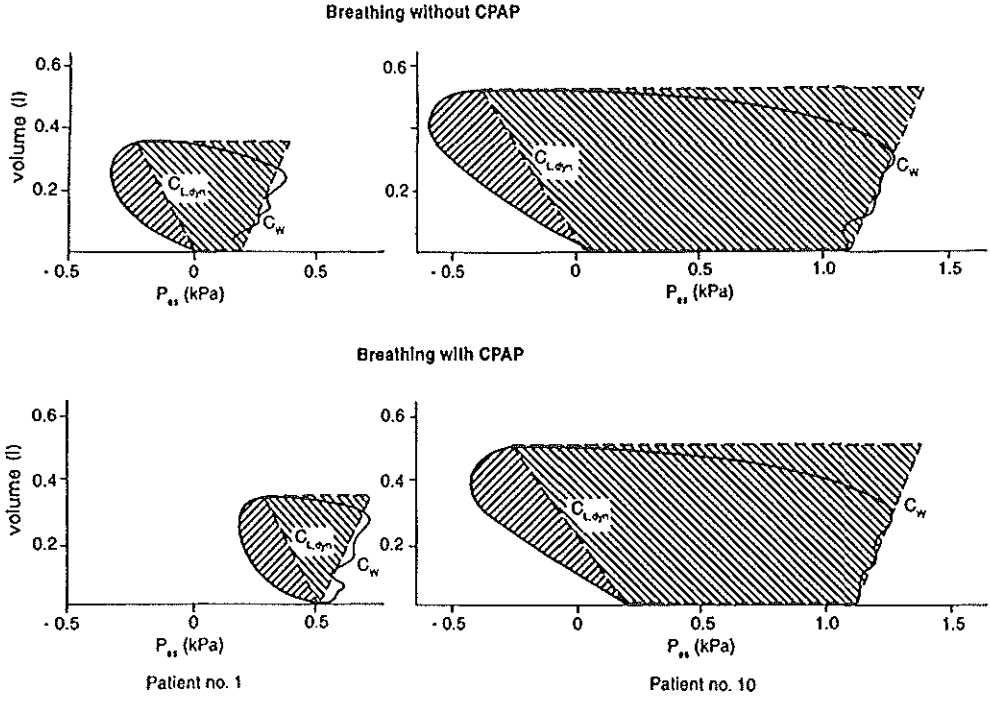

Figure 2 *Pressure-volume relationships obtained during spontaneous breathing with and without CPAP. The esophageal pressure (Pes) on the abcissa is plotted against volume on the ordinate. The $C_{L,dyn}$ is the dynamic lung compliance, the C_w is the static chest wall compliance. The slashed area's represent the resistive inspiratory work; the back-slashed area's the elastic inspiratory work.*

The elastic work of breathing was estimated using Campbell's diagram [10]. For this analysis the static volume-pressure relationship of the chest wall was used. According to the literature, the compliance of the chest wall (Cw) is assumed to be 40% of the vital capacity in 1 per kPa [11]. The Cw in patients with COPD is considered to be within normal limits and therefore normal predicted values of vital capacity have been used [12].

The line of Cw was fitted on the pressure-volume diagrams of each breath by passing it through the abrupt change in the pressure-volume loop at end-expiration, that occurred before the onset of the inspiratory flow [13]. The elastic work (WIel) was obtained by integration of the area subtended by the $C_{L,dyn}$ and Cw lines from the onset of inspiration to the onset of expiration (figure 2).

Total inspiratory work (WItot) was obtained by adding the inspiratory resistive work (WIres) to the inspiratory elastic work (WIel). Total inspiratory work per liter of inspired volume was calculated by dividing work by tidal volume for the breaths studied.

The elastic recoil pressure of the lung at the start of inspiration and the recoil pressure of the chest wall at end-expiration do not coincide in the pressure-volume loop of the breath obtained without positive pressure (figure 2). The deflection in the esophageal pressure between the two elastic recoil pressures is assumed to equal "dynamic" intrinsic PEEP (PEEPi,dyn) [3]. This deflection in esophageal pressure indicating a decrease in pressure without volume-displacement can be recognized in the pressure-volume loop of patient no. 1 obtained without positive pressure and the both loops of patient no. 10. The PEEPi,dyn-levels obtained during breathing without positive pressure were compared to those obtained during CPAP.

Statistical analysis

The measurements obtained during breathing without positive pressure were compared to those during breathing with CPAP. Unless stated otherwise, all data are presented as mean values $\pm$ standard deviations. For statistical analysis paired t-tests were used. Differences with p-values less than .05 were considered statistically significant. Correlations were examined by linear regression analysis [14].

Results

The results of the respiratory measurements are shown in table 2 and 3. The PEEPi,stat-levels of the patients, measured during tracheal occlusions ranged from 0.26 to 1.31 kPa. For all patients the PEEPi,dyn-levels were lower than the corresponding PEEPi,stat-levels. A significant correlation was found between the values of PEEPi,stat and PEEPi,dyn obtained during breathing without positive pressure. The regression equation for all values was: PEEPi,dyn = 0.67x PEEPi,stat - 0.079 ($r = .87$, $p < .002$).

Table 2

Respiratory measurements of the individual patients

	Breathing without CPAP			Breathing with CPAP	
	PEEPi,stat	PEEPi,dyn	WItot	PEEPi,dyn	WItot
no.	kPa	kPa	$J.l^{-1}$	kPa	$J.l^{-1}$
1	0.26	0.17.	0.59	0.09	0.53
2	0.39	0.28	1.03	0.16	0.85
3	0.42	0.31	1.19	0.16	0.87
4	0.43	0.18	1.55	0.12	1.20
5	0.54	0.19	1.03	0.12	0.72
6	0.66	0.33	1.42	0.19	1.27
7	0.76	0.23	1.34	0.14	1.26
8	1.00	0.52	1.76	0.40	1.60
9	1.28	0.64	2.11	0.46	1.96
10	1.31	1.10	2.22	0.96	2.10
mean	0.71	0.39	1.42	0.28**	1.24*
SD	0.36	0.28	0.48	0.26	0.50

PEEPi = intrinsic PEEP-level; WItot = total inspiratory work per liter of inspired volume; SD = standard deviation.

Paired t-tests: * = $p < .0005$

** = $p < .00001$

When the measurements obtained in the individual patients were compared, a high correlation was found between the PEEPi,stat-levels and the total inspiratory work per liter of ventilation obtained during breathing without positive pressure ($r = .91$ $p < .0005$) (figure 3).

When the patients were breathing through the experimental circuit with the PEEP-valve, the actual pressures measured at the endotracheal tube during expiration ranged from 0.4 to 0.5 kPa with a mean of 0.45 kPa.

Table 3

Respiratory mechanics

Data given are means ± SD

		Without CPAP	With CPAP
ΔPao	kPa	0.19 ± 0.07	0.22 ± 0.05
VTex	l.	0.43 ± 0.16	0.42 ± 0.15
Respiratory Rate	min^{-1}	23.4 ± 5.8	23.6 ± 5.2
V'e	$l.min^{-1}$	9.47 ± 2.30	9.48 ± 2.48
CL,dyn	$l.kPa^{-1}$	0.45 ± 0.26	0.54 ± 0.24

ΔPao = tidal excursions in airway opening pressure; VTex = expiratory tidal volume; V'e = expiratory minute volume; CL,dyn = dynamic lung compliance.

Compared to breathing without positive pressure, CPAP was associated with a significant reduction in total inspiratory work per liter of ventilation ($p < .0005$). In figure 2 actual pressure-volume curves of patient no. 1 and patient no. 10 are shown. The PEEPi,dyn-levels were also significantly reduced when the breathing with CPAP was compared with the breaths obtained without positive pressure ($p < .00001$). The decrease in inspiratory work due to CPAP proved to be related to the intrinsic PEEP-levels measured during tracheal occlusions. In figure 4 the decrease in inspiratory work due to CPAP with respect to breathing without positive pressure is shown. The decrease in inspiratory work is expressed as percentage of the values obtained during breathing without CPAP. In patients no. 2-5, with a static intrinsic PEEP-level from 0.39 to 0.54 kPa, the largest reductions in inspiratory work were found. When the difference between static intrinsic PEEP and CPAP-levels in absolute terms was related to the decrease in inspiratory work, a significant negative correlation was found ($r = -.72$ $p < .05$).

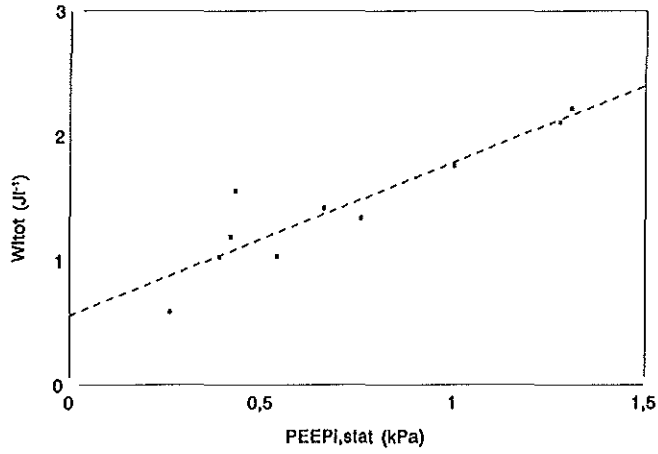

Figure 3 *Relationship between the static intrinsic PEEP-levels and the total inspiratory work per liter of inspired volume of the individual patients obtained during spontaneous breathing without positive pressure. The regression line is shown.*

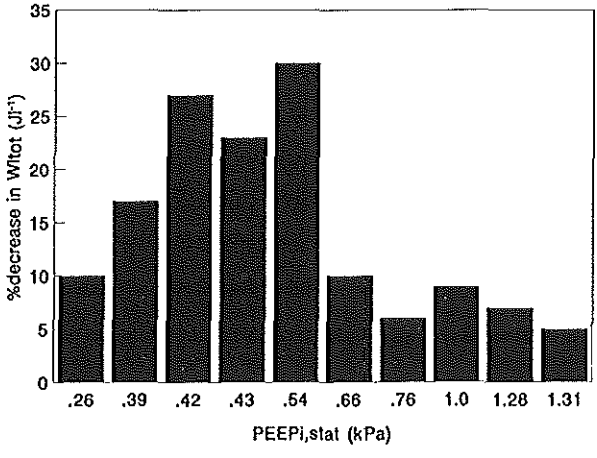

Figure 4 *The decreases in total inspiratory work per liter of inspired volume (Wltot) due to CPAP displayed according to the static intrinsic PEEP-levels of the individual patients. The decrease in Wltot is expressed as percentage of the values obtained during spontaneous breathing without positive pressure.*

The results of the respiratory measurements are shown in table 3. The tidal excursions in airway opening pressure amounted to 0.22 ± 0.05 and 0.19 ± 0.07 kPa for the experimental circuits with and without CPAP. Comparing the two conditions, no significant differences were found in tidal volume, respiratory frequency, minute ventilation or dynamic compliance calculated from the pressure-volume curves.

Discussion

In the present study, we established that the effect of CPAP on the inspiratory work of breathing depended on the level of intrinsic PEEP obtained during tracheal occlusions when no positive airway pressure was applied. The largest reductions in inspiratory work associated with CPAP were found in the patients with intrinsic PEEP-levels in the range of the CPAP-level applied. The effects of CPAP on inspiratory work were found to be only moderate in patients with intrinsic PEEP-levels exceeding a value of 0.1 kPa above or below the preset CPAP-level.

In this study, only one level of CPAP was applied. Due to their limited ventilatory reserves, most patients were unable to breath spontaneously during long periods of time. Consequently, only the measurements obtained during spontaneous breathing without positive pressure and with a CPAP of 0.5 kPa could be analyzed.

These findings should be interpreted in view of the results of previous studies in which dynamic hyperinflation and intrinsic PEEP were investigated in mechanically ventilated patients with COPD [4, 15, 16]. In these patients the occurrence of intrinsic PEEP was associated with dynamic airway compression leading to expiratory flow limitation. Expiratory flow limitation is assumed to be present when the application of ventilator-PEEP is associated with an unchanged expiratory flow at the same lung volume [15, 16]. It is assumed that the increase in airway pressure downstream of the critical site of flow limitation (the "equal pressure point") does not influence the expiratory flow until the applied ventilator-PEEP exceeds the level of the extramural pressure surrounding the airway [16].

In the present study, a significantly positive correlation was found between the PEEPi,stat and the total inspiratory work, obtained during spontaneous breathing without positive pressure. This underlines the importance of counterbalancing the intrinsic PEEP by application of a positive airway pressure for the reduction of inspiratory work. The patients with "static" intrinsic PEEP-levels in the range of the CPAP-level applied, demonstrated the largest reducti-

ons in inspiratory work. It is assumed that in these patients intrinsic PEEP was counterbalanced by CPAP associated with a reduction in the elastic component of the inspiratory work. In the patients with the highest PEEPi,stat-levels, the inspiratory threshold was only partly reduced, leading to a moderate decrease in inspiratory work. In patient no. 1, with the lowest inspiratory work, the CPAP applied exceeded the PEEPi,stat and is assumed to increase lung volume and consequently work of breathing. The decrease in inspiratory work due to CPAP in this patient can be explained by the effect of reduction of intrinsic PEEP exceeding the effect of the increased lung volume. Accordingly, in this study a decrease in PEEPi,dyn was demonstrated in all patients when CPAP was compared with breathing without positive pressure.

In all patients the PEEPi,dyn-levels were lower than the corresponding PEEPi,stat-values. These last PEEPi-values represent an average level of intrinsic PEEP, reflecting the alveolar pressure after readjustment of regional time constant inequalities. In contrast, the PEEPi,dyn represents the lowest regional value of intrinsic PEEP in an inhomogeneous lung. Thus, at the start of inspiration a pressure counterbalancing the PEEPi,dyn is required to start inspiratory flow. In this study, a positive correlation was found between the values of PEEPi,stat and PEEPi,dyn. The relationship between PEEPi,stat and PEEPi,dyn-values was described by the regression equation: PEEPi,dyn = 0.67 x PEEPi,stat - 0.079. This regression equation was comparable to the equation previously published by Petrof: PEEPi,dyn = 0.58 x PEEPi,stat - 0.048 [3].

No differences were found in tidal volume, respiratory rate or minute ventilation between the two conditions. This is in agreement with previous studies in which patients with COPD or acute respiratory failure were investigated [3, 17, 18].

Considering these results, it should be taken into account that the effects of CPAP on work of breathing could be related to the CPAP-assembly used. It is well established that both the physical properties of the CPAP-circuit and the PEEP-valve affect work of breathing [9, 19]. A CPAP-assembly was considered optimal if the change in Pao during respiration was minimized [11]. In this study the mean ΔPao amounted to 0.22 ± 0.05 and 0.19 ± 0.07 kPa during breathing with and without CPAP respectively, indicating that the addition of the PEEP-valve did not increase the ΔPao.

In conclusion, the decrease in Witot due to application of a CPAP of 0.5 kPa was found to be related to the levels of intrinsic PEEP estimated during tracheal occlusions. 'Static' intrinsic PEEP measurements should be used to estimate the effect of CPAP on the inspiratory work. As

only one level of CPAP was studied, no recommendations can be made with respect to the adjustment of CPAP to the 'static' intrinsic PEEP-levels.

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CHAPTER 4

Elastic work of breathing during Continuous Positive Airway Pressure in intubated patients with Chronic Obstructive Pulmonary Disease (Theoretical analysis and experimental validation)*

J.G.J.V. Aerts, B. van den Berg, A.F.M. Verbraak, J.M. Bogaard

Abstract

Continuous positive airway pressure (CPAP) is known to decrease inspiratory work of breathing in patients with chronic obstructive pulmonary disease (COPD). This effect is primarily attributed to a reduction in inspiratory elastic work of breathing (Wi,el) related to a decrease in intrinsic PEEP.

The aim of this study is to design a model for computation of Wi,el on the basis of respiratory mechanics in patients with COPD, at various intrinsic PEEP- and CPAP-levels. The model was used to estimate the optimal CPAP-level with respect to the intrinsic PEEP-level in terms of reduction of Wi,el. Calculations of the decrease in Wi,el due to CPAP obtained with the model were compared to changes in Wi,el and total work of breathing (WI,tot) determined from respiratory measurements in patients with COPD.

Model calculations revealed that Wi,el was minimal whenever a CPAP-level equal to the intrinsic PEEP-level was applied. When a CPAP-level exceeding the intrinsic PEEP-level was applied, the reduction in Wi,el was less. Comparing these results to the respiratory measurements a similar pattern in reduction of Wi,el and WI,tot was established, although absolute values of the differences were smaller in the experimental data.

This study indicates that in patients with COPD in order to reduce Wi,el, intrinsic PEEP should be measured and the CPAP-level adjusted to the intrinsic PEEP-level.

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Introduction

In mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) hyperinflation is commonly observed [1-7]. Due to airways obstruction the rate of lung emptying is limited and expiration is terminated by the next inspiration before functional residual capacity (FRC) i.e. the relaxed static equilibrium lung volume of the respiratory system has been reached [2, 4]. Consequently, an end-expiratory lung volume (EEV) exceeding the level of FRC is found. This dynamic hyperinflation is associated with a positive elastic recoil pressure of the respiratory system present at end-expiration, referred to as intrinsic positive end-expiratory pressure, intrinsic PEEP [3, 4]. Intrinsic PEEP is defined as the pressure gradient between alveoli and airway opening at the end of a relaxed expiration [4].

Although intrinsic PEEP has at first been detected in mechanically ventilated patients with COPD, it soon became clear that intrinsic PEEP can also be present in spontaneously breathing patients with COPD [2, 4].

It is well established that in mechanically ventilated patients with COPD the application of external PEEP can reduce the level of intrinsic PEEP without increasing EEV [1, 8]. External PEEP elevates the airway opening pressure in those patients without affecting the alveolar pressure: consequently the level of intrinsic PEEP being the pressure gradient between alveoli and airway opening is reduced.

As intrinsic PEEP has to be counterbalanced before the inspiratory flow starts, it acts as an inspiratory threshold and increases the inspiratory work of breathing [5, 6]. This has clearly been demonstrated in patients with COPD who had been intubated for acute respiratory failure [8]. In those patients the application of continuous positive airway pressure (CPAP) was found to reduce work of breathing [5, 9]. It is assumed that the reduction in inspiratory work due to CPAP is mediated by a decrease in intrinsic PEEP [5]. In an earlier investigation in spontaneously breathing intubated patients with COPD we studied the decrease in total inspiratory work of breathing due to CPAP and related this decrease to the level of intrinsic PEEP [7]. In that study only one level of .5 kPa CPAP was applied and therefore no conclusions about the optimal CPAP-level for the individual patient could be drawn.

The aim of the study is to design a model for computation of elastic work of breathing (Wi,el) on the basis of respiratory mechanics in patients with COPD. This model is applied to estimate the maximum reduction in Wi,el at various levels of CPAP and of intrinsic PEEP. Estimations of the decrease in Wi,el due to CPAP obtained with the model were also compared to the

changes in Wi,el and WI,tot determined from respiratory measurements in a group of patients with COPD. Further investigations on respiratory mechanics of these patients were described in an earlier paper [7].

Patients and Methods

Theoretical model

Analysis

In this model Wi,el was estimated taken into account total respiratory system compliance, lung volume and the level of intrinsic PEEP. The variables were chosen in such a range that the model represented patients with COPD.

In order to calculate Wi,el, estimates of mean pressure-volume curves of the lungs and of the chest wall of patients with COPD were computed.

For the description of the pressure-volume curve of the lung the generally applied exponential model was used [10-13]. The mathematical expression of the pressure-volume curve described by Salazar and Knowles was applied [10], however with a constant (Po) representing the curve position with respect to the pressure axis [12]:

$$V = V_m^* \left(1 - e^{-\kappa(p - p_0)}\right)$$

In which V = lung volume, V_m = maximum volume (asymptote of the exponential equation), κ = parameter related to curvature of the pressure-volume curve, p = transpulmonary pressure, p_0 = transpulmonary pressure at zero volume.

As model calculations represented respiratory mechanics in patients with emphysema, κ was chosen 3.3 kPa^{-1} and p_0 0 kPa, being representative values for these patients from other studies [12, 13]. V_m, as scaling factor for the volume axis, was arbitrary assumed to be 6 l.

In order to estimate the pressure-volume relationship of the chest wall, the chest wall compliance was assumed to be equal to 40% of the predicted vital capacity in 1 kPa^{-1} [2, 8] over the whole volume range up to total lung capacity. Vital capacity was calculated as reference value

taken into account age and maximal volume [2, 8]. The elastic recoil pressure of the thoracic wall was assumed to be zero at 80% of total lung capacity (V = 4.8 l) [14].

From the pressure-volume relationships of chest wall and lungs, that of the total respiratory system was derived. Wi,el was calculated using the total respiratory system compliance line (figure 1a). Wi,el is defined as the area between the static pressure-volume relationship of the respiratory system and the volume axis, using a tidal volume of 0.5 l as derived from earlier measurements and a certain intrinsic PEEP-level from which the end-expiratory volume level was calculated [7].

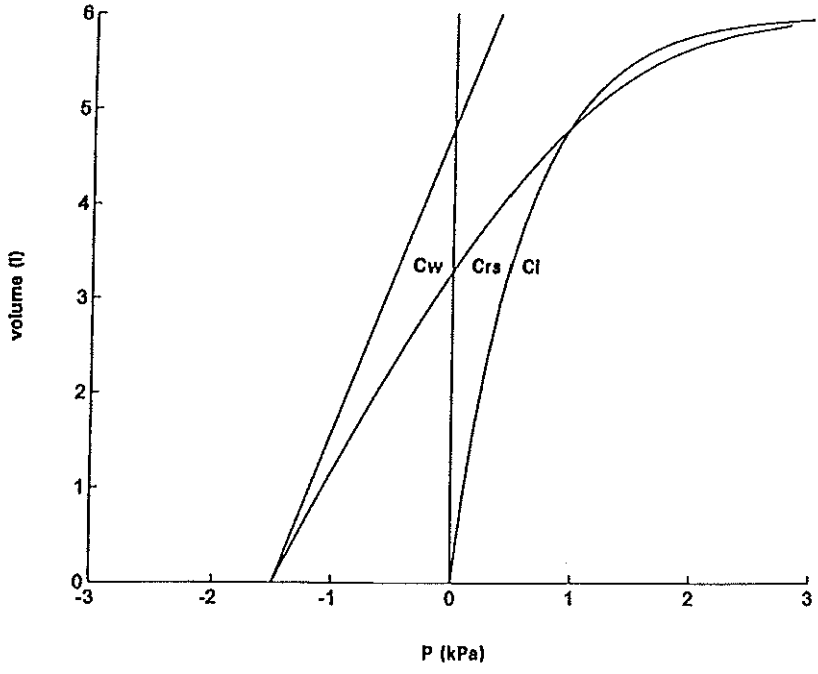

Figure 1a Volume-pressure relationship of the lung (Cl), chest-wall (Cw) and the total respiratory system (Crs), calculated by summation of the elastic recoil pressures exerted by the chest-wall and the lung. Lung compliance is according to a loss of lung elasticity (emphysema).

