RESPIRATORY MECHANICS IN PATIENTS WITH COPD ON VENTILATORY SUPPORT

RESPIRATOIRE MECHANICA BIJ PATIËNTEN MET COPD TIJDENS ADEMHALINGSONDERSTEUNING

Lourens, Marlies Sandra

Respiratory mechanics in patients with COPD on ventilatory support.
Thesis Erasmus University Rotterdam. -With ref.- With summary in Dutch.
ISBN 90-73235-84-7

Cover: "Non puede más, el viejo vapor" – "he's had it, the old smook"
Jaime De Cordoba, 2001

Photographs: Ina Daniels

Printed by: Optima Grafische Communicatie, Rotterdam

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RESPIRATOIRE MECHANICA BIJ PATIËNTEN MET COPD TIJDENS ADEMHALINGSONDERSTEUNING

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.ir. J.H. van Bemmel
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 20 juni 2001 om 13.45 uur

door

Marlies Sandra Lourens

Geboren te Haan (Duitsland)

PROMOTIECOMMISSIE

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Dr. B. van den Berg

The work presented in this thesis was performed at the Department of Respiratory and Intensive Care Medicine of the Erasmus Medical Centre Rotterdam. The Netherlands Asthma Foundation is gratefully acknowledged for their financial support of this work.

Printing of this thesis was kindly supported by AstraZeneca, GlaxoWellcome, Boehringer Ingelheim, Janssen Cilag, Merck Sharp & Dome, Novartis Pharma, Organon Teknika, Siemens and the Netherlands Asthma Foundation.

VOOR MIJN OUDERS

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Erasmus Medical Centre Rotterdam

COPD

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality throughout the world. Approximately 6 % of deaths in men and 4 % of deaths in women are due to COPD[1]. COPD currently ranks as number six in the global impact of disease scale and is expected to rise to number three by the year 2020[2]. In the Netherlands it already is the third cause of death[3]. The major cause of COPD is cigarette smoking. The percentage of smokers in the Netherlands is among the highest in Europe[4].

COPD is defined physiologically as chronic airflow obstruction and may be due to a mixture of emphysema and peripheral airway obstruction from chronic obstructive bronchitis. Emphysema is a pathological diagnosis characterised by destruction of alveolar walls resulting in abnormal and permanent enlargement of airspaces and loss of lung elasticity, with consequent obstruction of peripheral airways[1]. Chronic obstructive bronchitis is due to obstruction of peripheral airways as a result of an inflammatory response[1]. The population of patients studied in this thesis consists of patients in whom loss of elasticity of lung tissue is assumed to be present. However, this assumption is based on clinical and lung function findings, since destruction of elastic tissue is difficult to demonstrate in a living person.

The most characteristic symptoms in patients with COPD are breathlessness, cough and increased sputum production[5-7]. Other symptoms as wheezing, chest tightness, poor sleep quality, haemoptosis and neuropsychiatric abnormalities are less common[8-11].

In patients with severe COPD acute exacerbations are frequent; an overall prevalence of 1.3 -1.5 exacerbations per year per patient has been reported[12,13]. COPD exacerbations result in disturbed respiratory physiology that can lead to respiratory failure requiring hospitalisation and even intubation and mechanical ventilation[12]. Hospital mortality ranges from 10 to 30% and is even higher in the patients requiring mechanical ventilation[14-17]. Severely altered respiratory mechanics are the major cause of the unfavourable outcome of mechanical ventilation in these patients. The studies described in this thesis are aimed at both detection and improvement of the disturbed respiratory mechanics in patients with COPD during mechanical ventilation.

ALTERED RESPIRATORY MECHANICS

During mechanical ventilation, inspiration is imposed by the ventilator, while expiration is passive and depends on the patient's respiratory mechanics. In mechanically ventilated patients with COPD, expiration can be severely hampered.

During passive expiration the driving force to expire the air out of the lungs is the elastic recoil pressure of the respiratory system, while the opposing force is the airways resistance. In patients with COPD driving pressure is reduced, due to loss of elastic recoil of the lung tissue. On the other hand airways resistance is increased. This increase in resistance is amongst others related to the loss of elastic support of the airways and the inward elastic recoil pressure of the thoracic cage, which may lead to compression of the airways during expiration[18,19] (see Chapter 2). A consequence of airways compression is flow limitation[20]. As a result of flow limitation the lung may not completely empty prior to the next inspiration, which results in dynamic hyperinflation[21]. Dynamic hyperinflation is associated with a positive alveolar pressure at end-expiration, which is called intrinsic positive end-expiratory pressure (iPEEP)[22].