Model application

Wi,el was calculated taking into account various intrinsic PEEP- and CPAP-levels. For our theoretical analysis intrinsic PEEP-levels were used, ranging form 0 to 1.0 kPa with steps of .25 kPa. For each level of intrinsic PEEP the effects on Wi,el of CPAP ranging from 0 to 1.0 kPa, also with steps of .25 kPa, were studied. The elastic recoil pressure at a given EEV was assu-

med to equal the corresponding total PEEP-level, being the sum of CPAP-level and intrinsic PEEP-level [4]. In the theoretical analysis a one-compartment model for the lungs was assumed discarding the presence of ventilation inhomogenieties. In this way the effect of CPAP on intrinsic PEEP was assumed as an absolute one to one substitution [6]. Total PEEP-levels were calculated taken into account the following equations:

intrinsic PEEP > CPAP : total PEEP = CPAP + (intrinsic PEEP-CPAP)

intrinsic PEEP < CPAP : total PEEP = CPAP

It was assumed that no changes in respiratory rate and tidal volume were present comparing breathing with and without CPAP. Elastic work done during inspiration by CPAP was calculated as the product of the CPAP-level and tidal volume. In order to compare model results to the patient measurements also calculations were made at the intrinsic PEEP-levels of the patients with a CPAP at .5 kPa.

Experimental data

Patients

Ten patients with COPD were studied who had all been ventilated for exacerbations of COPD. Their mean age was 74 years ranging from 65 to 81 years; 6 were male, mean FEV_1 was .72 l (range .54- .98 l), measured prior to the period of mechanical ventilation. All patients were alert during the study and informed consent was obtained.

Respiratory measurements

The measurements were performed both during spontaneous breathing with .5 kPa CPAP and spontaneous breathing without positive pressure via a continuous flow CPAP system. With a pneumotachometer (Jaeger, Würzburg, Germany), a differential pressure transducer (Validyne) at the airway opening and a differential pressure transducer (Validyne) coupled to an oesophageal balloon flow, displaced volume, tracheal pressure and oesophageal pressure were obtained. As recording system a X-Y recorder (X-Y733, Brown Boveri Company, Rotterdam, Holland) was used. The occlusion method was used for correct positioning of the balloon.

No distortions of pressure-volume loops were caused by the dynamic properties of the pneumotachometer, pressure transducers and recording systems used [1, 7].

During tracheal occlusions at end-expiration which were maintained for 3 consecutive inspiratory efforts, the elastic recoil pressure of the total respiratory system at end-expiration was estimated as the plateau in the airway opening pressure during expiration [5]. This static elastic recoil pressure at end-expiration was assumed equal to static intrinsic PEEP, PEEPi,stat, the mean end-expiratory recoil pressure over the respiratory system of the patients.

After the esophageal balloon was properly positioned, work of breathing and related variables of respiratory mechanics were determined. Elastic work of breathing was calculated using the Campbell diagram [13].

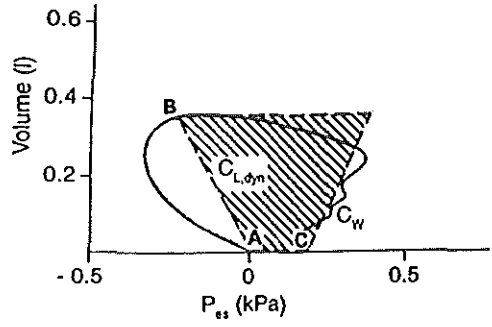

Figure 1b Inspiratory elastic work of breathing when dynamic intrinsic PEEP is present using the Campbell diagram. Hatched lines indicate elastic work. A = start of inspiratory flow; B = start of expiration; C = start of inspiratory effort.

Using this approach, as shown in figure 1b, the line indicating the dynamic lung compliance was drawn through the values of esophageal pressure at the start of inspiratory flow (A) and expiratory flow (B). The line indicating chest wall compliance was drawn on the pressure-volume diagram by passing it through the abrupt change in the pressure-volume loop at end-expiration, that occurred before the onset of inspiratory volume displacement (C). The AC interval indicates inspiratory effort before the start of inspiratory flow i.e. dynamic intrinsic PEEP, the pressure gradient counterbalancing the lowest recoil pressure at end-expiration in a lung region. Wi,el (J l^{-1}) was calculated as the area between the dynamic lung and chest wall compliance and tidal volume divided by the tidal volume. WI,tot was obtained by adding the inspiratory resistive work to the Wi,el.

Study protocol

Patients were breathing in a semirecumbent position through a continuous flow CPAP system consisting of a continuous high flow (approximately 100 l min^{-1}) generator (Downs Flow generator #9250 Vital Signs Inc., Totowa, USA). The inspiratory oxygen concentration was monitored (Oxygen Monitor 404, Instrumental Laboratory), and kept constant at 0.4 throughout the study. The flow resistance of the system including the pneumotachometer amounted to .023 kPa l^{-1} at a flow of 1l s^{-1}. A spring-loaded PEEP-valve of .5 kPa (Vital Signs) was used to apply .5 kPa CPAP.

After mechanical ventilation was discontinued patients were allowed to breathe spontaneously through the circuit for 10 minutes after which the respiratory measurements were obtained. Subsequently the PEEP-valve was added or removed from the circuit. After 10 minutes of observation, respiratory measurements were repeated.

Results

Figure 2 shows the results of model calculations of the change in Wi,el related to varying intrinsic PEEP- and CPAP-levels.On the y-axis the change in Wi,el is shown, expressed as percentage of the value obtained during spontaneous breathing without CPAP. On the x-axis the difference between the intrinsic PEEP-level and the applied CPAP-level for each of the five intrinsic PEEP-levels is shown. This figure reveals that the reduction in Wi,el is maximal when the applied CPAP-level counterbalances the level of intrinsic PEEP.

This figure also shows that when the CPAP-level exceeds the intrinsic PEEP-level and causes an increase in total PEEP, Wi,el will increase with respect to the Wi,el at the CPAP-level counterbalancing the intrinsic PEEP- level. When no intrinsic PEEP is present, any level of CPAP will increase Wi,el.

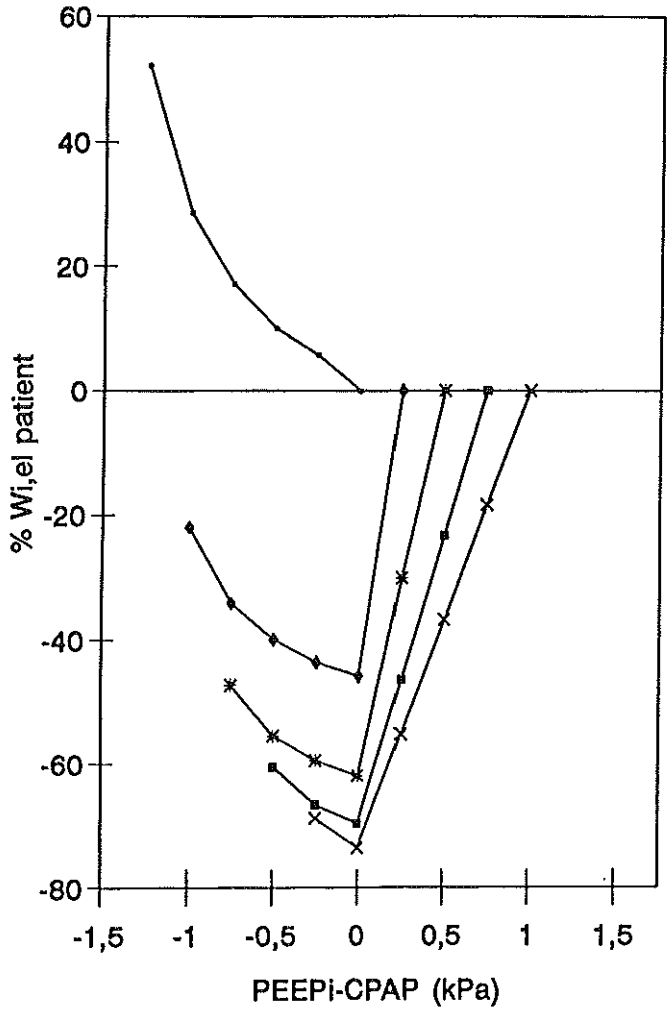

Figure 2 *Effect of different intrinsic PEEP and CPAP-levels on Wi,el, presented in percentage of the original Wi,el as calculated from the model at that intrinsic PEEP-level when no CPAP is applied. Small squares: intrinsic PEEP = 0 kPa, diamond: intrinsic PEEP = .25 kPa, double crosses: intrinsic PEEP-level = .5 kPa, great squares: intrinsic PEEP = .75 kPa, single crosses: intrinsic PEEP = 1 kPa.*

In the patient measurements intrinsic PEEP was present and the applied CPAP-level reduced Wi,el in all patients. These measurements yielded a mean Wi,el of 1.02 ± .37 Jl^{-1} (mean ± SD) without positive pressure which was reduced to .84 ± .35 Jl^{-1} during breathing with a CPAP-level of .5 kPa ($p < .0005$). In all patients intrinsic PEEP-levels were encountered.

During breathing without CPAP static intrinsic PEEP-levels ranged from .26 to 1.31 kPa and dynamic intrinsic PEEP-levels from .17 to 1.10 kPa. The greatest reductions of Wi,el in both patient measurements and in the theoretical analysis were found when static intrinsic PEEP-level minus CPAP-level was about zero. In patients with the highest levels of intrinsic PEEP a reduction in Wi,el was found in accordance to the assumption that the intrinsic PEEP "threshold" was reduced by the level of CPAP applied. A decrease in Wi,el was also found in the patients in whom the applied CPAP-level exceeded the intrinsic PEEP-level.

Figure 3 shows the effects of CPAP on Wi,el as calculated by the model and as computed in the patient study. One level of CPAP (.5 kPa) was applied to the patients in whom different levels of intrinsic PEEP were obtained. The x-axis represents the intrinsic PEEP-level minus the CPAP-level applied. The y-axis represents the change in Wi,el expressed as percentage of the value of Wi,el computed without CPAP (crosses).

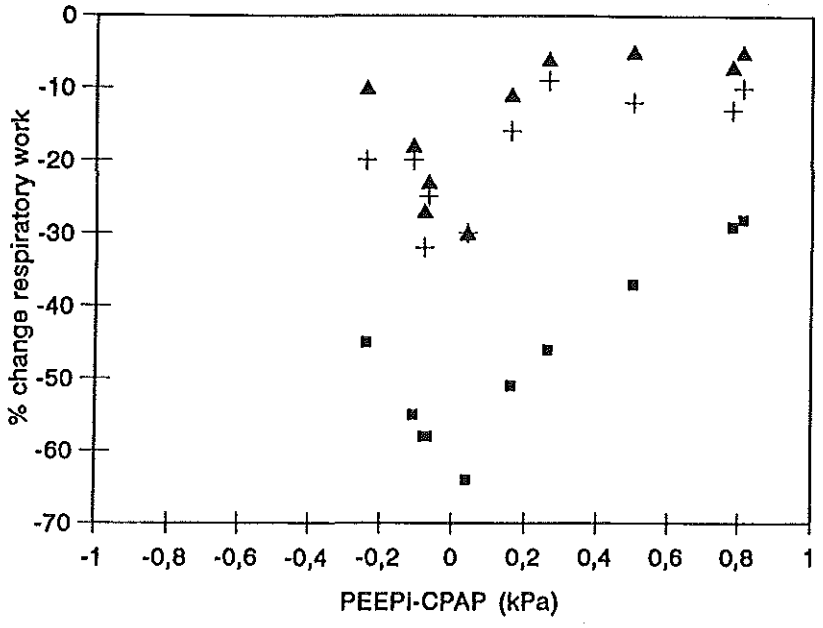

Figure 3 Percentage change in Wi,el, J per liter of ventilation, breathing with and without a CPAP-level of .5 kPa, comparing model calculations and patient measurements. Squares indicate model calculations. Crosses represent the patient measurements. Also the percentage change in WI,tot for the patients is shown (triangular dots).

The model was found to overestimate the effect of CPAP compared with the patient measurements. As can be seen in figure 3 the shapes of the curves of both theoretical analysis and patient measurements are similar: a maximal percentage decrease in Wi,el at the same point on the x-axis being the area where intrinsic PEEP and CPAP are equal. A considerable difference in absolute percentage change is present.

In figure 3 also the decreases in WI,tot are plotted. A minimum is also observed at equal intrinsic PEEP and CPAP-levels at slightly smaller reductions of WI,tot compared to the decreases in Wi,el.

Discussion

In this study a model approach was used to compute elastic work of breathing (Wi,el) on the basis of respiratory mechanics in patients with COPD. As in these patients the increase in total inspiratory work is for the greater part caused by elevated elastic work related to dynamic hyperinflation, and modelling of the elastic work can be achieved with appreciable accuracy, we have only focused on modelling the elastic work. The effect of various levels of intrinsic PEEP and CPAP on the elastic work of breathing was estimated and compared to results obtained in respiratory measurements.

The data predicted from the model suggest an optimal effect of CPAP regarding minimal elastic work of breathing when a CPAP-level equal to the intrinsic PEEP-level is applied. The results computed from respiratory measurements in patients with COPD revealed a similar optimal effect of CPAP on both elastic and total inspiratory work. This underlines the importance of determining the level of intrinsic PEEP in a patient with COPD in order to adjust the CPAP-level.

The operating characteristics of the CPAP assembly are known to affect the respiratory effects of the CPAP applied. The swings in the airway opening pressure should be minimal during tidal breathing [5]. In the patient-measurements we used a high-flow continuous circuit with a minimally flow-dependent PEEP-valve. A marked influence of the circuit characteristics on our study results could therefore not be expected.

Our model approach was based on a number of assumptions. In a recent investigation of COPD a model of a linear pressure-volume curve with a transition into an exponential part at a certain volume level above FRC gave the most accurate mathematical description of experimental

curves determined in patients [15]. The authors concluded however that, although the linear-exponential fit was more accurate, the κ factor of this fit was not related to other elasticity indices and has no physiological meaning, whereas the κ factor of the exponential model was related to overall lung elastic behaviour. For this reason we used the exponential fit with a κ factor as found in emphysema patients [12, 13]. The Po of 0 kPa indicates low elastic recoil over the whole volume range, whereas an arbitrary chosen TLC of 6 l can be considered a scaling factor for the volume axis. Based on an earlier study we assumed no appreciable changes in the elasticity behaviour of the thoracic cage [16].

A considerable absolute difference between model calculations and experimental results on the effect of CPAP on Wi,el was found. This difference can be attributed to a number of mechanisms which will be discussed in the following paragraphs.

Partly the difference can be explained by our assumption of a one compartment model in case of lungs with a large inhomogeneity with respect to regional ventilation [17]. In that case different regions may have different values of intrinsic PEEP and the various inspiratory thresholds may be only partly counterbalanced by the applied CPAP-level [6, 9].

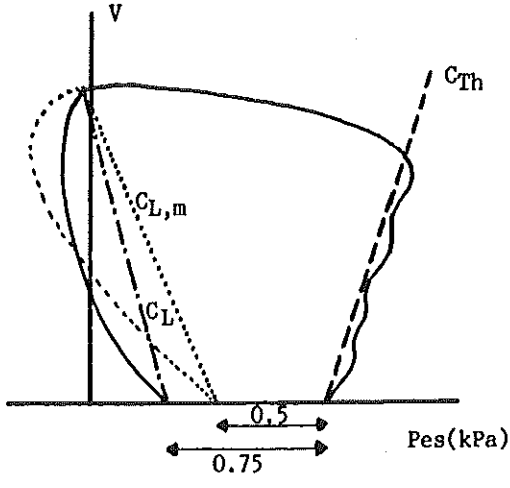

Figure 4 *Schematic illustration of the influence of lung inhomogeniety on calculation of Wi,el. Lung two-compartment model with intrinsic PEEP levels of .5 and 1.0 kPa. Static intrinsic PEEP = .75 kPa. Dynamic intrinsic PEEP = .5 kPa. C_L = lung compliance. $C_{L,m}$ = measured lung compliance. C_{th} = thorax compliance. Pressure-volume loop in a one compartment model (_____). Measured pressure-volume (-----)*

In figure 4 this is shown schematically for a two compartment model with equal compartments and an assumed intrinsic PEEP-level of .5 and 1.0 kPa respectively, yielding a static intrinsic PEEP of .75 kPa after equilibration at end-expiration. In the dynamic situation the inspiratory flow will start, if the inspiratory threshold of .5 kPa is counterbalanced.

Consequently, part of the viscous work of breathing comprises elastic work to overcome the higher intrinsic PEEP-level in the second compartment. This figure elucidates that erroneously low dynamic lung compliance values can be computed, when dynamic intrinsic PEEP-levels are substantially lower than static intrinsic PEEP-levels [5, 17, 18]. Only in case of absence of ventilation inhomogenieties dynamic and static intrinsic PEEP-levels will be equal [18].

Furthermore, a direct relationship between EEV and the total PEEP-level has been assumed in the model. Although this seems valid, no experimental studies have been published to verify this assumption. Thus patients might breathe at a higher lung volume which could affect the percentage decrease in Wi,el due to CPAP. At higher lung volumes the Wi,el might increase disproportionately due to the concomitant decrease in lung compliance.

Although a number of the assumptions may cause a difference in absolute values of decreases in work of breathing, in our opinion it does not influence the maximum of the decreases found at equal CPAP- and intrinsic PEEP-levels. Figure 3 shows the same pattern of reduction in elastic work and total work. The slightly smaller reductions in total work are due to minimal changes in viscous work at equal decreases in Wi,el causing the percentage decrease to be less.

As in the patients only one level of CPAP was applied, no recommendations about the optimal level of CPAP could be made [7]. Because the highest reductions in elastic work of breathing were found in patients with an intrinsic PEEP-level in the range of the applied CPAP-level, it is suggested that also in the patients a CPAP-level would be optimal when intrinsic PEEP is just counterbalanced. Petrof et al. in their study on CPAP did apply different CPAP-levels to the patients but did not relate the decrease in work of breathing due to a certain level of CPAP to the intrinsic PEEP-level of the patient [5]. They found the highest reductions in work of breathing at the highest CPAP-level.

It has to be stressed that our approach deals only with improvements of respiratory mechanics in case of the application of CPAP.

Impeding venous return by an increased intrathoracic pressure due to high CPAP-levels, and consequently a decrease in cardiac output and oxygen delivery to tissues are not taken into account [8]. Changes in gas-exchange area and ventilation-perfusion ratios may also affect blood

gasses [8]. It is beyond doubt that in clinical applications of CPAP all these mechanisms have to be taken into account.

Although further research is needed to establish the impact of the differences between dynamic and static intrinsic PEEP on dynamic lung compliance and work of breathing estimations, we conclude that in order to minimize work of breathing in patients with COPD by application of CPAP, the CPAP-level should be adjusted to the static intrinsic PEEP-level of the patient.

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CHAPTER 5

Imposed work of breathing during demand and continuous flow CPAP in intubated patients*

J.G.J.V. Aerts, B. van den Berg, J.M. Bogaard

Abstract

The ventilator-humidifier circuit is known to impose additional work (Wapp) on the patient when the ventilator is used for weaning purposes. We investigated Wapp and derived variables in relation to minute volumes of patients in whom CPAP was applied as weaning mode. 13 Patients were studied; in each patient a CPAP of 0.5 kPa was provided both by a ventilator and a continuous flow system (CF-CPAP).

At both systems the Wapp (J/l) increased at higher minute volumes: the Wapp raised from 0.10 to 0.68 J/l for ventilator-CPAP and from 0.08 to 0.39 J/l for CF-CPAP at minute volumes rising from 7.2 to 20.8 l. The increments in Wapp imposed by the ventilator correlated significantly to the end-expiratory pressures that exceeded the preset CPAP-level increasingly at higher minute volumes.

The difference in Wapp between the ventilator and the CF-CPAP was found to be magnified at higher ventilatory needs of the patients. An inspiratory threshold due to a gradient between actual end-expiratory pressure and preset CPAP appeared to add greatly to the increments in Wapp imposed by the ventilator. As this threshold was attributed to the resistance of the PEEP-device of the ventilator, this indicates that the additional work related to the expiratory valve should be taken into account when the ventilator is used for weaning purposes.

* This manuscript is submitted for publication

Introduction

It is well known that in mechanically ventilated patients the process of weaning is hampered by the additional work of breathing imposed by the endotracheal tube [1-3]. If the ventilator is used for weaning purposes, the additional work of the ventilator-humidifier circuit is superimposed on this workload [4, 5]. The effects of various breathing patterns on the respiratory work imposed by the endotracheal tube have been studied extensively [1-3]. The interaction between the breathing patterns of the patients and the performance of the ventilators has however received less attention.

We therefore investigated the additional work imposed by the ventilator, in relation to the minute ventilation of patients weaning from mechanical ventilation. Various parameters derived from the imposed work were obtained to determine the interactions between patient and ventilator. For this study CPAP was applied as ventilatory mode: this enabled us to compare the performance of the ventilator (Siemens Servo 900C) to a continuous flow-CPAP system (Dräger CF800).

Methods

Patients

Mechanically ventilated patients were included if they were able to breathe spontaneously for at least 1 hour.

13 patients mechanically ventilated for various medical and surgical illnesses were studied. Patient's characteristics are shown in table 1. They were intubated with an endotracheal tube (inner diameter range 7.5 tot 9.0 mm) or a tracheostomy tube (inner diameter 6.0 to 8.5 mm). Maximal inspiratory pressures (MIP) were determined prior to the weaning procedure. Informed consent was obtained from each patient or their next of kin. The study was approved by the local ethics committee.

Table 1

Patient data

Patient no	Age (yr)	MIP (kPa)	ET/TC (size)	days on mechanical ventilation	primary diagnosis
1	60	-4.0	ET8.5	14	brain damage
2	31	-5.5	ET9.0	8	endocarditis
3	53	-4.1	ET9.0	4	sepsis
4	67	-5.7	ET9.0	9	abdominal surgery
5	63	n.d.	ET8.5	13	sepsis
6	62	-6.9	TC8.0	15	TBC, destroyed lungs
7	24	-5.9	TC8.0	36	poly-trauma
8	19	-7.3	TC8.5	9	poly-trauma
9	66	-4.1	ET8.0	12	ARDS
10	63	-8.2	ET7.5	5	atelectasis
11	77	-4.9	TC6.0	25	brain damage
12	70	-4.5	ET8.0	7	poly-trauma
13	59	-5.1	TC6.0	2	ARDS

MIP = maximal inspiratory pressure, ET/TC = endotracheal tube/tracheal canula
n.d. = not done

Respiratory circuits

A Siemens Servo ventilator 900c was used as ventilator CPAP-device. The Servo 900c was equipped with standard ventilator tubings including a humidifier. The inspiratory trigger level was set at the minimal value at which no self-cycling occurred. A preset CPAP-level of 0.5 kPa was applied in all patients. The patients were breathing at the same inspiratory oxygen concentration as was applied during the ventilatory support prior to the study.

A Dräger CF800 was used as CF-CPAP system. The Dräger CF800 consists of a continuous high flow system with a spring-loaded reservoir incorporated, to minimize pressure fluctuations. The CF-CPAP system was set at a basal flow of 60 l/min. A minimally flow-dependent Vital-Signs PEEP-valve of 0.5 kPa was added to the expiratory circuit [6].

Protocol

All patients were studied in a semi-recumbent position, breathing at random first with the CF-CPAP or with the ventilator CPAP. The patients were allowed to breathe spontaneously for approximately 15 minutes after which respiratory measurements were obtained. Airway opening pressure was measured with a differential pressure transducer (Validyne) at the mouth end of the endotracheal tube. Flow was measured with a heated pneumotachometer (Lilly) placed at the end of the endotracheal tube, distal to the airway opening pressure outlet. Esophageal pressure was measured using an esophageal balloon, attached to a nasogastric catheter. The balloon was filled with 0.5-1.0 ml of air and properly positioned using the occlusion-method [7]. Flow- and pressure data were continuously sampled at a frequency of 100 Hz. Volume displacements were calculated by computerized integration of the flow signal. The derived variables as described in the analysis were obtained with a personal computer (Commodore 486 SX33).

Analysis

For each condition 15 to 20 consecutive breaths per patient were analyzed. From the recording of the flow-signal in time, respiratory rate, duration of inspiration and expiration (TI and TE) and tidal volume (Vt) were computed. The TI/Ttot was calculated from the duration of inspiration and total breathing cycle.

The following computations from the airway pressure and esophageal pressure curves were obtained:

The pressure-level just before the steep deflection of airway pressure indicating the onset of inspiratory effort was measured. This pressure was considered to be the actual end-expiratory airway pressure (EEP, figure 1). The pressure decline between this EEP and the airway pressure at zero flow was referred to as opening airway pressure (opening Paw). Airway pressure-volume diagrams were traced as shown in figure 1, additional work of breathing imposed by the CPAP-system (Wapp) was obtained by integration of the area bordered by the changes in airway opening pressure and volume during in- and expiration. Wapp was calculated per liter of ventilation.

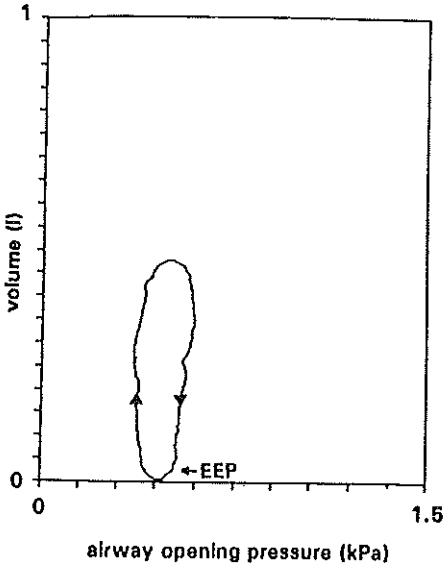

Figure 1a Airway pressure-volume loop of a patient breathing with CF-CPAP. EEP = end-expiratory pressure at the airway opening. Inspiration and expiration are indicated by arrows.

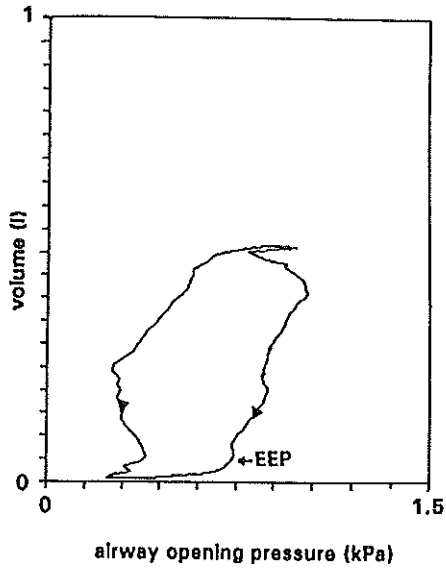

Figure 1b Airway pressure-volume loop of a patient breathing with ventilator CPAP. EEP = end-expiratory pressure at the airway. Inspiration and expiration are indicated by arrows.

Esophageal pressure-curves were analyzed in relation to airway pressure- and flow-curves (figure 2). Two components of the esophageal pressure-curves were determined: dynamic intrinsic PEEP and opening Pes. Dynamic intrinsic PEEP was calculated as the pressure decline from the steep deflection of Pes at end-expiration to the Pes-level corresponding with the deflection of the Paw. Opening Pes was referred to as the pressure decline corresponding in time with the opening Paw.

Statistical analysis

Student's t-tests and linear regression analysis were used. Differences with p-values less than .05 were considered statistically significant.

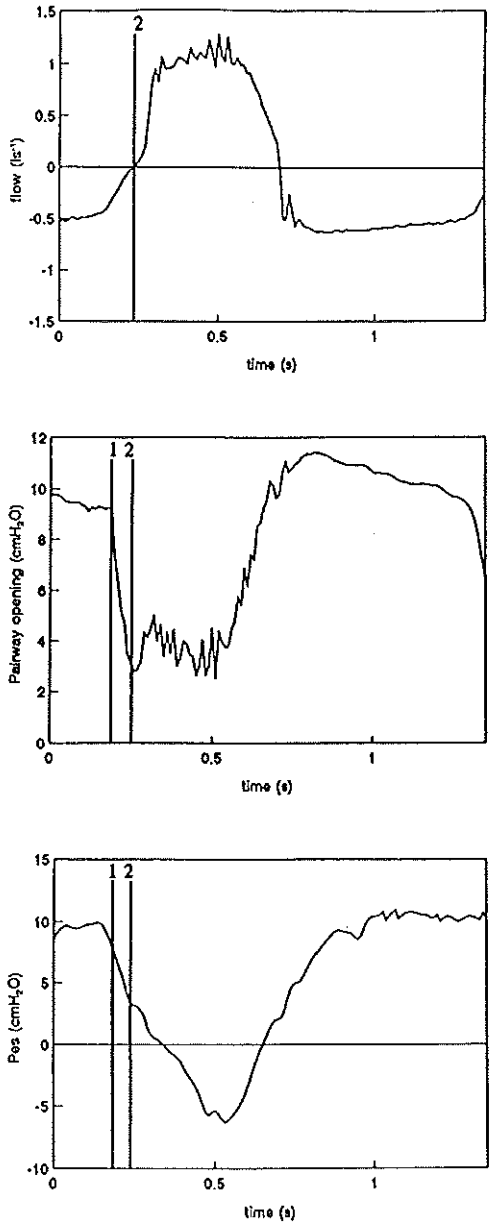

Figure 2 *Flow-, airway pressure-, and esophageal pressure versus time curve of a patient breathing with ventilator CPAP. Line 2 in the flow time curve indicates zero flow. In the airway pressure versus time curve opening Paw is equal to the pressure difference between line 1, first decline in Paw, and 2, start of inspiratory flow. In the esophageal pressure versus time curve the pressure difference between end-expiratory Pes and line 1 indicates intrinsic PEEP. The pressure difference between line 1 and 2 indicates Pes opening. For further explanation see text.*

Table 2

Work of breathing during ventilator CPAP and CF-CPAP

n=13		ventilator CPAP	CF-CPAP	p-value
Wapp	J/l	0.32 ±0.19	0.19 ±0.09	< .001
EEP	kPa	0.72 ± 0.16	0.50 ±0.05	< .001
Opening Paw	kPa	0.41 ±0.22	0.05 ±0.03	< .0005
PEEPi,dyn	kPa	0.02 ±0.02	0.01 ±0.01	n.s.
Opening Pes	kPa	0.45 ±0.29	0.09 ±0.05	< .0005

Wapp = imposed work of breathing, EEP = end-expiratory airway pressure, Opening Paw = pressure difference between the start of inspiratory effort and the onset of inspiratory flow at airway opening, PEEPi,dyn = dynamic intrinsic PEEP-level, Opening Pes = esophageal pressure difference between the start of inspiratory effort and the onset of inspiratory flow, n.s. = not significant.

Results

The results of the variables related to the additional work of the CPAP systems are shown in table 2. The Wapp of the ventilator-CPAP ranged from .10 to .68 J/l and exceeded the Wapp imposed by the CF-CPAP system ranging from .08 to .39 J/l. The relationships between the Wapp and the minute ventilation of the individual patients ranging from 7.2 to 20.8 l are shown in figure 3. This figure reveals increases in Wapp in relation to minute ventilation for both systems, which were more pronounced for the ventilator-CPAP. The Wapp imposed by both systems correlated with the minute ventilation ($r = .89$, $p < .0001$ for ventilator-CPAP and $r = .91$, $p < .0001$ for CF-CPAP).

At ventilator-CPAP the EEP exceeded the preset CPAP-level of 0.5 kPa increasingly at higher minute volumes and the level of EEP was found to correlate both with minute ventilation and Wapp ($r = .81$, $p < .001$ $r = .79$, $p < .005$). With the CF-CPAP system the EEP was equal to the preset CPAP-level and did not alter at higher minute volumes.

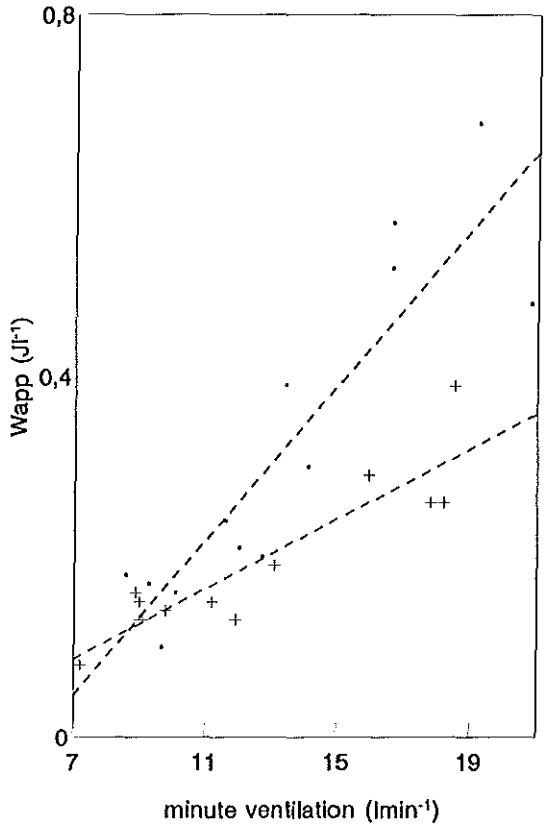

Figure 3 *Linear regression analysis of the imposed work of breathing at both CPAP-modes and minute ventilation ($r = .89$ $p < .0001$ for ventilator CPAP, $r = .82$, $p < .0005$ for CF-CPAP). Squares indicate ventilator CPAP, crosses indicate CF-CPAP.*

The opening Paw at the ventilator-CPAP exceeded the value obtained at CF-CPAP in all patients. The opening Paw correlated with EEP-values and minute ventilation at ventilator-CPAP (both r-values: .90; p-value: < .00005).

Analysis of the esophageal pressure signal revealed very low dynamic intrinsic PEEP-levels for both CPAP-systems. The opening Pes was equal to the opening Paw-level for both systems,

giving for the ventilator CPAP also a close correlation between opening Pes and minute volume ($r = .87$, $p < .0001$).

Table 3

Respiratory variables during ventilator CPAP and CF-CPAP

n=13		ventilator CPAP	CF-CPAP	p-value
Vtex	l	0.50 ±0.18	0.45 ±0.18	< .001
freq	/min	29 ±8	29 ±8	n.s.
min. vol.	l/min	13.4 ±3.9	12.3 ±4.0	< .01
TI/Ttot		0.39 ±0.05	0.40 ±0.07	n.s.

Vtex = expiratory tidal volume, freq = respiratory frequency, min. vol. = minute volume, TI/Ttot = ratio of inspiratory time to total breath cycle duration, n.s. = not significant.

The variables related to the breathing patterns of the patients are shown in table 3. Compared to CF-CPAP, ventilator-CPAP was associated with significantly higher tidal volumes and minute ventilation (both $p < .005$). No differences were found in respiratory rate and TI/Ttot comparing the two CPAP-systems.

Discussion

This study shows that during ventilator-CPAP the additional work imposed by the ventilator is substantially increased at higher minute volumes. The corresponding increments in inspiratory effort are largely caused by increases in end-expiratory airway pressure above the preset CPAP-level imposing an inspiratory threshold. The latter may be explained by the mechanical characteristics of the PEEP-device of the ventilator: at higher minute volumes the flow-dependent resistance of this valve precludes the patient to expire to the preset CPAP-level. In contrast to ventilator-CPAP, the end-expiratory pressure remains unchanged at elevated minute volumes when the continuous flow system is applied. Consequently, the additional work imposed by the continuous flow system is only increased to a minor degree at higher ventilatory needs.

In this study CPAP was used as this ventilatory mode can be applied both by the ventilator and by a continuous flow-CPAP system. At the ventilator-CPAP system the onset of inspiratory and expiratory flows is affected by the opening of valves incorporated in the ventilator. These systems can provide two different methods for initiating flow: pressure- or flow triggering. In contrast to ventilator-CPAP, continuous flow CPAP (CF-CPAP) operates without opening of inspiratory and expiratory valves. The flow provided with this system can be sustained at the inspiratory effort of the patient by means of an extra gas supply from the reservoir in the inspiratory line [8].

Ventilator-CPAP systems are considered to impose higher work loads than CF-CPAP systems [9, 10]. In this study the additional work imposed by the CPAP systems has not been separated into inspiratory and expiratory work. In order to obtain this subdivision, the line between the end-inspiratory and end-expiratory pressures has to be drawn in the airway pressure-volume diagram. As pressure at the end of inspiration, the pressure at zero flow might be applied. Analysis of the airway pressure-volume diagrams computed at ventilator-CPAP reveals however that the end-inspiratory pressure is affected by the mechanical properties of the ventilator (figure 1). During inspiration the ventilator applies a slightly higher pressure than the preset CPAP-level, leading to variable flow-dependent bias and an elevated end-inspiratory pressure. Consequently, inspiratory and expiratory imposed work cannot be separated from airway pressure-volume diagrams obtained at ventilator-CPAP. According to this analysis, total work of breathing can neither be computed from esophageal pressure-volume diagrams, when the Campbell approach is used at breaths obtained during ventilator-CPAP.

The additional workload imposed at ventilator-CPAP has been attributed to the mechanical characteristics of the ventilator [4, 9, 11]. The time delay between the start of inspiratory effort and the onset of inspiratory flow is considered a major determinant of this workload and has therefore to be minimized [12, 13]. This study revealed that with ventilator-CPAP the magnitude of the inspiratory effort is profoundly affected by the end-expiratory airway pressure. As at higher minute volumes the EEP increasingly exceeded the preset CPAP-level, the threshold required to trigger the ventilator was accordingly augmented.

It is well established when the esophageal pressure curve is analyzed, that the early deflection in esophageal pressure equals the dynamic intrinsic PEEP-level [14]. In the patients studied, very low levels of intrinsic PEEP were detected: a finding to be expected as no patients with severe COPD were included. It is well known that in severe COPD CPAP can reduce work of breat-

hing by counterbalancing intrinsic PEEP [15, 16]. The effects of CPAP on work of breathing have predominantly been studied with CF-CPAP-systems [15, 16, 17]. This study indicates that when a ventilator is applied for CPAP, the mechanical characteristics of the ventilator should be taken into account.

Comparison of the respiratory variables presented in table 3 revealed significantly higher tidal volumes and minute volumes at the ventilator-CPAP. These differences, which have also been described by other authors, may be attributed to the low levels of pressure support applied by the ventilator [10].

In conclusion, due to the mechanical characteristics of the ventilator, ventilator-CPAP is associated with increasing levels of additional work at higher ventilatory needs of the patients. These increments in additional work are largely caused by an inspiratory threshold attributed to the flow-dependent resistance of the PEEP-device of the ventilator.When the ventilator is used for weaning purposes, the additional work related to the expiratory valve of the ventilator should be taken into account.

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CHAPTER 6

Detection of flow limitation during tidal breathing by the interruptor technique*

R. Hage, J.G.J.V. Aerts, A.F.M. Verbraak, B. van den Berg, J.M. Bogaard

Abstract

In patients with airflow obstruction flow limitation can be established in various ways. Using body plethysmography flow limitation is assumed when expiratory flow decreases whilst alveolar pressure increases at the same time. During forced expiration flow limitation can be established by means of the flow interruptor technique; flow limitation is assumed when after release of an occlusion a spike flow, superimposed on the ongoing alveolar flow (Δpeakflow) is detected. In this study the flow interruptor technique was applied to detect flow limitation during tidal breathing. The results were compared to those obtained with the body plethysmograph.

The expiratory flow pattern, post-interruption, was analyzed in 33 subjects; 11 patients with airflow obstruction and flow limitation established with the body plethysmograph (AO+); 11 patients with airflow obstruction without flow limitation (AO-); and 11 healthy volunteers.

Mean spike area's were 27.6 ± 18.3, 4.6 ± 2.3 and 3.4 ± 2.0 ml for the AO+, AO- and control group respectively, showing a highly significant difference between the AO+ patients and the other groups ($p < 0.001$ and $p < 0.0005$). Also significantly higher Δpeakflows were found in the AO+ patients compared to the other groups. No differences in Δpeakflows or spike-area's between patients without flow limitation and controls could be established.

We conclude that the interruptor technique may be a useful means of assessing flow limitation during tidal breathing.

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Introduction

The interruptor technique to estimate airways resistance has been firstly described by von Neergaard and Wirz [1]. The mouth pressure measured at the end of a short interruption of expiratory flow was assumed equal to alveolar pressure. From the ratio between this mouth pressure and flow immediately before the interruption airways resistance was estimated [1]. The collapsibility of the airways can also be established by application of the interruptor technique, from the overshoot or spike in the flow pattern after reopening of the interruptor. During an occlusion a compressed airway or a flow limiting segment (FLS) will be abolished. After opening of the interruptor valve, the FLS reestablishes, which can be assessed by the expiratory flow pattern. The flow due to the reappearance of the compressed airways segment is assumed to be superimposed on the ongoing mouth flow. In various studies this analysis has been validated in, during forced expiration flow limited, healthy subjects [2, 3]. In addition to healthy subjects, it has been suggested that in mechanically ventilated patients also during quiet breathing flow limitation can be present [4, 5]. The analysis of the expiratory flow after interruption has been used in a qualitative way to demonstrate flow limitation during mechanical ventilation [6, 7].

To our knowledge, no validation of the interruptor method to establish flow limitation has been performed in patients, during quiet breathing, in whom the presence of flow limitation was demonstrated by an independent method. Therefore, we compared the flow magnitude and area under the curve of the spike flow in spontaneously breathing healthy volunteers and patients with airflow obstruction, with (AO+) and without (AO-) flow limitation. The presence of flow limitation during expiration was assumed from the time course of alveolar pressure and expiratory flow determined in a whole body plethysmograph.

Patients and methods

Subjects

A total of 33 subjects was studied. Airflow obstruction was based on a clinical history of chronic obstructive pulmonary disease, with or without emphysema, asthma or cystic fibrosis. One group (Group A) of 11 (10 males and 1 female) patients suffered from airflow obstruction with flow limitation during part of the expiratory phase (AO+), as established with body ple-

thysmography; mean age was 51 yr (range 28-75 yr). Another group (Group B) of 11 patients (8 males and 3 females) suffering from airflow obstruction had no flow limitation during expiration (AO-); mean age was 39 yr (range 19-71 yr). Additionally, 11 non-smoking healthy volunteers (8 males, 3 females) mean age 36 yr (range 17-77 yr) were included in the study (Group C).

The group of AO+ patients included three patients with chronic airflow obstruction due to CF, six had a clinical diagnosis of emphysema of whom in one patient the emphysema was due to α_1-antitrypsin deficiency.

The group of AO- patients included seven patients with CF. None of the volunteers suffered from diseases of cardiopulmonary origin. All subjects gave informed consent.

Lung function

With a heated pneumotachometer system (Jaeger, Würzburg, Germany) forced expiratory volume in 1 s (FEV_1) and inspiratory vital capacity (VC) were determined. Before each measurement, volume calibration was performed and volumes were corrected to body temperature, atmospheric pressure and saturation with water vapour (BTPS) conditions.

Body plethysmography

A volume-constant body plethysmograph (Jaeger, Bodytest, Würzburg, Germany) was used to determine functional residual capacity (FRC) and airways resistance, and to establish the presence of flow limitation during expiration. All data were sampled and stored on a personal computer at a frequency of 100 Hz. The subjects were seated in the closed box for 2 minutes to allow stabilization of the box pressure (Pbox) fluctuations. Thereafter, they were asked to pant with a frequency of 0.5-1.0 Hz against a closed shutter. Applying Boyle's law, both the intrathoracic gas volume (ITGV) and the conversion factor from Pbox to alveolar pressure (P_A) changes were determined. FRC was calculated from the ITGV determination. The effective resistance (R_{eff}) was determined from flow and Pbox changes during breathing in a heated and humidified rebreathing bag, keeping the inspiratory and expiratory flow at BTPS conditions [8]. In each patient, three reproducible body plethysmographic measurements were performed. In most obstructive patients the P_A/flow (V') relationship shows a complex impedance behaviour, therefore the derived R_{eff} can be considered as a measure of the energy dissipation (resistive behaviour) during a breathing cycle. In an earlier investigation, R_{eff} proved to be the most

reliable resistance variable in these circumstances [8]. During the rebreathing procedure, the lung volume changes were taken into account in the R_{eff} estimation.

Presence of flow limitation from body plethysmography

Flow limitation was assumed to be present when a decrease in flow occurred during expiration together with an increase in P_A. This could be recognized from the characteristic looping pattern in the body plethysmogram during expiration (figure 1a).

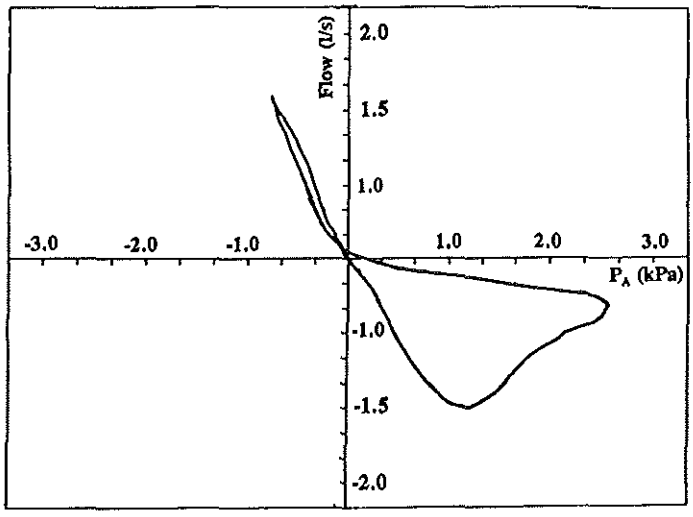

Figure 1a Body plethysmogram pattern representative of a patient with airflow obstruction and flow limitation (AO+).

To determine the time interval in which flow limitation was present the following procedure was used. A third degree polynomial was fitted to both the V' and P_A time course. From the calculated time derivatives, $dP_A(t)/dt$ and $dV'(t)/dt$, dP_A/dV' was calculated as $(dP_A(t)/dt) / (dV'(t)/dt)$. During the time interval in which dP_A/dV' was negative, flow limitation was assumed to be present. Figure 1b shows the actual $P_A(t)$ and V(t), the polynomial fits and the time interval of flow limitation associated with the body plethysmogram of figure 1a.

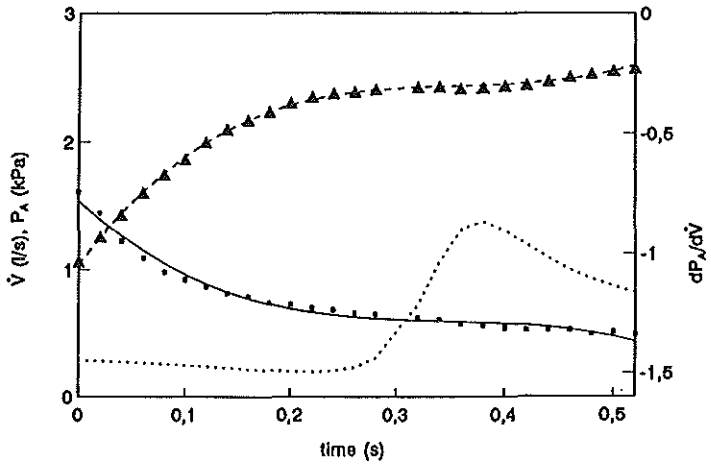

Figure 1b Actual alveolar pressure (P_A) and V'-time recording, the polynomial fits and dP_A/dV'-time interval of the body plethysmogram presented in figure 1a.
■ = flow (V'); _____ = polynomial fit of the flow signal; ▲ = alveolar pressure (P_A); ····· = polynomial fit of the P_A-time signal, ... = dP_A/dV'.