COMPLICATIONS

Dynamic hyperinflation and thus iPEEP have deleterious side effects. With dynamic hyperinflation lung volume and intrathoracic pressure increase, which results in cardiovascular compromise[21,23]. Furthermore, dynamic hyperinflation results in overdistention of the already fragile lung tissue, which may lead to lung damage (barotrauma)[24]. The presence of iPEEP is associated with a significant increase in the work of breathing[21,25]. IPEEP acts as an inspiratory threshold; the patient must first generate enough pressure to overcome iPEEP before inspiratory flow can be initiated. At the same time, respiratory muscle efficiency is decreased due to hyperinflation[26]. Furthermore, gas exchange is impaired due to overdistention of the lungs causing ventilation / perfusion mismatch[27].

The combination of these factors causes that mechanical ventilation in patients with COPD is often cumbersome and that these patients are at risk of difficult weaning and chronic ventilator dependency.

ASSESSMENT OF DISTURBED RESPIRATORY MECHANICS

In view of the difficulties encountered in mechanical ventilation and weaning, monitoring of respiratory mechanics is important. By gaining insight in the patient's respiratory condition and patient-ventilator interaction, ventilator settings and medical treatment can be optimised. Many studies have addressed the issue of the mechanical properties of the respiratory system during lung inflation. However, data obtained during inspiration are severely affected by the mode and setting of the ventilator. Furthermore, in patients with COPD the major underlying problem leading to respiratory failure is the disturbed expiration. The assessment of respiratory mechanics during relaxed expiration with simple tools, in clinical settings, has been rather unsuccessful so far.

In spontaneously breathing nonintubated patients, the maximal expiratory flow volume curve and the forced expiratory volume in 1s are the mainstay in the assessment of lung mechanics during expiration. In mechanically ventilated patients forced expiration is not feasible. Nevertheless, the flow-volume curve as means of describing expiration remains theoretically appealing. Also practically the flow-volume curve is simple to obtain, since in the current generation of ventilators, respiratory variables such as flow, volume and pressure are displayed on a screen on-line and flow-volume relationships are easily visualised.

IMPROVING RESPIRATORY MECHANICS

Various methods have been proposed to improve respiratory mechanics and gas-exchange in mechanically ventilated patients with COPD. The basic principle in these studies is to counteract airways compression and consequently reduce flow limitation, hyperinflation and iPEEP.

It is well known that spontaneously breathing patients with COPD relief dyspnoea by pursing their lips during expiration. Several studies have suggested that pursed lip breathing decreases airways compression[28-32]. However, mechanically ventilated patients are unable to exert pursed lip breathing due to the presence of a tube. Consequently, other methods of applying a positive pressure at the mouth have been developed. In clinical practise the application of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) are most frequently used. Although these methods decrease the work of breathing, neither of these methods has been reported to counteract airways compression or improve lung emptying without increasing the end-expiratory lung volume[33-36]. An other expiratory pressure regulation method is the diminished early expiratory flow (DEEF)[37]. In mechanically ventilated pigs this method was shown to improve gas-exchange, however, this could not be confirmed in patients[37, 38]. More promising results stem from a preliminary study about the application of an external resistance during expiration[39]. This study showed in mechanically ventilated patients with COPD, that application of an external expiratory resistance could counteract airways compression and reduce flow limitation.

OUTLINE OF THE THESIS

The two main questions of this thesis are :

- How can we measure respiratory mechanics with simple tools at the bedside in mechanically ventilated patients with COPD ?
- Can we improve the disturbed respiratory mechanics / lung emptying in patients with COPD on ventilatory support ?

The studies described in the chapters 3 until 7 deal with the first question, while the chapters 8 until 10 apply to the second question.

CHAPTER 2 is an introduction to the underlying mechanisms of flow limitation, with emphasis on mechanically ventilated patients. Furthermore, an overview of detection methods and modalities of influencing of flow limitation is given.

CHAPTER 3 describes the feasibility of the expiratory flow-volume curve as a measure of respiratory mechanics during ventilatory support; to what extent the shape of the flow-volume curve is affected by external elements ?
CHAPTER 4 describes the applicability of a time constant determined from the expiratory flow-volume curve in mechanically ventilated patients with and without COPD.
CHAPTER 5 gives account of the feasibility of the expiratory time constant in patients with COPD during ventilatory support without sedation and muscle relaxants.
CHAPTER 6 shows a new technique (fuzzy clustering) to assess time constants and time constant behaviour during expiration in mechanically ventilated patients.
In CHAPTER 7 three methods are compared for the detection of flow limitation in mechanically ventilated patients: the resistance method, the negative expiratory pressure method and the interrupter method.
CHAPTER 8 describes the effect of application of various expiratory resistance levels on lung emptying in mechanically ventilated patients with COPD.
In CHAPTER 9 the effect of an individually adapted level of expiratory external resistance on gas exchange is described in mechanically ventilated patients with COPD.
CHAPTER 10 deals with the question if in intubated patients with COPD application of an external resistance could produce the same beneficial effects as pursed lip breathing on breathing pattern and gas exchange.
In CHAPTER 11 the general considerations and a summary of the thesis are presented.