The interruptor technique

The interruptor (4200 series Type TM 7/8 Hans Rudolph,Inc. Kansas City, USA) consists of a sliding pneumatic piston. In series with the interruptor, flow was measured with a heated pneumotachometer (Lilly) (figure 2). Mouth pressure was measured (Validyne P45 transducer, Validyne, Northridge, USA) proximal to the interruptor valve. Pressure and flow signals were stored on a personal computer with a sample frequency of 500 Hz. The opening and closing of the piston was computer controlled. The switching speed, defined as the elapsed time from complete opening to closure was 65-110 ms.

Ohya et al. [3] performed interruptions of variable length during forced expirations in healthy volunteers with flow limitation. They found a triphasic pattern in the time course of mouth pressure. The first phase consisted of a rapid rising pressure representing pressure equilibration of upper airway segments. During this phase, an airflow into the re-expanding compressed airway segment was assumed. The second phase consisted of a slower rising pressure during which the airway wall further expanded from its compressed state. In the third phase, equilibration between alveolar and mouth pressure was completed.

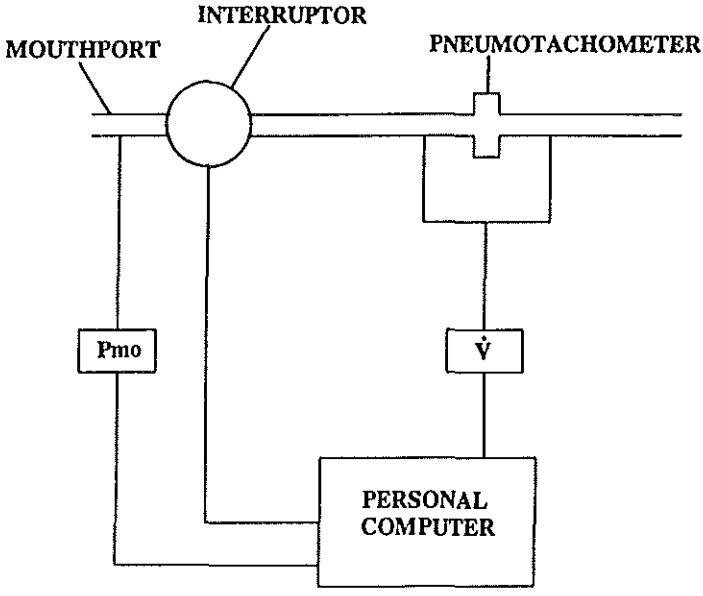

Figure 2 Schematic representation of interruption measurement. V' = flow, Pmo = mouth pressure.

Reopening of the interruptor after closure of more than 0.1 s yielded equal flow spikes. This indicates that within that period the expansion of the compressed airway segment has been completed [3]. In our investigation, flow was interrupted for 0.25 s, permitting the compressed segment to be fully expanded to the uncompressed state.

All subjects, provided with a noseclip, were studied in sitting position, supporting cheeks and mouth floor with their hands, in order to keep the distensibility of the extrathoracic airways as low as possible [9]. About 30 interruptions were performed, one interruption per expiration, randomly distributed over the expiratory phase.

Flow at the onset of interruption (occlusion flow) and after reopening maximal flow, flow overshoot (Δpeak flow) and volume displacement associated with the flow overshoot (spike area) were obtained from three representative recordings within the interval of flow limitation derived from body plethysmography (figure 3).

In case of absence of flow limitation, three recordings were used within the same time interval as mentioned above. The flow overshoot was determined after back-extrapolation of the flow during the interval 0.1-0.4 s after reopening of the interruptor. The spike-area was obtained by integration of the flow overshoot.

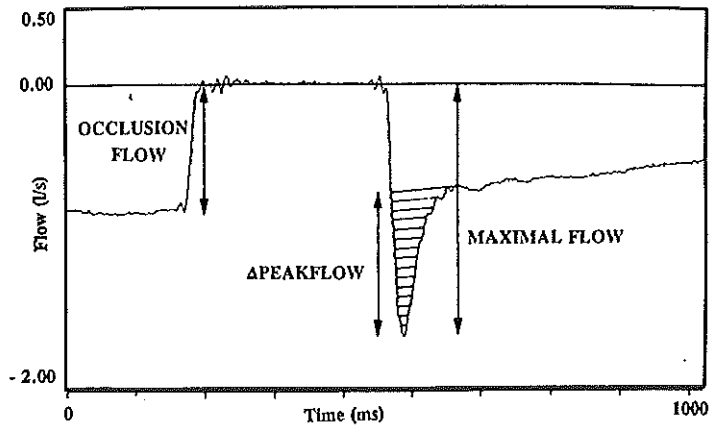

Figure 3 Interruption pattern with Δpeakflow, maximal flow, occlusion flow and spike area (shadded area).

Measuring device accuracy and dynamic properties

To study the dynamic properties of the interruptor device and measuring equipment a constant flow generator was used. The interruption procedure was performed as in the patient measurements. A tubing connected to the pressure transducer of the pneumotachometer was used with a length and a resistance such that the flow response after reopening of the interruptor was critically damped. Ninety percent rise time was less than 25 ms, which was considered sufficiently accurate for the purpose of the measurements.

Statistical methods

Comparisons between mean values of the three groups were made using analysis of variance, assuming significance at a p-value of less then 0.05.

Results

The body plethysmographic and interruption measurements were completed in all 33 subjects. Table 1 shows the mean FEV_1, VC, R_{eff} and functional residual capacity/total lung capacity ratio (FRC/TLC) values of the subjects studied.

Table 1

Pulmonary function data of the three groups studied

	AO+ (n=11)	AO- (n=11)	C (n=11)	p-value AO+ vs AO-	AO+ vs C	AO- vs C
FEV_1 (%pred)	55 ±19 (31-87)	76 ±22 (39-130)	101 ±12 (84-132)	<0.005	<0.0001	<0.005
VC (%pred)	88 ±21 (59-118)	91 ±12 (72-116)	102 ±13 (84-136)	ns	ns	ns
Reff (kPa.s/l)	0.83 ±0.49 (0.22-1.93)	0.33 ±0.14 (0.18-0.64)	0.20 ±0.06 (0.10-0.26)	<0.005	<0.001	<0.01
FRC/TLC	0.72 ±0.10 (0.57-0.87)	0.66 ±0.10 (0.47-0.82)	0.58 ±0.07 (0.45-0.65)	ns	<0.005	<0.05

Values are presented as means ± SD, and range in parenthesis. AO+: patients with airflow obstruction and flow limitation; AO-: patients with airflow obstruction without flow limitation; C: controls. FEV_1: forced expiratory volume in one second; VC: vital capacity; Reff: effective resistance; FRC/TLC: functional residual capacity/total lung capacity ratio; ns: nonsignificant. Significance of difference is indicated.

In the AO+ and AO- patients mean FEV_1 (% of predicted) was significantly lower, mean R_{eff} and mean FRC/TLC ratios were significantly higher, than in the control group. Mean R_{eff} was significantly higher and FEV_1 significantly lower in the AO+ patients compared to the AO- patients. With respect to the mean VC values no significant differences were found between the three groups.

The polynomal fits of the P_A- and V' time-course during the last 75% of expiration, during which flow limitation was assumed, yielded mean values of r^2 (coefficient of determination) of 0.96 (range 0.80-0.99) and 0.97 (range 0.81-0.99), respectively.

Figure 4a-c shows representative examples of flow patterns during closure and reopening of the interruptor in an AO+ patient, an AO- patient and a healthy subject.

Analysis of the variables shown in figure 3 yielded the mean values given in table 2. Both the Δpeak flow and spike area were found to be significantly higher in the AO+ patients compared to the AO- patients and to the controls. No significant differences in Δpeak flow and in spike area were present between the AO- patients and the control group.

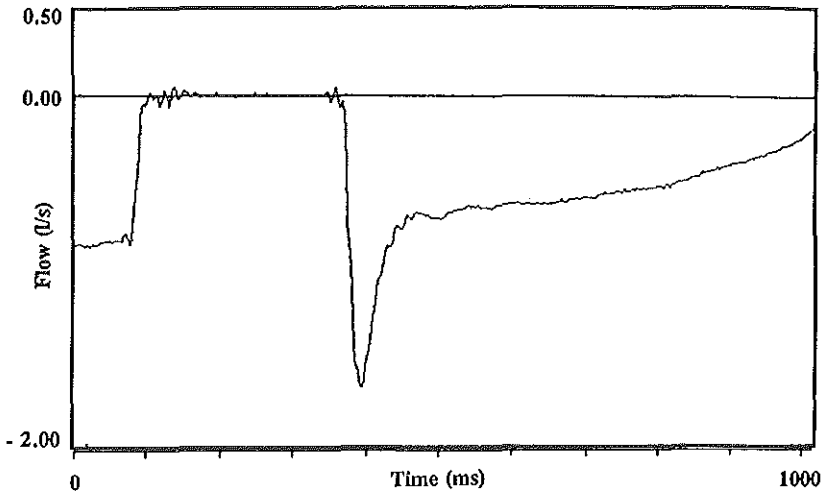

Figure 4a Representative interruption pattern of a patient with airflow obstruction and flow limitation (AO+).

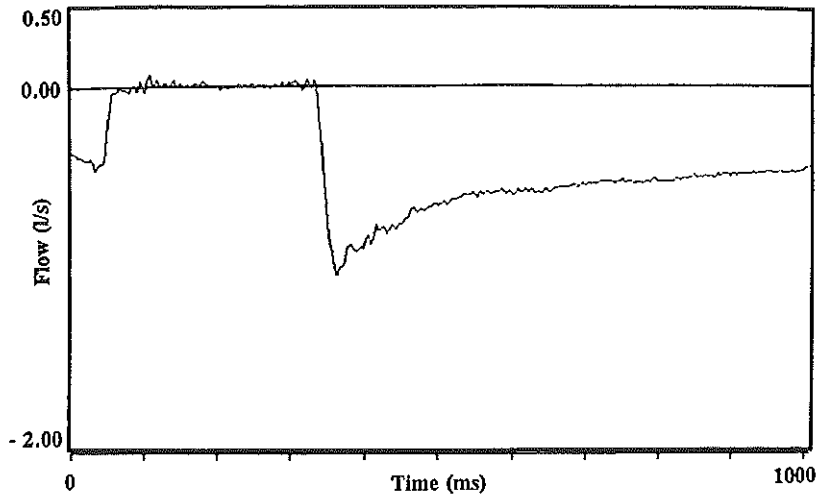

Figure 4b Representative interruption pattern of a patient with airflow obstruction and without flow limitation (AO-).

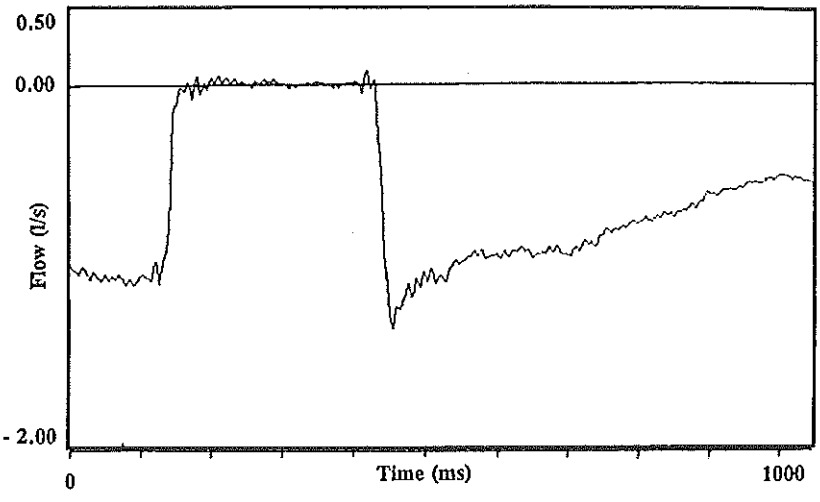

Figure 4c Representative interruption pattern of a healthy control.

Table 2

Occlusion flow, maximal flow, Δ peak flow and spike area for the three groups derived from the interruptor measurement

	AO+ (n=11)	AO- (n=11)	C (n=11)	p-value AO+ vs AO-	p-value AO+ vs C	p-value AO- vs C
occlusion flow (ml/s)	646 ±155 (422-1005)	496 ±116 (357-697)	623 ±216 (266-975)	<0.05	ns	ns
maximal flow (ml/s)	1747 ±633 (1152-3309)	934 ±185 (693-1333)	1267 ±420 (559-1840)	<0.001	<0.05	<0.05
Δpeakflow (ml/s)	954 ±676 (532-2905)	203 ±76 (101-297)	211 ±115 (72-415)	<0.005	<0.005	ns
spike-area (ml)	27.6 ±18.3 (10.6-70.8)	4.6 ±2.3 (1.3-6.3)	3.4 ±2.0 (1.0-6.9)	<0.001	<0.0005	ns

Data are presented as mean ± SD and range in parenthesis. For abbreviations see legend to table 1. Significance of difference is indicated.

Maximal expiratory flow was significantly higher in the AO+ patients compared to the other two groups. In the AO- patients, maximal expiratory flow was significantly lower compared to the controls. The occlusion flow was only significantly higher in the AO+ patients compared to the AO- patients.

Within the group of AO+ patients no significant correlation between spike area and FEV_1 or between spike area and R_{eff} was found.

End-occlusion mouth plateau pressure ranged from 0.5-3 kPa in the three groups.

Discussion

In this study the applicability of the interruptor method to establish quantitative indices for flow limitation was assessed during quiet breathing.

It is assumed that interruption of expiratory flow will abolish the flow limiting segment and that flow limitation will be reinstalled after opening of the valve, which is demonstrated by an overshoot in expiratory flow [3, 6, 7]. We have applied the interruptor method in patients with airflow obstruction with (AO+) and without (AO-) flow limitation and in healthy volunteers, during quiet breathing. The presence or absence of a compressed airway segment, and consequently flow limitation, was established using whole body plethysmography. During plethysmography, flow limitation was defined as an increasing P_A in association with a decreasing V', leading to a negative dP_A/dV' ratio. A third degree polynomial was fitted through the P_A and V' time curves in order to describe the presence of flow limitation in time mathematically as $dP_A/-dV'$. In all cases, an accurate fit was obtained considering the r^2 values and consequently, calculation of dP_A/dV versus time could be used to assess the presence of flow limitation. A flow limiting segment was probably even present when dP_A/dV' was slightly above zero.

From the interruptor flow time curve, the Δpeak flow and the spike area were calculated. In earlier investigations, the presence of flow overshoots has been attributed to decompression of extrathoracic airways, restoration of the compressed airway segment, and ongoing alveolar flow [2, 3, 10, 11].

Quantitative data from spike areas have been obtained in healthy volunteers during forced expiration. Knudson et al., excluding the influence of the extrathoracic airways by a head canopy, found compressed volumes between 50 and 150 ml [10]. Ohya et al. determined spike-areas of about 100 ml after occlusions at 50% FVC [3]. Based on the anatomy of the bronchial

tree the decompression volume of the extrathoracic airways was assumed to be 10 ml in case of an alveolar pressure of about 10 kPa [12]. In our study end-occlusion pressures ranged from 0.5-3 kPa, consequently the spike areas in the AO- patients and in the healthy volunteers are most probably due to decompression of gas in extrathoracic airways.

During the generation of a flow limiting segment the ongoing alveolar flow affects the spike area, as has been demonstrated by Pedersen et al. [11]. Considering earlier findings in healthy volunteers during forced expiration and scarce data on patients with airflow obstruction during forced expiration, it has been suggested that the presence of flow limitation provides the main contribution [2, 3, 10]. However, in this study, in the patients with flow limitation, no relationship between spike-area and R_{eff} neither between spike-area and FEV_1 has been found.

In this study, the post-interruption flow pattern was analysed in order to obtain indices for flow limitation from this flow pattern. Maximal expiratory flow was found to be significantly different among the three patient groups studied, indicating that maximal expiratory flows cannot be used to establish the presence or absence of flow limitation. The occlusion flow was higher in AO+ patients compared to AO- patients, a finding which remains to be explained.

The large differences in Δpeak flow and spike area comparing AO+ patients to AO- patients and healthy volunteers, and the absence of differences in these parameters between AO- patients and healthy volunteers, indicate the feasibility of deriving quantitative indices for flow limitation.

Further research is needed to establish the value of analysis of Δpeak flow and spike area using an interruptor measurement in clinical practice. Because the interruptor measurement requires minimal subject co-operation, is easy to perform, and can be carried out during tidal breathing, it offers a feasible alternative to conventional lung function measurements to detect the presence of flow limitation, such as in critically ill patients and in neonates [6, 7, 13, 14].

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CHAPTER 7

Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease*

J.G.J.V. Aerts, B. van den Berg, J.M. Bogaard

Abstract

Forced expiratory flow-volume curves are commonly used to assess the degree of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). In mechanically ventilated subjects airways obstruction can only be estimated from relaxed expirations. Quantitative data on airflow obstruction have however not been reported in these patients. The aim of this study was to assess the degree of airways obstruction from relaxed expiratory flow-volume curves in mechanically ventilated patients with COPD.

As measure of airflow obstruction the slope of the flow during the last 50% of expired volume, the SF50, was calculated. In order to study reproducibility the SF50 was calculated from consecutive breaths and subsequently at different levels of end-expiratory lung volume (ΔEEV). The SF50 was also correlated with the FEV_1 measured prior to the start of ventilatory support.

27 patients were studied with a FEV_1 expressed as percentage predicted of 31 ± 12% (mean ± SD). The SF50 amounted to 19 ± 10°. A positive correlation was established between SF50 and the FEV_1, ($r = .90$, $p < .001$). From 5 consecutive breaths the mean variation coefficient of SF50 was 5 ± 2%. Changing the ΔEEV from .05 to 1.00 l did not affect the SF50 significantly.

It was concluded that the SF50 can be used to assess the degree of airflow obstruction in mechanically ventilated patients with COPD.

* This manuscript is submitted for publication

Introduction

Forced expiratory flow-volume curves are commonly used to estimate the degree of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The maximal flows in the second half of the flow-volume curve are considered effort-independent, because expiratory flow limitation develops within flow limiting segments. The determinants of these flows are well established [1-4]. Amongst these are airways resistance proximal to the flow limiting segment, the elastic recoil of the lung parenchyma and the elastic properties of the airways generations where flow limitation develops [1-4]. A decrease in the maximal flows in patients with COPD may be caused by either an increased airways resistance, loss of the elastic recoil of the lung or changes in the elastic properties of airways segments where flow limitation develops [1-4]. Variables to quantify the degree in airflow obstruction at forced expiration are the flows after expiration of 25, 50 and 75% of the forced vital capacity and the forced expiratory volume in one second (FEV_1).

As most patients under ventilatory support are unable to perform forced manoeuvres, in these patients flow-volume relationships have been studied during tidal breathing [4-8]. In mechanically ventilated patients with severe COPD respiratory mechanics may be disturbed to such an extent that even during tidal breathing expiratory flow limitation develops. During a large part of the expiration flows become independent of driving pressures [4]. In that case a downward concavity in the flow-volume relationships has been described by several authors [4-11]. No quantitative data on the degree of airway obstruction have been reported in these studies.

In this investigation we analyzed expiratory flow-volume curves obtained in patients with COPD who were mechanically ventilated under sedation and paralysis, in order to assess the degree of airflow obstruction. As measure the slope of the expiratory flow during the last 50% of the expired volume was calculated by computation of the ratio between the decrease in flow divided by the corresponding expired volume. This variable was compared to standard lung function tests obtained prior to the period of ventilatory support.

Patients and methods

Patients

All patients with COPD who were mechanically ventilated in our intensive care unit between 1993 and 1995, were studied. Only patients of whom forced lung function data were available within a period of two years before the start of mechanical ventilation, were included in the study. In this way data of 27 patients of whom respiratory measurements both before and during the period of mechanical ventilation were available, were analyzed. The age of the patients at the start of ventilator support was 64 $\pm$ 13 yrs (mean $\pm$SD). 19 were males. Informed consent for the study was obtained from the patient's next of kin.

All patients were studied within the first 48 hrs after the start of mechanical ventilation. In all patients a Siemens Servo 900C ventilator (Siemens-Elema Solna Sweden) in the volume controlled mode was used. No ventilator PEEP was applied during the study. The patients were routinely sedated as standard treatment; for the study a muscle relaxans was administered. Patients were studied at least 4 hours after nebulization of β-mimetics.

Respiratory measurements

During ventilatory support flow was measured with a heated pneumotachometer (Lilly) positioned at the end of the endotracheal tube, connected to a pressure transducer (Validyne P45 transducer, Validyne, Northridge, USA). Volume displacement was obtained by computerized integration of the flow signal. Airway opening pressure was measured proximal to the pneumotachometer using a pressure transducer (Validyne). Data were stored and analyzed using a personal computer (Commodore 486 SX33, Commodore Business machines Inc, West Chester, USA) at 100 Hz.

Intrinsic PEEP was determined by the end-expiratory occlusion method.

The forced expired volumes during spontaneous breathing were obtained using similar equipment. The patients were breathing via a mouthpiece connected to the pneumotachometer. For the study the FEV_1 was expressed as absolute volume and as percentage of reference value [12]. Reversibility was defined as an increase in FEV_1 of more than 12% of the predicted value 10 minutes after inhalation of terbutaline [12].

Analysis of the flow-volume curves

The slope of the flow during the last 50% of expired volume (SF50) was obtained by calculation of the quotient between the difference of the flow at 50% of exhaled volume (V'50,ex) and the flow at end-expiration (V'end,ex) at the moment the valve of the ventilator closed and inspiration was started [6], divided by 50% of tidal volume (Vt). In formula:

$$SF50 = arctang \quad \frac{(V'50,ex - V'end,ex)}{.5 * Vt}$$

arctang	inverse tangens
SF50	in degrees,
Vt	in liters,
V'50,ex	in liters per second,
V'end,ex	in liters per second.

In order to study reproducibility, the SF50 was calculated in each patient from 5 consecutive flow-volume curves.

The effects of various degrees of hyperinflation on the SF50 were studied in 5 patients. For this purpose the SF50 was calculated from flow-volume curves obtained when a patient was ventilated with different tidal volumes at a constant expiratory time. Tidal volume was increased and decreased .1 l above and under the standard tidal volume at an unchanged respiratory rate. Two minutes of uninterrupted ventilation at this changed tidal volume were allowed in order to obtain a new equilibrium before respiratory parameters were measured. The dynamic hyperinflated volume (ΔEEV), the end-expiratory volume above functional residual capacity (FRC) was obtained by disconnecting the patient from the ventilator to allow a prolonged expiration time during which the dynamic hyperinflated volume was expired [11]. The dynamic hyperinflated volumes were determined at the different tidal volumes studied.

Data analysis

Linear regression and correlation analysis was used. Means ± standard deviations were calculated.

Results

The mean FEV_1 of the 27 patients obtained within two years before this period of mechanical ventilation was .89 ± .40 l, expressed as percentage predicted 31 ± 12 %, with a range from 16 to 61%. In none of the patients a reversibility of airflow obstruction was observed.

In all patients intrinsic PEEP was detected during the standard ventilatory support. The level of intrinsic PEEP amounted to .83 ± .38 kPa (range .35 to 1.70 kPa). Consequently an end-expiratory flow at the moment the expiratory valve of the ventilator closed, was observed in all patients.

SF50, calculated as mean of 5 consecutive flow-volume curves amounted to 19 ± 10°, with a range from 7 to 42°. The maximal variation for the SF50, calculated from these consecutive flow-volume curves was 10% (mean ± sd: 5 ± 2%).

Regression analysis showed a significant positive correlation between SF50 and FEV_1, expressed as percentage predicted ($r = .90$, $p < .0001$). The relationship between the values of the SF50 and those of the FEV_1 of the 27 patients is shown in figure 1.

The computations of the SF50 at various degrees of hyperinflation when patients were ventilated at different tidal volumes are presented in table 1.

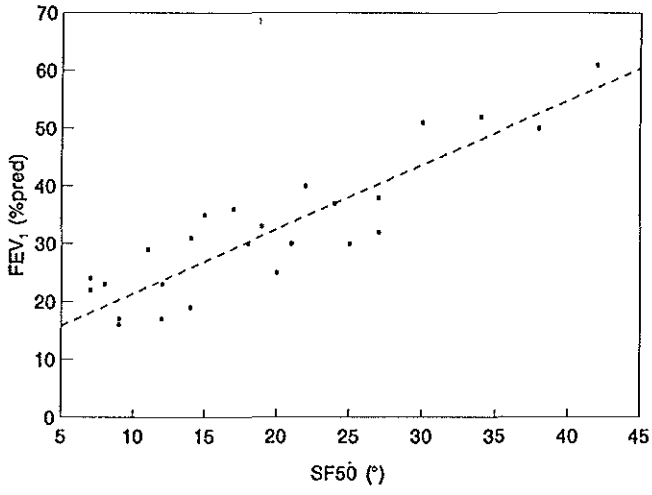

Figure 1 Regression analysis of the relationship between FEV_1 (% predicted) and the SF50 ($r = .90$, $p < .0001$).

Table 1

SF50 values calculated in 5 patients at standard setting of mechanical ventilation and after in or decreasing tidal volume with .1l at a constant respiratory rate.

Patient no.	Vtex = -0.1 L		Vtex			Vtex = +0.1 L	
	SF50 (˚)	ΔEEV (l)	SF50 (˚)	ΔEEV (l)	PEEPi (kPa)	SF50 (˚)	ΔEEV (l)
1	21	.20	18	.26	.37	18	.31
2	7	.80	7	1.12	.75	7	1.87
3	8	.39	11	.68	.75	11	1.25
4	21	.30	23	.34	.69	24	.45
5	29	.12	26	.22	1.31	25	.43

Vtex = tidal volume, ΔEEV = dynamic hyperinflated volume.

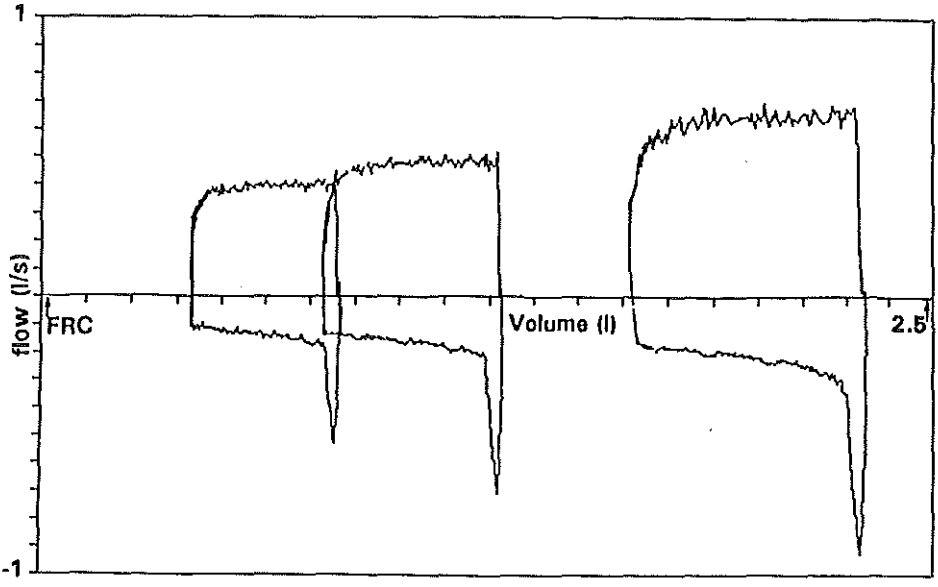

Figure 2 Flow-volume curves at different end-expiratory lung volumes obtained by changing tidal volume from .50 to .60 and .80 l, without altering respiratory rate. The SF50 remained unchanged at 7°. ΔEEV-levels equalled .43, .80 and 1.87 l above FRC respectively.

No significant differences in the values of the SF50 were established at the different end-expiratory lung volumes. An example of flow-volume curves at a tidal volume of .50, .60 and .80 l with an ΔEEV from .43, .80 and 1.87 l respectively is shown in figure 2.

Discussion

In this study the feasibility of a variable derived from expiratory flow-volume curves, the SF50, as a measure of expiratory airways obstruction, was assessed in 27 mechanically ventilated patients with COPD. The angle calculated from the quotient of the flow difference and the expired volume in the second part of the expiratory flow-volume curve was found to correlate positively with the forced expiratory volume in 1 second. Calculation of SF50 from consecutive breaths revealed only minor variations in the value of the SF50. Increasing and decreasing end-

expiratory lung volume was also found to have only minimal effect on the value of SF50 in a subgroup of patients.

Flow-volume curves of mechanically ventilated patients have been investigated in a number of studies [4-8, 13-17]. Only qualitative information on the shape of the flow-volume curve has been reported in ventilated subjects.

In order to characterize the shape of the forced expiratory volume curve quantitatively, Mead derived in ambulatory patients a "slope ratio" from the second part of the maximal forced expiratory flow-volume curve by computing the ratio of the instantaneous tangent slope at 50% of forced vital capacity, divided by the corresponding chord factor: the slope of the flow from 50% to 100% forced vital capacity (dV'/dV) / (V'/V) [18]. Further research on this slope factor did reveal a correlation between the slope ratio and the FEV_1 [19]. However, the large variability in the ratio calculated from consecutive breaths precluded the application of this measure in clinical practice [19].

In order to estimate airways obstruction from the flow pattern during tidal breathing Morris et al. proposed two indices. The first, volume-based index computed the volume expired until maximal flow was reached, divided by the tidal volume ($\Delta Vmax/\Delta V$). The second, time-based index computed the time interval between the start of expiration and maximal expiratory flow divided by total expiratory time (t(peak)/t(tot)) [20, 21].

These computations yielded however a wide range of results, even when intraindividual measurements of healthy subjects were compared [20-22]. Nevertheless, a significant correlation between these indices and FEV_1 was found suggesting that these indices might be useful for screening purposes, for instance in children who are unable to perform forced manoeuvres [22]. In mechanically ventilated subjects, these indices do not correlate with the level of airways obstruction as the expiratory valve of the ventilator profoundly affects the time interval before the peak flow is reached.

In most ventilated patients with flow limitation, when controlled ventilation is applied, the expiratory time set by the ventilator is too short to achieve complete expiration towards FRC [4-11]. Therefore dynamic hyperinflation, accompanied with intrinsic PEEP is to be expected and has also been observed in all patients of this study. Because an alveolar to airway-opening pressure gradient remains present during the whole expiratory time, expiratory flow will not be reduced to zero at the moment the expiratory valve of the ventilator closes. This can be seen in the flow pattern as a sudden drop in expiratory flow at end-expiration (V'end,ex) [6]. As the

level of intrinsic PEEP and the magnitude of the expiratory flow are highly dependent on lung volume, these variables cannot be used to estimate the level of airflow obstruction.

In anesthetized humans and animals a time-constant (τ) has been derived from the flow-volume relationships during spontaneous breathing. It is assumed that for this calculation the resistance of the total respiratory system (Rrs) and the compliance of the total respiratory system (Crs) behave linearly [14-16].

The lung emptying was then assumed to follow an exponential equation $V(t) = V(0)\exp(-t/\tau)$ with V(0) and V(t) the lung volume at the start and at t seconds from the onset of expiration respectively. From this equation it can be derived that the slope of the tail of the flow-volume curve (dV'/dV) equals $-1/\tau$.

In case of lung inhomogeneity a multi-compartment behaviour will exist. As a consequence the one-compartment model cannot be applied. Peslin et al. have described that in case of flow limitation calculation of τ by means of Rrs and Crs does not provide proper values of τ, because in patients with flow limitation no linear relationship between driving pressure and flow is present [9]. Consequently computation of the resistance of the airways to flow is invalid and computation of a time constant is also meaningless [9, 18].

The SF50 was derived from the second part of the flow-volume curve. It is assumed that in mechanically ventilated patients the shape of the first part of the expiratory flow-volume curve is not only determined by the driving pressure and airways resistance but also by external factors as the size of the endotracheal tube and the resistance of the ventilatory circuit and the expiratory valve of the ventilator [5]. In contrast, during the second part of the flow-volume curve, the shape of the curve is considered not to be affected by these external resistance elements.

In former studies in mechanically ventilated patients with flow limitation also a linear course of the second part of the expired flow-volume curve was described [8]. Based on a linear V'/V behaviour, the SF50 can be considered to be associated with the mean effective time constant of the latter part of expiration. Considering the significant correlation with FEV_1 this index is apparently linked to airways obstruction, despite the alinear behaviour of the resistance.

The SF50-values at different levels of end-expiratory lung volume revealed no substantial changes, although the V'50,ex and the V'end,ex were increased at higher levels of hyperinflation. This indicated that the flow difference per unit of volume remained unchanged.

For this study, the patients were paralysed prior to the respiratory measurements. The absence of respiratory muscle activity may have influenced the results of the study. During paralysis,

exhalation is passively driven by the elastic recoil of the total respiratory system, while flow resistance is the only opposing force [4,5]. In future studies the feasibility of the SF50 should be established in mechanically ventilated patients who are studied without sedation or paralysis.
In conclusion, calculation of the slope of the flow during the last 50% of expiratory volume from relaxed flow-volume curves can be used to assess the degree of airflow obstruction in mechanically ventilated patients with COPD.

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CHAPTER 8

Controlled expiration in mechanically ventilated patients with Chronic Obstructive Pulmonary Disease*

J.G.J.V. Aerts, B. van den Berg, J.M. Bogaard

Abstract

In patients with severe chronic obstructive pulmonary disease (COPD) lung emptying may be affected by flow limitation. We tested the hypothesis that the airways compression leading to flow limitation can be counteracted by controlling the expiratory flow.

The effects of an external resistor on lung emptying were studied in six patients with COPD who were mechanically ventilated while sedated and paralysed. Respiratory mechanics were obtained during ventilatory support with and without the resistor. Airways compression was assessed using the interruptor method. For the study a turbulent resistor was applied with the highest resistance-level that did not increase the end-expiratory lung volume. At this resistance-level external PEEP was generated in all patients. As total PEEP-levels remained unchanged at both settings, at the controlled expiration the levels of intrinsic PEEP were decreased from 0.96 ± 0.30 to 0.53 ± 0.19 kPa (mean ± SD, $p < 0.005$). Comparison of the expiratory flow-volume curves at both settings revealed that during the controlled expiration the flows were significantly decreased during the first 40% and significantly increased during the last 60% of the expired volume (both $p < 0.005$). As the end-expiratory lung volumes remained unchanged during both settings, these increments in flow indicated a decrease in effective resistance. Airways compression was observed during unimpeded expirations in all patients using the interruptor method. During the application of the resistor airways compression was no longer detectable.

In patients with COPD on ventilatory support the application of an external resistor could decrease effective expiratory resistance by counteracting airways compression without increments in end-expiratory lung volume.

* European Respiratory Journal, in press

Introduction

There is ample evidence that in patients with severe chronic obstructive pulmonary disease (COPD) lung emptying is affected by flow limitation [1-5]. Although flow limitation was initially described during forced expirations, it has also been established during relaxed expirations [1-5]. The latter has been shown in mechanically ventilated patients with COPD, in whom the respiratory muscles were paralysed [2-5].

It is assumed that by controlling the expiratory flow the airways compression leading to flow limitation can be counteracted. As early as 1972, an expiratory flow regulator was proposed in order to regulate lung emptying during mechanical ventilation in patients with COPD; the hypothesis was that reduction of early expiratory flow would improve lung emptying [6]. This concept was, however, never verified in patient studies.

In the present study the effects of an external resistor on lung emptying were investigated in mechanically ventilated patients with COPD while sedated and paralysed. Respiratory mechanics were obtained during expirations with and without the resistor. Effective airways resistance was estimated at both settings. Because of the non-linear relationship between driving pressure and flow during flow limitation, resistance cannot be properly calculated. The term effective resistance was used, derived from body-plethysmography [7]. The interruptor method was applied to detect airways compression and to compute iso-volume pressure-flow curves.

Patients and methods

Patients

Six patients (five male, one female), mean age 73 yrs (range 68 to 85 yrs) suffering from severe COPD were studied. In three patients lung function data were available with FEV_1 25 ± 5% predicted (mean ±sd) and VC 65 ± 7% predicted (mean ±sd). All were mechanically ventilated for acute respiratory failure due to exacerbations of COPD.

In all patients a Siemens Servo 900c ventilator (Siemens-Elema, Solna, Sweden) in the volume-controlled mode was used. Ventilatory settings were set by the primary physician and remained unchanged during the study except for application of the external resistance. Tidal volume equalled 0.63 ±0.15 l (mean ± SD), frequency equalled 14.7 ±3.0/min. No ventilator-PEEP was applied. During the study the patients were sedated and paralysed. Informed written

consent was obtained prior to the study from the patient's next of kin. The study was approved by the local Ethics Committee.

Respiratory measurements

Flow (V') was measured with a heated pneumotachometer (Lilly, Jaeger, Würzburg, Germany) connected to the endotracheal tube. Volume displacement was obtained by computerized integration of the flow signal. Airway opening pressure (Pao) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co, Northridge, USA). Data were stored and analyzed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc, West Chester, USA) at a sample frequency of 500 Hz.

Airway opening pressures at end-expiration and end-inspiration were obtained by means of the end-expiratory and end-inspiratory hold buttons, respectively, of the Servo-ventilator. The end-expiratory plateau pressure was indicated as total PEEP, being the sum of intrinsic PEEP and external PEEP. The Pao measured just before the end-expiratory occlusion was assumed to equal external PEEP. Although no ventilator-PEEP was applied during the unimpeded expirations, low levels of external PEEP were detected at airway opening in all patients. These pressures represented the pressure gradient over the ventilator circuit and the expiratory valve of the ventilator at the end of expiration. All pressure measurements were performed in duplicate.

ΔEEV, the lung volume above the elastic equilibrium volume at end-expiration was determined by the technique of prolonged expirations [8]. ΔEEV was calculated as mean of two determinations.

From flow-volume curves, peak expiratory flow (PEF), the expiratory flow at 50% of exhaled volume (V'50,ex), and the expiratory flow at the moment the expiratory valve of the ventilator closed, i.e. the end-expiratory flow (V'end,ex), were determined. All flow values were calculated from 5 consecutive flow-volume curves.

Interruptor measurements

A pneumatic valve placed in the ventilator circuit distal to the pneumotachometer was used for repeated occlusions of the airway during expiration (Hans Rudolph 4200A, Hans Rudolph, Kansas City, USA). The pneumatic valve was computer-controlled. Opening and closing of the valve was alternated at a time cycle of 500 ms. The dynamic properties of the interruptor device and measuring equipment were studied using a constant flow generator. Using this technique

oscillations were detected of the same magnitude, frequency and pattern during opening and closing of the interruptor valve [9]. After opening of the valve flow limitation was assumed to be present when the opening transient clearly exceeded the closing transient.After an end-inspiratory hold procedure applied by the ventilator the interruptor valve was closed and the patient disconnected from the ventilator tubings in order to allow a prolonged expiration time. Then the interruptor-procedure was started. After opening of the valve flow limitation was assumed to be present when the opening transient clearly exceeded the closing transient [9, 10]. In order to analyze the effect of the external resistor on respiratory mechanics the expiratory flows at various lung volumes were related to the corresponding driving pressures. For these iso-volume pressure-flow relationships driving pressure was calculated by subtraction of the pressure just before the occlusion from the plateau pressure during the occlusion. It is assumed that this plateau pressure equals alveolar pressure at the moment of interruption [4, 9, 10]. The flow just prior to interruption was used in this analysis.

External resistor

As external resistor a merry-go-round with holes of different sizes was used (Vitapep, Vitapep, IS Danmark). The merry-go-round was connected to the expiratory outlet of the ventilator. The pressure-flow relationships obtained with a constant flow generator at flow ranges, and the holes used in the patient studies, are shown in figure 1. As high resistance-level the smallest hole was chosen that did not increase the total PEEP-level. At this resistance-level positive end-expiratory airway pressures were generated without increments in ΔEEV. For this purpose in five patients hole A was used; in one patient hole B was applied. In five patients also a low resistance-level was applied (C in figure 1). As low resistance-level the smallest hole was chosen which did not increase the end-expiratory airway pressure more than .1 kPa.

In order to perform repeated occlusions during expiration with the resistor, the merry-go-round was connected to the outlet of the interruptor device during an end-inspiratory hold procedure. Then the interruptor-procedure was applied as described previously. In this way flow, airway opening-pressure and volume changes could be determined during application of the merry-go-round.

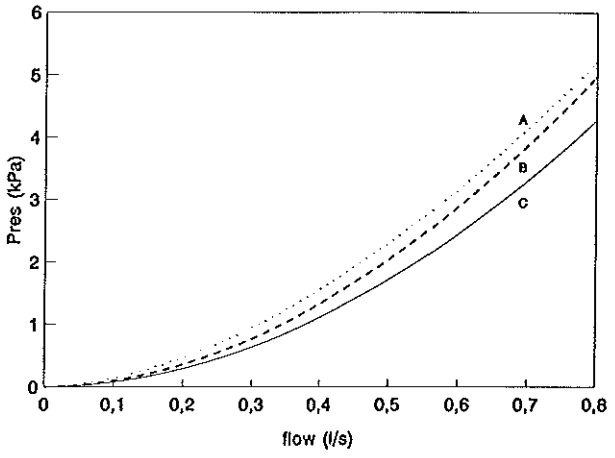

Figure 1 *Pressure-flow relationship of the applied external resistance. Pressure (Pres) caused by the resistance is calculated as Pres = a*V'^b (a and b are constants, r = .97). Broken line (---) represents resistance B (a= .77, b= .19); dotted line (...) represents resistance A (a= .76, b= .17). The third pressure-flow relationship (uninterrupted l;ine a= .67, b= .19), shown in this figure belongs to hole C, which was used as the low resistance-level in a group of five patients.*

Blood gas analysis

In four patients arterial blood PO_2 and PCO_2 were determined during unimpeded expiration and application of the high resistance.

Protocol

At first, flow-volume curves were obtained during unimpeded expiration after which end-inspiratory and end-expiratory holds were performed. Subsequently ΔEEV was determined by disconnecting the patient from ventilatory tubings. After 2 minutes of uninterrupted ventilation the ΔEEV determination was repeated. Then the interruptor procedure was applied in duplicate, again allowing two minutes of uninterrupted ventilation in between.

After completing the measurements during unobstructed expiration the resistor was added with the largest hole, i.e. the lowest resistance-level. By performing end-expiratory occlusions after 1 minute of controlled expiration the desired resistance-level was chosen. Two minutes of control-

led expiration at that resistance-level were allowed before the above-mentioned procedure was repeated.

Before sampling of arterial blood 20 minutes of uninterrupted ventilation were allowed. After this the ventilatory mode was changed.

Statistical analysis

Student's t-test was used, assuming significance at a p-value of less than 0.05.

Results

In all patients intrinsic PEEP-levels were detected ranging from 0.60 to 1.41 kPa during unimpeded expirations (table 1). During application of the low resistance the intrinsic PEEP-levels remained unchanged. As shown in representative flow-volume curves (figure 2) the low resistance only affected the expiratory flow during the first 20% of expired volume. At this resistance-level the peak expiratory flow (PEF) was reduced, indicating a deceleration in time of early expiration over the first 10% of expired volume. In the next 10% expiratory flows were found to be higher compared with unimpeded expiration. Subsequently, at 80% of expired volume the expiratory flows at low resistance were equal to those during unimpeded expiration, and remained parallel during the remaining part of expiratory volume displacement. This indicated that the low resistance did not influence the effective resistance after 20% of volume was expired.

The effect of the resistance on airways compression was established with the interruptor technique. An example of the expiratory flow- and pressure-patterns obtained with the interruptor in patient no. 3 during an unimpeded expiration is shown in figure 3a and 3b. These recordings revealed supramaximal flows immediately after opening of the interruptor valve, which clearly exceeded the closing transients, in all patients. Compared to unimpeded expirations, at the low resistance-level the flow-overshoots remained unchanged. In figure 3c the expiratory pressure- and flow patterns of the same patient are shown during application of the high resistance-level; with this resistance-level no flow-overshoots could be detected.

Table 1

Respiratory parameters during unimpeded expiration (u.e.) and controlled expiration with the high resistance-level (c.e.).

patient	resis-tance level	Pend,in (kPa)		PEEPi (kPa)		PEEPe (kPa)		PEEPtot (kPa)	
		u.e	c.e	u.e	c.e	u.e	c.e	u.e	c.e
1	A	1.95	2.00	1.16	0.77	0.02	0.45	1.18	1.22
2	A	2.33	2.44	1.41	0.66	0.06	0.86	1.47	1.52
3	A	1.40	1.57	0.60	0.26	0.08	0.53	0.68	0.79
4	B	1.40	1.50	0.75	0.42	0.01	0.44	0.76	0.86
5	A	1.69	1.73	0.80	0.64	0.00	0.16	0.80	0.80
6	A	1.91	1.82	1.02	0.41	0.00	0.55	1.02	0.97
mean		1.78	1.84	0.96	0.53	0.03	0.50	0.99	1.03
SD		0.36	0.34	0.30	0.19	0.03	0.23	0.30	0.29
p		n.s.		< 0.005		< 0.005		n.s.	

Pend,in = end-inspiratory pause pressure; PEEPi = intrinsic PEEP; PEEPe = external PEEP; PEEPtot = total PEEP.

Tables 1 and 2 give data on the respiratory measurements obtained in the individual patients during unimpeded expirations, and during controlled expirations with the high resistance-level. As the high resistance-level did not increase total PEEP-levels, the end-inspiratory pressures and the levels of ΔEEV were found to be unchanged at both settings. A decrease in intrinsic PEEP was observed at the high resistance-level as external PEEP was generated at this setting.

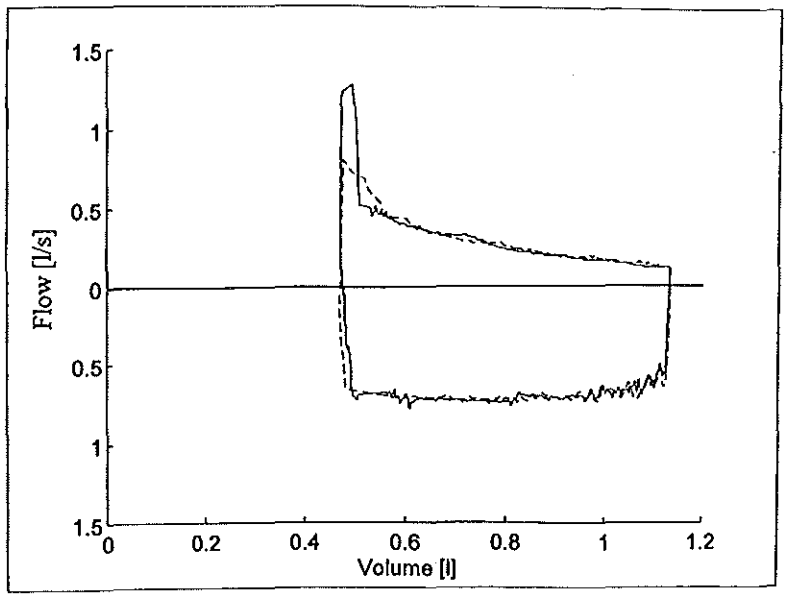

Figure 2 Flow-volume curves in patient no. 1. Uninterrupted line: unimpeded expiration; broken line: low expiratory resistance.

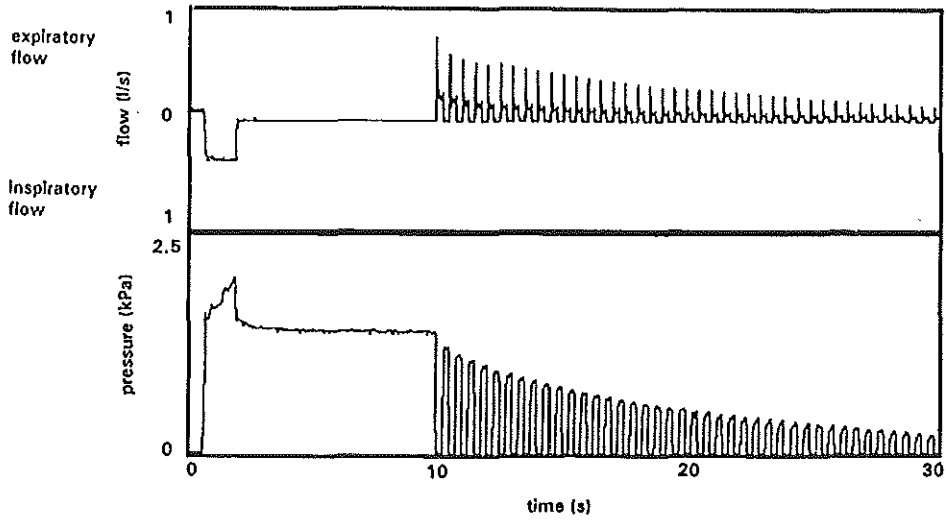

Figure 3a Pressure-time and flow-time diagram of an interruptor measurement during unimpeded expiration in a representative patient.

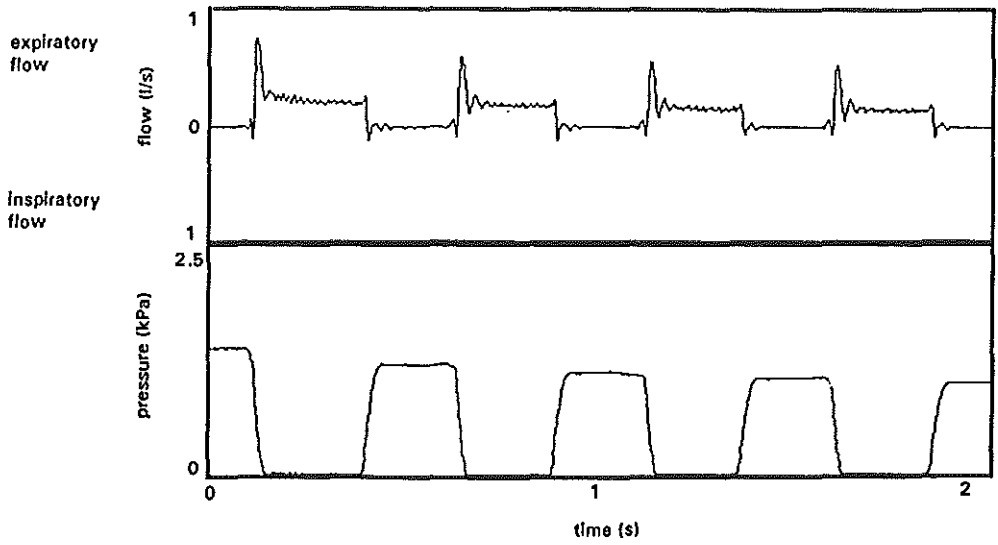

Figure 3b Detail of the pressure-time and flow-time diagram in figure 3a during interruptor measurement during unimpeded expiration.

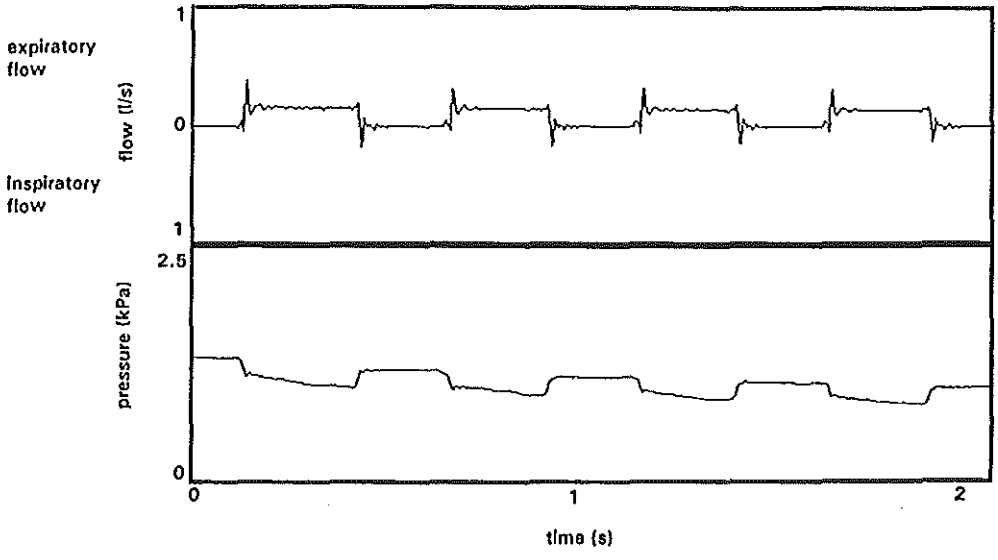

Figure 3c Detail of the pressure-time and flow-time diagram during interruptor measurement during decelerated expiration.

Table 2

Respiratory parameters during unimpeded expiration (u.e.) and controlled expiration with the high resistance-level (c.e.).

patient	PEF (l/s)		V'50,ex (l/s)		V'end,ex (l/s)		ΔEEV (l)	
	u.e	c.e	u.e	c.e.	u.e.	c.e.	u.e.	c.e.
1	1.23	0.41	0.24	0.26	0.12	0.16	0.56	0.53
2	1.40	0.73	0.26	0.29	0.17	0.23	0.99	1.04
3	0.86	0.37	0.24	0.27	0.17	0.21	0.79	0.87
4	0.78	0.31	0.19	0.20	0.14	0.16	0.80	0.87
5	0.90	0.43	0.22	0.24	0.11	0.14	0.67	0.71
6	0.96	0.38	0.24	0.26	0.16	0.19	1.28	1.21
mean	1.02	0.44	0.23	0.25	0.14	0.18	0.85	0.87
SD	0.24	0.14	0.03	0.03	0.03	0.03	0.26	0.24
p	< 0.0005		< 0.0005		< 0.005		n.s.	

PEF = peak expiratory flow (l/s); V'50,ex = expiratory flow at 50% of exhaled volume (l/s); V'end,ex = end-expiratory flow (l/s); ΔEEV = dynamic hyperinflation volume (l).

Comparison of the flow-volume curves revealed substantial decreases in peak expiratory flows and small but significant increases in V'50,ex and V'end,ex at the high resistance-level. Expiratory flows were decreased during the first 40% and increased during the latter 60% of expired volume at this setting. As the levels of ΔEEV did not differ, the flow-volume curves at both settings could be compared iso-volumetrically. Representative examples of these curves are shown in figure 4. This analysis indicated that the effective resistance during the latter part of expired volume with the high resistance-level was reduced compared to the unimpeded expiration.

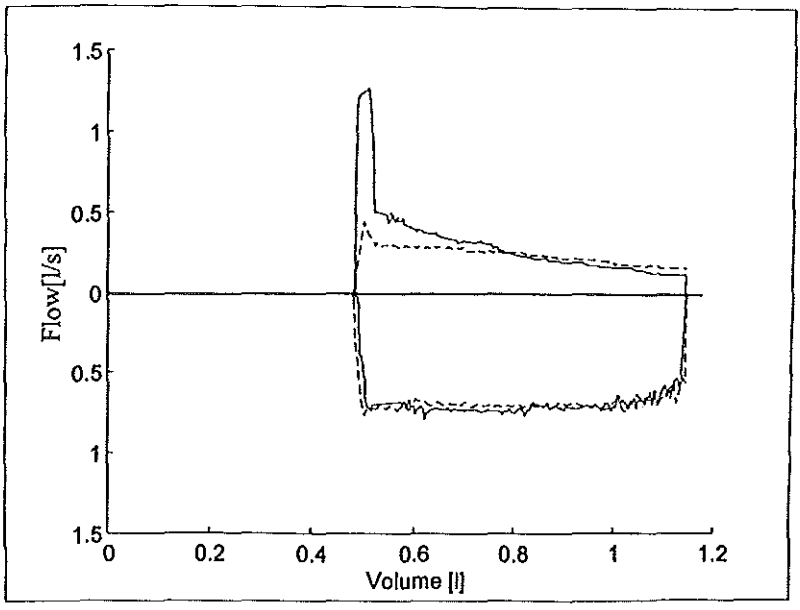

Figure 4 *Flow-volume curves in patient no. 1. Uninterrupted line: unimpeded expiration; broken line: high expiratory resistance.*

When iso-volume pressure-flow relationships were computed, the low resistance-level was found to decrease driving pressures while iso-volume flows remained unchanged. The high resistance-level resulted in larger reductions in driving pressures with concomitant increases in iso-volume flows at the lower lung volumes. Figure 5 shows the iso-volume pressure-flow curves obtained in patient no. 2.

In the four patients studied, no differences in blood gas parameters were established. Comparison of unimpeded expiration with the high resistance-level showed mean PaO_2 to be 10.8 $\pm$2.6 and 10.7 $\pm$1.9 kPa, and mean $PaCO_2$ to be 4.8 $\pm$.3 and 4.8 $\pm$.3 kPa, respectively (all data mean $\pm$SD).

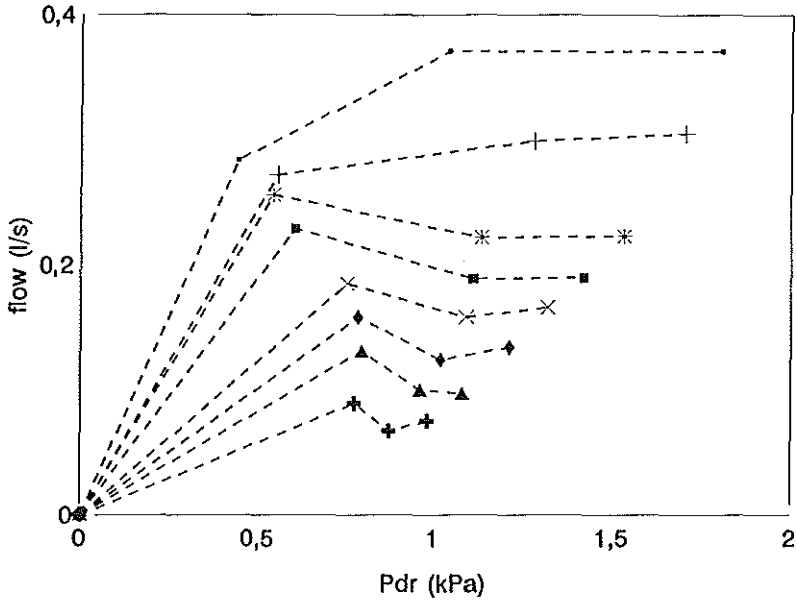

Figure 5 *Iso-volume pressure-flow diagram of patient no. 2 during unimpeded expiration and during application of high and low resistance-level at different lung volumes. Right-hand symbolst, i.e. highest driving pressures at each lung volume indicate unimpeded expiration; middle symbols at each lung volume indicate low resistance-level, left-hand symbolst, i.e. the lowest driving pressures at each lung volume indicate application of the high resistance-level. Pdr = driving pressure (kPa). ▪ lung volume .55 l above end-expiratory volume (EEV), + lung volume .45 l above EEV, ✳ lung volume .35 l above EEV, ■ lung volume .25 l above EEV, ⨯ lung volume .15 l above EEV, ♦ lung volume .05 l above EEV, ▲ lung volume .05 l below EEV, +lung volume .15 l below EEV.*

Discussion

The present study demonstrates the feasibility of decreasing effective airways resistance and counteracting dynamic airways compression in patients with severe COPD by use of an expiratory resistor. These results were obtained in mechanically ventilated patients who were sedated and paralysed. During relaxed expirations, in all patients the presence of flow limitation, associated with airways compression, was established.

Flow limitation may occur with negative pleural pressure according to the choke point theory [11]. In the presence of a choke point, wave speed flow will be present. In the present study

expiratory flows are most probably not limited by the presence of wave speed, but are limited by the presence of viscous flow limitation associated with airways compression [12]. The development of flow limitation due to dynamic airways compression in this situation can be elucidated by the presence of a positive pleural pressure (P_{pl}) during lung emptying. In patients with severe COPD a low elastic recoil pressure of the lung ($P_{l,el}$) may be found. In these patients the elastic equilibrium volume is elevated as the low $P_{l,el}$ is associated with a normal elastic recoil pressure of the chest wall (P_{cw}) [11, 13]. In most patients with COPD, even during quiet breathing, dynamic hyperinflation is encountered, i.e. expiration is terminated at a lung volume above the static equilibrium volume. In that case the P_{cw} is inward throughout the breathing cycle causing the P_{pl} to be positive during the entire expiration. Dynamic airways compression is assumed to develop when both a positive P_{pl} and a low $P_{l,el}$ are present.

Flow limitation caused by airways compression is present when iso-volume pressure-flow curves reveal a plateau: above a certain critical driving pressure the flow does not increase at further increments of the pressure [2]. At forced expirations even a decrease in flow has been observed at increasing driving pressures. This negative effort dependency has been described in patients with emphysema: during relaxed expirations the expired volume in one second can exceed that obtained during forced expirations [14].

Taking into account this concept, we investigated whether a decrease in driving pressure could preclude airways compression and, in case of negative effort dependency, could increase expiratory flow. The decrease in driving pressure was accomplished by an external resistor that reduced the pressure gradient between the alveoli and the airway opening.

In a number of studies on mechanically ventilated patients extrinsic PEEP, i.e. a positive end-expiratory pressure, has been imposed in order to reduce intrinsic PEEP [2, 15, 16]. In those studies threshold resistors have been applied to impose extrinsic PEEP. A pressure-level was applied at the airway opening below the level of intrinsic PEEP observed during unimpeded expirations. It was found, however, that threshold resistors did not affect either total PEEP-levels or expiratory flows; this because during the entire expiration the pressure difference between actual driving pressure and critical driving pressure is only partly counterbalanced by the applied extrinsic PEEP-level [15].

In contrast to the threshold resistors described above, the flow dependent resistor as used in the present study, did affect expiratory flows. This was accomplished without increments in total PEEP or in ΔEEV.

In this study the decline in airway opening pressure was controlled during expiration. This resembles pursed lips breathing, a breathing manoeuvre frequently observed in spontaneously breathing patients with COPD during dyspnea. When patients purse their lips during expiration they experience a relief in dyspnea [17-20]. Compared to unimpeded expiration, pursed lips breathing was associated with a prolonged expiratory time, a decreased breathing frequency and consequently an increased tidal volume [17-20]. The effects of the resistor were studied in mechanically ventilated patients with COPD who were sedated and paralysed. Tidal volumes and expiration times were fixed by the ventilator and did not change during application of the resistor, and respiratory mechanics could be determined when respiratory muscle activity was absent.

The effects of two resistance-levels on lung emptying were analyzed using volume displacements against time and expiratory flow-volume relationships. As end-expiratory lung volumes remained unchanged at the settings studied, both volume displacements and flow-volume curves could be compared at absolute lung volumes. At both resistance-levels the early PEF encountered during unimpeded expirations was abolished. This indicated a deceleration of early expiration. The low resistance-level only affected lung emptying during the first 20% of expiratory volume displacement; during the latter part the expiratory flow and effective airways resistance did not differ. In contrast to the low resistance-level, the high resistance-level affected lung emptying during the entire expiration time. During the latter part of expiration the iso-volume flows were found to be increased. As the relationship between alveolar pressure and lung volume was considered to be unchanged at both settings, the increase in expiratory flows in the second part was obtained at unaltered alveolar pressures. This indicates that total effective resistance, i.e. the resistance over the airway and the merry-go-round, was diminished at the controlled expiration.

Considering the latter assumption, it should be taken into account that a flow measured at airway opening, is the result of emptying of lung units with various time-constants [21]. Application of the resistance could retard the emptying of fast lung units. Analysis of a simplified model consisting of two parallel RC-units with a common serial resistance yields a delayed emptying in case of either equal or unequal time constants. At increasing serial resistance no increments occur, however, in iso-volume flows. So, in our opinion, the increments in flow cannot be explained by the slowing of fast lung units as they were established at iso-volume conditions. As table 1 indicates, a slight increment in ΔEEV was present in 4 out of 6 patients.

It may be questioned whether this increment has caused the increase in flow as was established during controlled expiration. When the external resistance would have had no effect on flow limitation the relationship between lung volume and flow will be comparable between unimpeded and controlled expiration. The increment in lung volume to achieve a similar increase in flow as was found experimentally, can be calculated. This calculated increment in lung volume was much higher than was established experimentally (0.15 ±0,05 l and 0.02 ±0.06 l (mean ±SD), respectively). Despite random inaccuracies which may have been present in the ΔEEV determinations, in our opinion a main effect of ΔEEV increments may therefor be excluded.

Iso-volume pressure-flow curves were computed from the interruptor measurements performed during expirations with and without the resistor. In accordance with other reports, the low resistance-level reduced the driving pressure without changes in iso-volume flows [2, 15, 16]. The driving pressures were further reduced at the high resistance-level; at lower lung volumes this was associated with increments in flow. These results are in agreement with the concept of negative effort dependency of flow at lower lung volumes.

The interruptor technique was also used to establish expiratory flow limitation by analysis of the expiratory flow-pattern after a short interruption of the flow. Flow limitation is considered to be present when supramaximal flow transients are observed [9, 10]. In the present study the flow transducer system was slightly underdamped. Because another study reported high supramaximal flows only in case of flow limitation [9], in the present study qualitative judgements of the presence of flow limitation from supramaximal flows were used. During unimpeded expirations these flow-overshoots were observed in all patients studied. At the low resistance-level the flow-pattern post interruption was found to be unchanged compared to unimpeded expiration, indicating that the low resistance-level did not affect flow limitation. In contrast, at the high resistance-level no flow-overshoots were observed after interruption of the flow. This observation indicates that the high resistance-level did counteract airways compression.

Although determined only in four patients, in the present study, deceleration of expiration did not affect arterial blood gases. In accordance with observations during pursed lips breathing it was expected that gas-exchange would be enhanced due to controlled expiration. This may be explained by the fixed respiratory rate and tidal volume, and the type of resistor used. The merry-go-round is a turbulent resistance and allowed increases in resistance by major steps. The deceleration in volume displacement may not be sufficient to improve gas-exchange. A higher

resistance-level would have increased end-expiratory lung volume, which was considered undesirable.

The application of an external resistor was found to decrease effective airways resistance during expiration in patients with COPD who were mechanically ventilated. This decrease in effective airways resistance was associated with a reduction of airways compression, which was achieved at unaltered end-expiratory lung volumes. No effects on gas-exchange were established. Further studies are required to determine whether application of a resistor can improve pulmonary gas-exchange by controlling lung emptying.

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CHAPTER 9

Ventilatory support with expiratory pressure regulation in patients with chronic obstructive pulmonary disease (COPD)*

J.G.J.V. Aerts, B. van den Berg, C. Hilvering, J.M. Bogaard

Abstract

In severe COPD impaired gas-exchange is commonly observed associated with disturbed respiratory mechanics. Airways compression, developing even during relaxed expiration, is considered to contribute to the disturbed respiratory mechanics.

We hypothesized that an external resistor can counteract this compression and enhance gas-exchange by regulating expiratory airway pressure .

10 patients with COPD on mechanical ventilation were studied while sedated and paralysed. The effects of an external resistor on respiratory mechanics and pulmonary gas-exchange were compared to those of unimpeded expiration. As resistor the expiratory pressure regulated mode of the César ventilator was used. The pressure was regulated to achieve an ascending flow pattern during the first part of expiration.

Compared to unimpeded expiration, the PaO_2 increased from 11.5 ± 2.8 to 12.6 ± 3.1 kPa at the pressure regulated mode (data presented as means ± SD, $p < .05$). The $PaCO_2$ and the physiological dead space (Vd/Vt) decreased from 5.9 ± 1.2 kPa and 61 ± 7% to 5.4 ± 1.0 kPa and 57 ± 8% (p-values < .05 and < .01 respectively).

Compared to unimpeded expiration, the expiratory pressure regulation significantly increased the mean volume above end-expiratory lung volume present in the lungs during one breathing cycle from .24 ±.08 l to .35 ±.10 l (p-value < .001). The expiratory pressure regulation was also associated with significantly increases of the level of intrinsic PEEP from 5.7 ± 2.4 to 8.0 ± 3.1 cmH_2O and the end-expiratory volume above functional residual capacity from .51 ± .42 l to .82 ± .49 l (p-values < .001 and < .0001 respectively).

Ventilatory support with expiratory pressure regulation was found to enhance pulmonary gas-exchange in patients with COPD. It is suggested that this increase in pulmonary gas-exchange is related to a deceleration of early expiratory volume displacement.

* This manuscript is submitted for publication

Introduction

Various methods have been proposed to improve respiratory mechanics and gas-exchange in patients with chronic obstructive pulmonary disease (COPD) who are mechanically ventilated. Modern technology incorporated in the mechanical ventilators of today allows adaptations in ventilatory modes in order to affect ventilation and gas-exchange.

In severe COPD loss of lung tissue and decreased elasticity contribute to the impaired gas-exchange. Both decreased elasticity of lung tissue and increased airways resistance are common features affecting lung emptying. Even during relaxed expirations airways compression is commonly encountered attributing to the elevated airways resistance [1]. As a consequence, dynamic hyperinflation and auto- or intrinsic PEEP are observed in most patients with COPD on ventilatory support [2-4].

In order to counterbalance intrinsic PEEP, application of external PEEP has been advocated [3-7]. This external PEEP imposed by a threshold resistor only affects lung emptying when external PEEP exceeds the intrinsic PEEP-level [4]. The effects of external PEEP on gas-exchange have been variable [3-7].

Apart from devices generating PEEP, resistances decelerating expiratory flow have been applied. As early as 1972 a Siemens ventilator was equipped with an expiratory flow regulator, aimed at achieving a more uniform emptying of the lung [8]. Although from a theoretical viewpoint the emptying of slow lung compartments should be promoted to improve evenness of ventilation, this mode has never been found to improve pulmonary gas-exchange or to show any advantage over external PEEP.

The concept of a variable flow resistance is to decrease the pressure gradient between alveoli and airway lumen during the early part of expiration, when this gradient is greatest, to counteract airways compression. Ideally lung emptying controlled by such a resistance should not be accompanied by a substantial increase of the end-expiratory lung volume.

In this study the effects of regulation of expiratory resistance on respiratory mechanics, dynamic hyperinflation and pulmonary gas-exchange were investigated. The controlled expiration imposed by this resistor was compared to unimpeded expiration in mechanically ventilated patients with COPD.

Table 1

Patient data

Patient no.	Age yrs	Sex m/f	VC %	FEV1 %	Interruptor
1	56	f	50	32	+
2	57	m	77	20	+
3	62	f	65	25	-
4	76	m	78	30	-
5	67	m	74	30	-
6	72	m	89	28	+
7	71	m	n.a.	n.a.	+
8	75	m	n.a.	n.a.	+
9	83	f	n.a.	n.a.	+
10	75	m	n.a.	n.a.	+

VC = vital capacity expressed as percentage of reference value; FEV1 = forced expiratory volume in 1 s, expressed as percentage of reference value; Interruptor = interruptor measurements obtained: + = yes, - = no n.a. = not available.

Patients and methods

Patients

Ten patients (7 male, 3 female), mean age 70 yrs (range 56 to 83 yrs) with COPD were studied. Patient data are shown in Table 1.

In six patients pulmonary function tests were available from the period preceding the ventilatory support. Expressed as percentage of reference values the mean vital capacity amounted to 70% (range 50 to 89%) and the mean FEV_1 (forced expiratory volume in 1 s.) amounted to 26% (range 20 to 32%). In seven patients the presence of expiratory airways compression during tidal breathing was established by means of the interruptor technique [9].

All patients were ventilated by a César ventilator (Taema, CFPO, France) via a cuffed endotracheal tube (inner diameter 7.5-9.0 mm), because exacerbations of their chronic condition had led to respiratory failure. Minute ventilation and oxygen concentration of inspiratory air were adjusted to achieve acceptable blood-gases.
During the study the patients were sedated and paralysed. Informed consent was obtained from the patient's next of kin. The study was approved by the local ethics committee.

Respiratory mechanics
A heated pneumotachometer (Lilly, Jaeger, Würzburg, Germany) was connected to the endotracheal tube to measure flow (V'). Volume was obtained by computerized integration of the flow signal. Airway opening pressure (Pao) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co. Northridge, USA). Data were stored and analyzed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sampling frequency of 100 Hz.
Airway opening pressures at end-expiration and end-inspiration were obtained by means of the end-expiratory and end-inspiratory hold buttons of the ventilator respectively. The end-expiratory plateau pressure was indicated as total PEEP, being the sum of intrinsic PEEP and external PEEP. The Pao measured just before the end-expiratory occlusion was assumed to equal external PEEP.
End-expiratory lung volume above functional residual capacity (FRC) was determined by the technique of prolonged expiration [7]. The patient was disconnected from the ventilator at end-inspiration. End-expiratory lung volume above FRC (ΔEEV) was then calculated by subtracting tidal volume from total exhaled volume.
The mean volume above the ΔEEV present in the lungs during a breathing cycle, Vmean, was obtained by integration of the volume-time curve, divided by the cycle time.

Interruptor measurements
A pneumatic valve placed in the ventilator circuit distal to the pneumotachometer was used for repeated occlusions of the airway during expiration (Hans Rudolph, 4200 A, Hans Rudolph, Kansas City, USA). The pneumatic valve was computer-controlled. Opening and closing of the valve were alternated every .25s. Dynamic characteristics of the interruptor system are presented in detail elsewhere [9]. After an end-inspiratory hold procedure applied by the ventilator the

interruptor valve was closed and the patient disconnected from the ventilator tubings in order to allow a prolonged expiration time. Then the interruptor-procedure was started and the valve was opened and closed until no expiratory flow could be detected. Airways compression was assumed to be present when after opening of the valve supramaximal flow transients (flow spikes) were observed [9,10]. The interruptor measurements could only be obtained during the unimpeded expiration as the technique required disconnection of the patient from the ventilator tubings, precluding the regulation of expiratory flow by the ventilator.

Blood gases and physiological dead space

Blood samples were obtained from a indwelling catheter in the radial artery to measure arterial PO_2 (PaO_2) and arterial PCO_2 ($PaCO_2$). This catheter was also connected to a blood pressure monitoring system and the effect of controlled expiration on blood pressures was monitored.
Physiological dead space (Vd/Vt) was determined from the values of $PaCO_2$ and $PECO_2$, the PCO_2 from a mixed expired gas sample. The expiratory gas passed through a mixing bag, from which it was continuously sampled and analyzed by a capnometer (Siemens Ultramat M).
Vd/Vt was calculated as:

$$\frac{P_aCO_2 - P_ECO_2}{P_aCO_2}$$

where the value of the P_ECO_2 was determined at the moment the bloodsample was obtained.

Ventilator settings

For both unimpeded and controlled expiration the volume controlled mode was used. Inflation took up 35% of breathing cycle time and the expiration 65% of the cycle. No external PEEP was applied. Tidal volume and respiratory rate were set by the primary physician and remained unchanged during the study.
For mechanical ventilation with controlled expiration the ventilatory mode of the César ventilator was applied which allowed control of the drop of the airway opening pressure during expiration by regulating expiratory resistance. The decay in expiratory Pao was mediated by a mathematical expression:

$$Pao(t) = Pb - ((Pb - Pe) * (\frac{t}{t_m})^2)$$

Pao(t) = Pao at time t (cmH_2O).

Pb = Pao at which the control of expiration is started, in % of end-inspiratory pressure during the preceding inspiration.

Pe = Pao at the end of the controlled expiration.

t = randomly chosen time during decelerated expiration (s).

t_m = duration of expiratory control, maximum 75% of total expiratory time (s).

In order to institute the controlled expiration the values of Pb, Pe and t_m should be chosen. In all patients a t_m of 75% of total expiratory time and a Pe equal to 25% of Pb was applied. Pb was adjusted to achieve an ascending flow pattern during the first part of expiration. A schematic example of a representative pressure pattern with an indication of the parameters is given in figure 1.

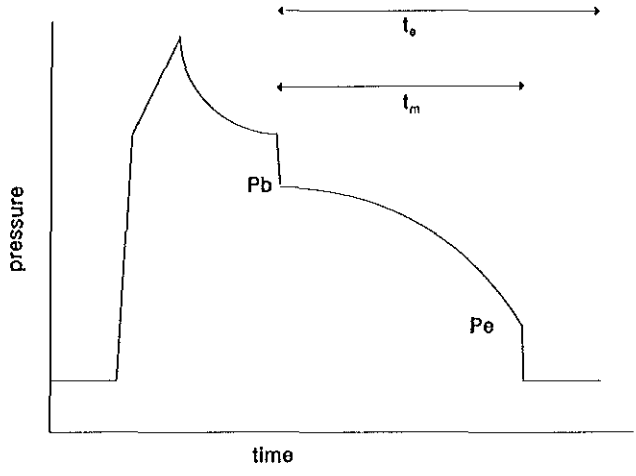

Figure 1 *Schematic example of a representative pressure pattern with an indication of the parameters. Pb = airway opening pressure at which the control of expiration is started, Pe = airway opening pressure at the end of the controlled expiration, t_e total expiratory time, t_m = duration of expiratory control, maximum 75% of total expiratory time.*

Study protocol

In all patients mechanical ventilation with unimpeded expiration was applied before ventilatory support with controlled expiration. After removal of secretions by tracheal suction the first mode was applied for 15 minutes before volumetric measurements were done. Bloodsampling and measurement of mixed expiratory CO_2-concentration were obtained 40 minutes later. Then the unimpeded ventilatory mode was changed to that with controlled expiration and the procedure described above repeated.

Statistical analysis

Student t-tests were used for paired samples. Linear regression analysis was used. Differences with p-values less than .05 were considered statistically significant.

Results

During unimpeded expirations the shape of the relaxed expiratory flow volume curve was suggestive of flow limitation in all patients. After the peak flow a sudden sharp decline in the expiratory flow was observed. In the 7 patients in whom the interruptor technique was applied, airways compression was established.

The flow-, pressure- and volume-curves against time, of one breath during unimpeded expiration and during controlled expiration of patient no. 6 are shown in the figures 2 and 3 respectively.

Compared with unimpeded expiration, controlled expiration was characterized by an increasing flow during the first part of the expiration. In figure 3 is shown that the early expiratory volume-displacement is slowed down compared with the unimpeded expiration.

The effects of the controlled expiration on respiratory mechanics are shown in table 2.

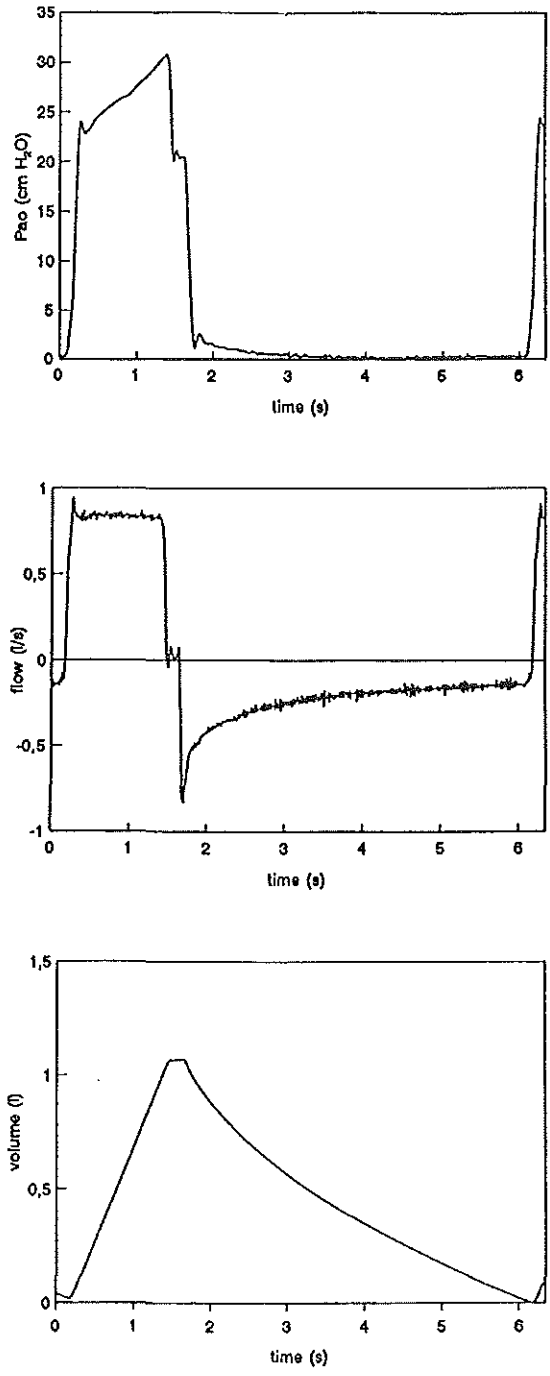

Figure 2 The recording of pressure, flow and volume displacement against time of one breath during conventional ventilatory support of patient no.6

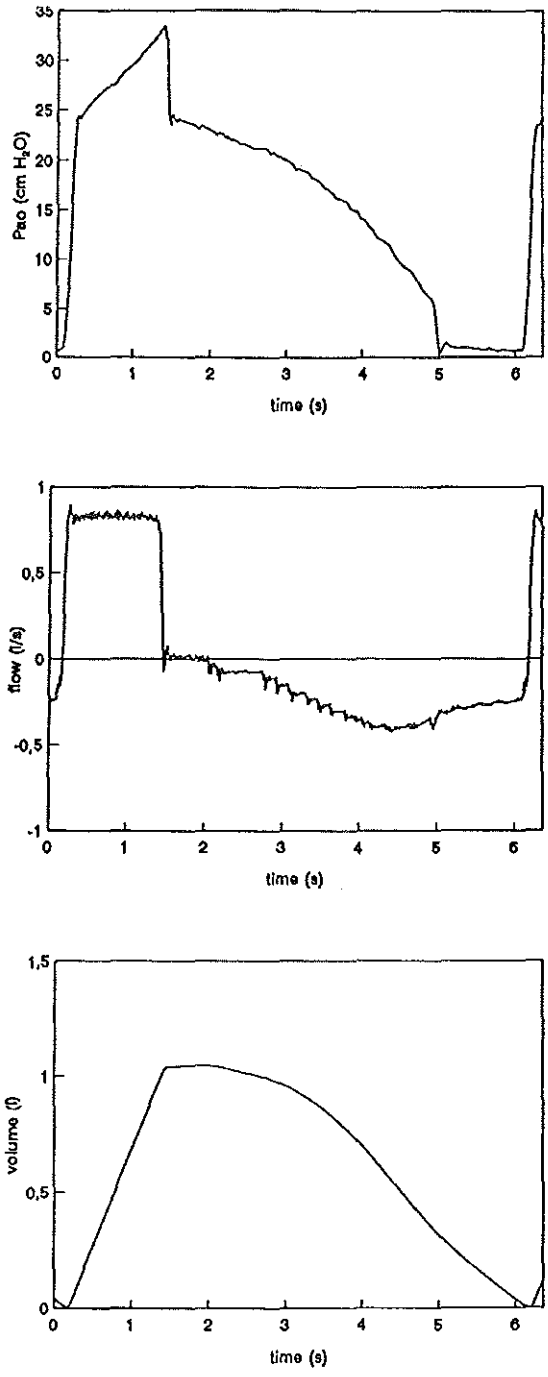

Figure 3 *The recording of pressure, flow and volume displacement against time of one breath during ventilatory support with decelerated expiration of patient no. 6.*

Table 2

Respiratory mechanics

No = 10	Unimpeded expiration (mean ± SD)	Controlled expiration (mean ± SD)
Pendinsp cmH_2O	14.2 ± 3.1	17.5 ± 3.8*
PEEPe cmH_2O	.5 ± .5	.7 ± .5
PEEPi cmH_2O	5.7 ± 2.4	8.0 ± 3.1*
ΔEEV l	.51 ± .42	.82 ± .49**
Vmean l	.24 ± .08	.35 ± .10*

Pendinsp = end-inspiratory pressure; PEEPe = external PEEP; PEEPi = intrinsic PEEP; ΔEEV = end-expiratory lung volume above FRC; Vmean = mean lung volume above ΔEEV during one breathing cycle.

* = $p < .001$ *between unimpeded expiration and controlled expiration*

** = $p < .0001$ *between unimpeded expiration and controlled expiration.*

At a virtually unchanged level of extrinsic PEEP, intrinsic PEEP and consequently total PEEP were significantly increased respectively from 5.7 ±2.4 cm H_2O and 6.2 ±2.5 cmH_2O during unimpeded expiration to 8.0 ±3.1 cmH_2O and 8.7 ±3.0 cmH_2O during controlled expiration (both $p < .001$). The end-expiratory lung volume above FRC, ΔEEV, was increased from .51 ±.42 l during unimpeded expiration to .82 ±.49 l during controlled expiration ($p < .0001$). Controlled expiration was also associated with an increase of the mean lung volume above ΔEEV during one breathing cycle, Vmean ($p < .001$).

The effects of controlled expiration on pulmonary gas-exchange of individual patients are shown in table 3.

Table 3

Effects of decelerated expiration on gas-exchange

Patient no.	Unimpeded expiration			Decelerated expiration		
	PaO_2 kPa	$PaCO_2$ kPa	Vd/Vt %	PaO_2 kPa	$PaCO_2$ kPa	Vd/Vt %
1	9.6	7.3	69	13.6	5.5	60
2	10.3	8.3	66	10.7	7.8	63
3	9.4	5.9	61	9.8	5.0	56
4	9.9	6.6	58	9.8	6.2	57
5	12.3	5.6	57	13.4	5.3	57
6	12.8	4.5	54	14.9	4.0	50
7	16.7	5.0	68	15.8	4.6	62
8	15.9	5.8	48	18.3	5.7	39
9	8.8	5.3	65	10.4	5.1	64
10	9.3	4.8	62	9.2	4.8	62
Mean	11.5	5.9	61	12.6*	5.4*	57**
SD	2.8	1.2	7	3.1	1.0	8

Vd/Vt = physiological dead space

* = $p < .05$ *between unimpeded expiration and decelerated expiration*

** = $p < .01$ *between unimpeded expiration and decelerated expiration*

Significant increases of PaO_2 ($p < .05$) and decreases of $PaCO_2$ ($p < .05$) and Vd/Vt ($p < .01$) were found. The changes of PaO_2 did not correlate with those of respiratory mechanics, whereas positive correlations were found between the changes of $PaCO_2$ and Vd/Vt and those of Vmean expressed as percentage of the value during unimpeded expiration (r-values .67 and .70 respectively p-values both < .05).

In none of the patients a significant fall in blood pressure was observed during controlled expiration.

Discussion

The effects of controlled expiration by regulation of expiratory resistance on respiratory mechanics and pulmonary gas-exchange were studied in mechanically ventilated patients with COPD. Compared to unimpeded expiration, the ventilator mode with controlled expiration did increase the Vmean above ΔEEV and did enhance pulmonary gas-exchange at minor increases of the EEV.

In patients with COPD the rate of lung emptying is diminished due to the decreased lung elastance and the increased airways resistance. It is assumed that in patients with severe COPD during a relaxed expiration compression of peripheral airways occurs leading to flow limitation and a further fall of expiratory flow rate [1, 2]. The presence of airways compression may be suggested by the shape of the flow-volume curves and be established by means of the interruptor technique [9, 10]. In all patients flow-volume curves were suggestive of the presence of airways compression whereas flow spikes were observed in all patients in whom the interruptor technique was applied.

Compression of peripheral airways develops where the pressure surrounding the airway exceeds the distending forces [2, 11]. It has been demonstrated that at a certain lung volume, in the presence of flow limitation, the pressure at the airway opening can be increased to a critical value below which flow is not impeded. It is assumed that at this critical airway opening pressure, the pressure within the airways of peripheral areas of the lung is increased to such an extent that compression of airways in these areas is prevented. A decrease of airways compression will result in a more uniform emptying of lung units and consequently an improvement of gas-exchange.

In this study the César Ventilator (Taema, CFPO, France) was applied which has the facility to control the resistance to flow during the first part of expiration in patients on ventilatory support. This mode allows to control the fall in airway opening pressure during the first 75% of expiration time. In order to achieve deceleration of expiratory volume displacement, a decay of airway opening pressure was applied, resulting in an ascending flow during the first part of expiration (figure 3). This mode of controlled expiration resulted in a slight increase of hyperinflation, associated with a new equilibrium at minor increases of ΔEEV. The ventilator technology did not provide the facility to tune pressure regulation in such a way as to achieve an ascending expiratory flow without increasing end-expiratory lung volumes.

As the interruptor technique could not be applied during the expiratory pressure regulation, we could not determine the effect of this ventilator mode on airways compression. Indirect evidence that the expiratory pressure regulation decreased airways compression may be deduced from the expiratory flow pattern and the early course of the airway opening pressure counteracting the development of a wide pressure gradient between alveoli and airway opening.

As at the pressure regulated mode no control was applied during the last 25% of expiration time, airways compression is assumed to appear during this part of expiration. This allowed the airway opening pressure to fall to zero at end-expiration.

In this study the expiratory pressure regulation was associated with significant increases in PaO_2 and significant decreases in $PaCO_2$ and Vd/Vt. These findings are in agreement with previously published results obtained with the César ventilator [12]. In that study however an expiratory resistance to flow was imposed leading to a square-wave flow pattern. Compared with this investigation, increases of intrinsic PEEP of the same magnitude were reported [12]. As other investigations on expiratory pressure regulation are lacking, the results of our study can only be compared to studies reporting on the effects of external PEEP.

Several studies have been published on the effects of ventilator PEEP on pulmonary gas-exchange [3, 5-7]. Ranieri et al studied 9 mechanically ventilated patients with COPD in whom during ventilator support without external PEEP a mean intrinsic PEEP-level of 9 cmH_2O was found [3]. Application of 15 cmH_2O of ventilator PEEP was associated with an increase of ΔEEV of .60 l without a change in $PaCO_2$. That level of external PEEP, exceeding the intrinsic PEEP-level, resulted in a significant increase of PaO_2, but was found to reduce cardiac output [3]. Lower levels of external PEEP were found to have no effect on bloodgases in that study. Georgopoulos et al also studied 9 mechanically ventilated patients with COPD [6]. In this study a ventilator PEEP-level equal to 86% of the intrinsic PEEP-level was applied. This ventilator PEEP-level resulted in an increase of .12 l of ΔEEV without affecting PaO_2, $PaCO_2$ or dead space. Rossi et al published results of an investigation in 8 patients with COPD [5]. They applied a ventilator PEEP-level equal to 50% of the intrinsic PEEP-level and reported significant decreases in $PaCO_2$ and dead space. That level of external PEEP was also associated with a significant increase of PaO_2 without affecting cardiac output. The effect of external PEEP on ΔEEV was however not reported in that study.

Tuxen studied 6 patients with severe airflow obstruction, in 4 of whom the diagnosis of asthma was made [7]. At 15 cmH_2O of external PEEP an increase in ΔEEV of 1.00 l was observed.

The corresponding elevation of airway pressures resulted in a significant increase in PaO_2, but was found to compromise the circulation of the patients. The effects of external PEEP on $PaCO_2$ or dead space were not determined in that study.

The results of the studies in which a threshold resistor was used, suggest that in patients with COPD only at major elevations of the ΔEEV induced by external PEEP, significant increases in PaO_2 are observed. A beneficial effect of external PEEP on alveolar ventilation was only reported by Rossi et al [5]. The ventilatory support with expiratory pressure regulation applied in this study was found to improve pulmonary gas-exchange at a mean increase in ΔEEV of only .31 l. As in this study cardiac output was not determined, the effect of controlled expiration on oxygen delivery could not be established. The absence of any correlation between the changes in PaO_2 and Vmean may indicate that an increase of mean effective lung area for gas exchange was not the primary cause of the improvement of PaO_2. An abolishment of at least a part of the airways compression during expiration may result in an improvement of the ventilation/perfusion ratio in underventilated lung regions. The correlation between the decrease of $PaCO_2$ and the relative increase of Vmean may be attributed to the decrease of dead space. The controlled expiration probably resulted in a more uniform deflation, thus reducing the number of overinflated lung units at end-expiration. This effect probably explain the decrease of dead space and $PaCO_2$.

In this study the effects of ventilator support with an expiratory pressure regulator were compared to unimpeded expiration in 10 patients with COPD. In contrast to other studies where external PEEP was applied, application of a controlled expiration was associated with a significant enhancement in pulmonary gas-exchange at minor increases in end-expiratory lung volumes.

Further adjustments to the expiratory pressure regulator are required to improve lung emptying and pulmonary gas-exchange in patients with COPD on ventilatory support without increases in end-expiratory lung volumes.

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CHAPTER 10

General Considerations and Summary

General Considerations

The main subject of this thesis was to study respiratory mechanics in patients with Chronic Obstructive Pulmonary Disease (COPD) on ventilatory support and to assess the effects of various expiratory interventions on the respiratory variables both during spontaneous breathing and mechanical ventilation.

Patients

The patient population that is the subject of this thesis consists of patients suffering from severe airway obstruction in whom loss of elasticity of lung tissue is assumed. Although the term COPD may not apply for the condition present in the patients studied, the term was used in this thesis as destruction of elastic tissue of a minor degree is difficult to demonstrate or exclude.

Flow limitation

As one of the features of COPD the expiratory flow is decreased by a reduction in driving pressure and an increase in airway resistance. The increased resistance is, amongst others, related to compression or even collapse of the airways during expiration. This dynamic compression of the airways is known to lead to flow limitation. Flow limitation can be defined as the phenomenon that at a certain lung volume, elevation of driving pressure above a critical level, does not result in an increase of respiratory flow. This can be elucidated by the condition that increments in driving pressure will elevate the pressure surrounding the airways leading to a further narrowing of these airways.

Various ways to detect flow limitation are described in this thesis. Amongst these are the interruptor technique and the isovolume pressure-flow relationship. Flow limitation is commonly encountered in mechanically ventilated patients with COPD in whom the respiratory muscles are relaxed. This can be detected from flow-volume curves when the driving pressure for the expiratory flow is reduced by imposing a positive pressure at airway opening. Flow limitation is of paramount importance as the decreased flow precludes expiration to functional residual capacity within the available expiratory time in most patients. This implicates both during spontaneous breathing and mechanical ventilation the occurrence of dynamic hyperinflation and

intrinsic PEEP, i.e. the pressure gradient between alveoli and airway opening at end-expiration. As at the start of the inspiratory effort the alveolar pressure has to be reduced to airway opening level before flow is initiated, this pressure gradient acts as an inspiratory threshold and increases inspiratory work of breathing.

Expiratory interventions

In this thesis various interventions imposed during expiration have been studied in patients with COPD both during spontaneous breathing and mechanical ventilation. The aim of these studies has been to improve lung emptying and in that way to enhance gas-exchange and to reduce overdistention of the lungs. For these investigations respiratory variables pertaining flow limitation and dynamic hyperinflation were obtained.

In order to influence lung emptying various types of resistors were applied at airway opening. Threshold resistors imposing a fixed positive pressure during the entire expiration were studied in spontaneously breathing patients. Such intervention is well known as positive end-expiratory pressure (PEEP) as these resistors were originally described to prevent the airway opening pressure to fall to ambient pressure at end-expiration. The effects of this threshold resistor on respiratory mechanics in patients with COPD on ventilatory support have been extensively studied. The effect of external PEEP depends on the level of intrinsic PEEP present when the airway opening pressure equals ambient pressure at end-expiration. When a level of external PEEP is imposed, lower then the intrinsic PEEP-level, lung emptying and end-expiratory lung volume remain unaltered. This implicates that the external PEEP counterbalances intrinsic PEEP without affecting iso-volume flows. Such threshold resistors have been incorporated in systems used to maintain a positive pressure at airway opening. In spontaneously breathing patients imposing external PEEP by continuous positive airway pressure (CPAP) has been shown in this thesis to reduce inspiratory work of breathing by counterbalancing intrinsic PEEP. In order to minimize work of breathing a positive pressure at the airway opening equal to intrinsic PEEP has to be applied. It was further shown that when a ventilator is used to impose CPAP in patients with higher ventilatory needs, the mechanical characteristics of the ventilator may have a deleterious effect on work of breathing, which may be of clinical importance.

When a level of external PEEP exceeding the intrinsic PEEP-level is imposed in mechanically ventilated patients, lung emptying is affected due to an increased end-expiratory lung volume.

However the latter is considered hazardous as a further increase in end-expiratory lung volume may jeopardize gas-exchange and respiratory mechanics.

In order to improve lung emptying without further distension of the lungs other types of resistors were used in this thesis. It is assumed that by controlling expiratory flow during mechanical ventilation airways compression leading to flow limitation can be counteracted. For controlling expiratory flow a variable airway opening pressure is applied during expiration. In mechanically ventilated patients a turbulent resistor, applying a variable declining airway opening pressure, was found to counteract airways compression and after a decrease in early expiration, to increase iso-volume flows compared to unimpeded expiration at an unchanged end-expiratory lung volume. Another resistor incorporated in a ventilator was found to improve gas-exchange at minor increases in end-expiratory lung volume. Application of external PEEP at similar increases in end-expiratory lung volume was not found to improve gas-exchange.

From these results, it can be deduced that application of variable airway opening pressure during expiration improves gas-exchange and increases iso-volume flows. Further research is required to establish the pattern of lung emptying associated with the 'best' gas-exchange and respiratory mechanics.

Summary

Mechanical ventilation may be considered as rescue therapy for life threatening respiratory failure due to Chronic Obstructive Pulmonary Disease (COPD).
In many patients ventilatory support is hampered by the altered respiratory mechanics encountered in COPD. The aim of this thesis was to study respiratory mechanics in patients with COPD on ventilatory support and to assess the effects of various expiratory adaptations of this support on the respiratory variables during both spontaneous breathing and mechanical ventilation.

In chapter 1 the alterations of respiratory mechanics in patients with COPD affecting ventilatory support are reviewed. A decrease of expiratory flow, due to a reduction of driving pressure and an increase of resistance, is considered one of the main features of COPD. The consequences during both mechanical ventilation and spontaneous breathing are discussed. The existing adaptations of the equipment used for ventilatory support and weaning purposes which may improve ventilation and gas-exchange in patients with COPD are reviewed.

In chapter 2 the equipment and measurements as applied in this thesis are described. An outline is given of the respiratory mechanics monitoring system for patients on ventilatory support. The system input consists of flow, airway opening pressure and esophageal pressure. The acquisition of derived variables obtained from these parameters is described. Various interventions of ventilatory support applied to obtain specific respiratory variables are reviewed.

In chapter 3 the effects of continuous positive airway pressure (CPAP), applied as mode of weaning from mechanical ventilation, were investigated in patients with COPD. A high airflow system was used to impose a continuous positive pressure at airway opening during both inspiration and expiration. Static intrinsic PEEP-levels were obtained in all patients with the occlusion method applied during breathing without positive pressure. Respiratory work and dynamic intrinsic PEEP-levels were determined during spontaneous breathing with and without positive pressure. Breathing with CPAP was associated with a significant decrease of intrinsic PEEP-levels and inspiratory work of breathing. The decrease of inspiratory work was related to static intrinsic PEEP-levels obtained without application of positive pressure. In patients in whom a CPAP-level in the range of their static intrinsic PEEP-level was applied the reduction

in inspiratory work proved to be most evident. It is concluded that in intubated patients with COPD static intrinsic PEEP-levels can be used to estimate the effect of CPAP.

In chapter 4 a model is described for computation of elastic work of breathing on the basis of respiratory mechanics in patients with COPD. The model was applied to estimate the maximum reduction of elastic work at various levels of CPAP and intrinsic PEEP. The results of the model calculations were compared to the patient measurements described in chapter 3. Model calculations revealed that elastic work of breathing was minimal whenever a CPAP-level equal to the intrinsic PEEP-level was applied. Comparison of the patient measurements to model calculations revealed a similar pattern in reduction of inspiratory work. Absolute values of these reductions were however smaller in the patient measurements. Possible causes of this difference are discussed. None of these however did affect the maximum decreases found at equal CPAP- and intrinsic PEEP-levels. It is concluded that in order to minimize work of breathing in patients with COPD by application of CPAP, the CPAP-level should be adjusted to the static intrinsic PEEP-level of the patient present when no positive pressure is applied.

In chapter 5 the results of studies on additional work of breathing during CPAP provided by both a ventilator and a continuous flow CPAP system in patients who were weaned from mechanical ventilation are described. Additional work and variables derived from the airway and esophageal pressure during ventilator CPAP were compared to those obtained during continuous flow CPAP and related to minute volumes of the patients. At both modes a positive correlation between imposed work and minute ventilation was found. At elevated minute volumes the additional work was increased much more during ventilator CPAP, resulting in a significantly higher additional work compared to that during continuous flow CPAP. These increments in additional work during ventilator CPAP are largely caused by increases in end-expiratory pressure resulting in an elevated inspiratory threshold. The increase of end-expiratory pressure at higher minute volumes was attributed to the flow-dependent resistance of the PEEP-device of the ventilator. As no intrinsic PEEP was present in the patients studied, the increases in end-expiratory pressure were equal comparing airway opening to esophageal pressure. This implicates that the increments in additional work also increase total work of breathing. In conclusion, when the ventilator is used for weaning purposes, the additional work imposed by the expiratory valves should be taken into account.

In chapter 6 a validation of the interruptor method applied to detect flow limitation in spontaneously breathing subjects is described. The expiratory flow pattern post interruption was compared to results obtained from body plethysmography. Using body plethysmography, flow limitation was assumed to be present when expiratory flow decreased while alveolar pressure increased. Data of patients with airflow obstruction with flow limitation, of patients with airflow obstruction without flow limitation and of healthy volunteers were compared. Only in patients with airflow obstruction with flow limitation a spike flow, a flow superimposed on the ongoing alveolar flow, was observed after release of the occlusion. No difference between patients with airflow obstruction without flow limitation and healthy controls was found. It is concluded that the interruptor technique can be used to assess flow limitation during tidal breathing by analysis of the flow pattern post interruption.

In chapter 7 a parameter derived from expiratory flow-volume curves during mechanical ventilation in patients with COPD to assess the degree of airflow obstruction is discussed. The slope of the flow difference during the last 50% of expired volume during mechanical ventilation was calculated and compared to the forced expiratory volume in one second (FEV_1) as a percentage of the predicted value. A close correlation was established between this slope value and the FEV_1. From these results it is concluded that during mechanical ventilation in patients with COPD equivalent information on the degree of airflow obstruction can be obtained from expiratory flow volume curves as from forced expiration.

In chapter 8 results on studies on the effects of an external resistor on lung emptying in patients with COPD who were mechanically ventilated while sedated and paralyzed are reported. Respiratory mechanics were obtained during ventilatory support with and without the resistor. The interruptor method, as was described in chapter 6, was used to assess airways compression. A resistance-level was chosen that generated an external positive end-expiratory pressure (PEEP) without increasing total PEEP. Consequently intrinsic PEEP-level was decreased. At this unchanged total PEEP-level, end-expiratory lung volume proved to be unchanged as well. Comparing the expiratory flow-volume curves at both settings revealed that during controlled expiration, flows were significantly lower during early expiration and higher later in expiration. As these increments in flow were found at iso-volume conditions, they indicate a reduction in effective airways resistance at the second half of expiration. Airways compression was establis-

hed in all patients during unimpeded expiration. During application of the resistance airways compression was no longer detectable. It is concluded that in mechanically ventilated patients with COPD the application of an external resistor can decrease effective resistance by counteracting airways compression without increments in end-expiratory lung volume.

In chapter 9 the effects of controlled expiration on respiratory mechanics and gas-exchange are compared to unimpeded expiration in mechanically ventilated patients with COPD who were sedated and paralysed. In order to control the expiration the expiratory pressure regulated mode of the César ventilator was used. An ascending expiratory flow pattern was generated by a predefined expiratory pressure-time pattern. Compared to unimpeded expiration, PaO_2 increased while $PaCO_2$ and physiological dead space decreased during controlled expiration. Mean volume above end-expiratory lung volume during a breathing cycle and the end-expiratory lung volume increased during controlled expiration. At equivalent increments in end-expiratory lung volume imposed by extrinsic PEEP no improvement of gas-exchange was found. It is concluded that ventilatory support with controlled expiration results in an improvement of gas-exchange which is related to a decrease of early expiratory volume displacement.

Samenvatting

Beademing kan beschouwd worden als levensreddende behandeling van respiratoire insufficientie ten gevolge van Chronisch Obstructief Longlijden (COL). Bij veel patiënten wordt deze ademhalingsondersteuning gehinderd door de veranderde ademmechanica gepaard gaande met COL. Het doel van dit proefschrift was om ademmechanica bij patiënten met COL tijdens ademhalingsondersteuning te bestuderen en de effecten van verschillende expiratoire aanpassingen aan deze ondersteuning op ademhalingsvariabelen, zowel tijdens spontaan ademen als tijdens beademing, te bepalen.

In hoofdstuk 1 wordt een overzicht gegeven van de veranderingen in ademmechanica bij COL die de ademhalingsondersteuning beïnvloeden. Een vermindering van de expiratoire stroomsterkte, veroorzaakt door een verminderde drijvende druk en een verhoogde weerstand, kan beschouwd worden als een van de belangrijkste kenmerken van COL. De gevolgen zowel tijdens beademing als spontaan ademen worden behandeld. Een overzicht wordt gegeven van de bestaande aanpassingen aan de apparatuur, gebruikt tijdens beademing en pogingen tot ontwenning hiervan, welke ventilatie en gaswisseling zouden kunnen verbeteren bij patiënten met COL.

In hoofdstuk 2 worden de apparatuur en de metingen zoals ze in dit proefschrift toegepast zijn beschreven. Een overzicht wordt gegeven van het ademmechanica monitoring systeem voor patiënten tijdens ademhalingsondersteuning. De invoer in het systeem bestaat uit stroomsterkte, luchtwegopening-druk en oesophagus-druk. De afgeleide variabelen verkregen van deze parameters worden besproken. Verscheidene interventies van de ademhalingsondersteuning, toegepast om specifieke ademhalingsvariabelen te bepalen, worden beschreven.

In hoofdstuk 3 werden de effecten van continue positieve luchtweg druk (CPAP), toegepast als modus voor ontwenning van beademing, onderzocht bij patiënten met COL. Een systeem met hoge stroomsterkte werd gebruikt om een continue positieve druk aan de luchtwegopening op te leggen zowel tijdens inademing als uitademing. Statische intrinsieke positieve eind-expiratoire druk (PEEP) niveaus werden bepaald bij alle patiënten met de occlusie-methode, toegepast tijdens ademen zonder positieve druk. Ademarbeid en dynamische intrinsieke PEEP-niveaus werden bepaald tijdens spontaan ademen, met en zonder positieve druk. Ademen met CPAP ging gepaard met een significante afname van het intrinsieke PEEP-niveau en inspiratoire ademarbeid. De afname van inspiratoire ademarbeid was gerelateerd aan het statische intrinsieke

PEEP-niveau bepaald wanneer geen positieve druk werd opgelegd. Bij patiënten, bij wie een CPAP-niveau opgelegd werd dat ongeveer gelijk was aan het statische intrinsieke PEEP-niveau, werd de sterkste afname in inspiratoire ademarbeid gevonden. Hieruit wordt geconcludeerd dat bij geïntubeerde patiënten met COL het statische intrinsieke PEEP-niveau, bepaald als geen positieve luchtwegopenings druk wordt opgelegd, gebruikt kan worden om het effect van CPAP te schatten.

In hoofdstuk 4 wordt een model beschreven om elastische ademarbeid te berekenen op basis van ademmechanica bij patiënten met COL. Het model werd toegepast om de maximale afname in elastische ademarbeid op verschillend niveaus van CPAP en intrinsieke PEEP te schatten. De resultaten van de berekeningen aan het model werden vergeleken met de resultaten van de patiëntenmetingen zoals beschreven in hoofdstuk 3. Modelberekeningen toonden aan dat de elastische ademarbeid minimaal was wanneer een CPAP-niveau gelijk aan het intrinsieke PEEP-niveau werd opgelegd. Vergelijking van de patiëntenmetingen met modelberekeningen liet een gelijk patroon zien wat betreft de afname van ademarbeid. Absolute waarden van deze afnames waren echter kleiner bij de patiëntenmetingen dan de modelberekeningen. Mogelijke oorzaken hiervoor werden besproken. Geen van deze echter beïnvloedden het maximum van de afnamen zoals deze gevonden werden bij gelijke CPAP- en intrinsieke PEEP-niveaus. Geconcludeerd wordt dat, om ademarbeid te verminderen bij patiënten met COL door de toepassing van CPAP, het CPAP-niveau aangepast moet worden aan het statische intrinsieke PEEP-niveau zoals dat aanwezig is als geen positieve druk wordt opgelegd.

In hoofdstuk 5 worden de resultaten van studies naar de additionele ademarbeid tijdens CPAP opgelegd door zowel een ventilator als een continue stroom CPAP systeem beschreven bij patiënten die ontwend werden van beademing. Additionele ademarbeid en variabelen afgeleid van de luchtweg- en oesophagus-druk tijdens ventilator CPAP werden vergeleken met continue stroom CPAP en gerelateerd aan het minuutvolume van de patiënten. Bij beide modus werd een positieve correlatie vastgesteld tussen de additionele ademarbeid en het minuutvolume. Bij hogere minuutvolumes nam de additionele ademarbeid veel meer toe tijdens ventilator CPAP, leidend tot een significant hogere additionele ademarbeid, dan met continue stroom CPAP. Deze toenamen van additionele ademarbeid tijdens ventilator CPAP worden grotendeels veroorzaakt door toenamen van de eind-expiratoire druk leidend tot een hogere inspiratoire drempel. De

verhoogde eind-expiratoire druk bij hogere minuutvolumes werd toegeschreven aan de stroomsterkte-afhankelijke weerstand van de PEEP-klep van de ventilator. Omdat er geen intrinsieke PEEP aanwezig was in de bestudeerde patiënten waren de toenamen van eind-expiratoire druk gemeten aan de luchtwegopening en in de oesophagus gelijk. Dit brengt met zich mee dat de toenamen van additionele ademarbeid ook de totale ademarbeid verhogen. Geconcludeerd wordt dat, wanneer de ventilator gebruikt wordt voor pogingen tot het ontwennen van beademing, rekening gehouden moet worden met de additionele ademarbeid veroorzaakt door de uitademingsklep van de ventilator.

In hoofdstuk 6 wordt een validering van de interruptor-methode, toegepast om stroomsterkte-limitering aan te tonen in spontaan ademende personen, beschreven. Het expiratoire stroomsterktepatroon na een interruptie werd vergeleken met resultaten bepaald uit lichaamsplethysmografie. Gebruik makend van de lichaamsplethysmograaf werd stroomsterkte-limitering verondersteld als de expiratoire stroomsterkte afnam terwijl de alveolaire druk toenam. Resultaten van patiënten met stroomsterkte-beperking en stroomsterkte-limitering zijn vergeleken met resultaten van patiënten met stroomsterkte-beperking zonder stroomsterkte-limitering en van gezonde controles. Uitsluitend bij patiënten met stroomsterkte-beperking en stroomsterkte-limitering werd een supramaximale stroomsterkte, dat wil zeggen een stroomsterkte gesuperponeerd op de doorgaande alveolaire stroomsterkte, waargenomen na opheffen van de occlusie. Geen verschil werd vastgesteld in deze parameter tussen patiënten met stroomsterkte-beperking zonder stroomsterkte-limitering en gezonde controles. Geconcludeerd wordt dat de interruptor-methode gebruikt kan worden om stroomsterkte-limitering aan te tonen tijdens rustig ademen door middel van analyse van het stroomsterkte-patroon na de interruptie.

In hoofdstuk 7 wordt een parameter beschreven, afgeleid van expiratoire stroomsterkte-volume curven tijdens beademing van patiënten met COL, om de mate van stroomsterkte-beperking vast te stellen. De helling van het stroomsterkte-verschil gedurende de laatste 50% van het geëxpireerde volume tijdens beademing werd berekend en vergeleken met het geforceerde expiratoire volume in een seconde ($\dot{FEV}_1$) in percentage van de voorspelde waarde. Een hoog significante correlatie werd vastgesteld tussen het getal voor de helling en de FEV_1. Uit deze resultaten wordt geconcludeerd dat tijdens beademing van patiënten met COL gelijkwaardige informa

tie over de mate van stroomsterkte-beperking verkregen kan worden uit expiratoire stroomsterk te-volume curven als uit geforceerde expiratie.

In hoofdstuk 8 worden de effecten van een externe weerstand op ontlediging van de long beschreven bij patiënten die werden beademd tijdens sedatie en verslapping. Ademmechanica werd bepaald tijdens ademhalingsondersteuning met en zonder de weerstand. De interruptor methode, zoals beschreven in hoofdstuk 6, werd gebruikt om luchtwegcompressie aan te tonen. Een zodanig weerstands-niveau werd gekozen dat een externe positieve eind-expiratoire druk (PEEP) werd gegenereerd zonder verhoging van de totale-PEEP. Hiermee werd het intrinsieke PEEP-niveau verlaagd. Op dit onveranderde totale PEEP-niveau bleek het eind-expiratoire longvolume ook onveranderd. Vergelijking van de expiratoire stroomsterkte-volume curven met en zonder weerstand lieten zien dat tijdens de gecontroleerde expiratie stroomsterktes significant lager waren tijdens de vroege expiratie en hoger in het overblijvende deel. Omdat deze toenamen in stroomsterkte gevonden werden op een gelijk volume niveau, betekenen zij een vermindering van de effectieve weerstand in het tweede deel van de expiratie. Luchtwegcompressie werd vastgesteld bij alle patiënten tijdens vrije expiratie. Tijdens toepassing van de weerstand kon luchtwegcompressie niet meer aangetoond worden. Geconcludeerd wordt dat bij beademde patiënten met COL de toepassing van een externe weerstand de effectieve weerstand kan verminderen door luchtwegcompressie tegen te gaan zonder toenamen in eind-expiratoire longvolumina.

In hoofdstuk 9 worden de effecten op gaswisseling en ademmechanica van gecontroleerde uitademing vergeleken met vrije uitademing bij beademde patiënten met COL tijdens sedatie en verslapping. Om de uitademing te controleren werd de gestuurde expiratoire druk beademingsmodus van de César ventilator toegepast. Een stijgende expiratoire stroomsterkte werd gegenereerd volgens een van te voren vastgelegd expiratoire druk-tijd verloop. Vergeleken met vrije uitademing nam de arteriële zuurstofspanning toe, en namen de arteriële koolzuurspanning en fysiologische dode ruimte gedurende gecontroleerde expiratie af. Het gemiddelde volume boven het eind-expiratoire longvolume tijdens een ademhalingscyclus en het eind-expiratoire longvolume namen toe tijdens gecontroleerde uitademing. Bij dezelfde toenamen in longvolumina opgelegd door extrinsieke PEEP werd geen verbetering in de gaswisseling aangetoond. Geconcludeerd wordt dat ademhalingsondersteuning met gecontroleerde uitademing de gaswisseling in

de long kan verbeteren gerelateerd aan een afname van de vroege expiratoire volumeverplaatsing.

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en Kristien...

Curriculum vitae

De auteur van dit proefschrift werd op 17 juli 1969 geboren te Bergen op Zoom. In 1987 werd het diploma Gymnasium β behaald waarna gestart werd met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. In 1989 werd begonnen met een onderzoek op de afdeling Longfunctie van het Academisch Ziekenhuis Rotterdam Dijkzigt naar de 'modellering van methacholine log-dose response-curven' (begeleider: Prof.dr. J.M. Bogaard) in het kader van een onderzoek naar 'de effecten van fluticasone-dipropionaat op de bronchiale hyperreactiviteit' (projectuitvoerder: Drs. S.E. Overbeek, longarts). Het doctoraal examen werd in januari 1992 behaald.

Vanaf januari 1992 tot april 1995 was de auteur verbonden aan de afdeling Beademing/Interne Intensive Care van het Academisch Ziekenhuis Rotterdam Dijkzigt (hoofd: Prof.dr. C. Hilvering) waar met financiële steun van het Nederlands Astma Fonds het in dit proefschrift beschreven onderzoek (begeleiders: Prof.dr. J.M. Bogaard, Dr. B. van den Berg) werd verricht.

Aansluitend werden de co-assistentschappen vervuld en werd gewerkt aan de afronding van dit proefschrift.

In januari 1997 zal gestart worden met de Interne vooropleiding in het Sint Franciscus Gasthuis te Rotterdam (opleider: Dr. H.L.S.M. Tjen), in het kader van de opleiding tot arts voor Longziekten en Tuberculose aan het Academisch Ziekenhuis Rotterdam (opleider: Prof.dr. H.C. Hoogsteden).