REFERENCES

1. Barnes P. Managing Chronic Obstructive Pulmonary Disease: Science Press Limited, London, UK, 1999.
2. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998; 4:1241-3.
3. Rutten-van Mölken MP, Postma MJ, Joore MA, Van Genugten ML, Leidl R, Jager JC. Current and future medical costs of asthma and chronic obstructive pulmonary disease in The Netherlands. Respir Med 1999; 93:779-87.
4. Thie M. De roker als sociale outcast. NRC Handelsblad 2001; Jaargang 31:nr 111;2.
5. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 154:1726-34.
6. Mahler DA, Tomlinson D, Olmstead EM, Tosteson AN, O'Connor GT. Changes in dyspnea, health status, and lung function in chronic airway disease. Am J Respir Crit Care Med 1995; 151:61-5.
7. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995; 8:1398-420.
8. Agusti A. The science of symptoms in chronic obstructive pulmonary disease. Eur Repir Rev 1999; 9:160-164.
9. Calverley PM, Brezinova V, Douglas NJ, Catterall JR, Flenley DC. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis 1982; 126:206-10.
10. Cormick W, Olson LG, Hensley MJ, Saunders NA. Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. Thorax 1986; 41:846-54.
11. Group NOTT. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980; 93:391-8.
12. Calverley P, Rennard S, Agusti A, et al. Current and future management of acute exacerbations of chronic obstructive pulmonary disease. Eur Respir Rev 1999; 9:195-205.
13. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106:196-204.
14. Connors AF, Jr., Dawson NV, Thomas C, Harrell FE, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute

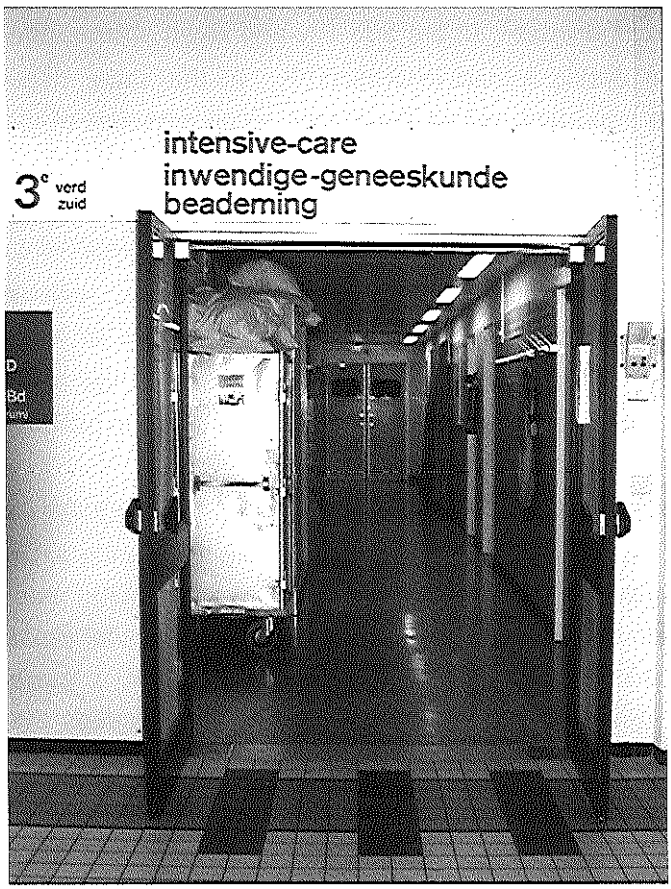
exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996; 154:959-67.

15. Hudson LD. Survival data in patients with acute and chronic lung disease requiring mechanical ventilation. Am Rev Respir Dis 1989; 140:S19-24.
16. Moser KM, Shibel EM, Beamon AJ. Acute respiratory failure in obstructive lung disease. Long-term survival after treatment in an intensive care unit. Jama 1973; 225:705-7.
17. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. Jama 1995; 274:1852-7.
18. West J. Pulmonary pathophysiology - the essentials. Baltimore, U.S.A.: The Williams & Wilkins Company, 1977:59-91.
19. Mead J, Agostoni E. Dynamics of breathing. Handbook of physiology. Vol. 1. Washington DC: American Physiological Society, 1964:411-476.
20. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 1967; 22:95-108.
21. Gladwin MT, Pierson DJ. Mechanical ventilation of the patient with severe chronic obstructive pulmonary disease. Intensive Care Med 1998; 24:898-910.
22. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. Am Rev Respir Dis 1982; 126:166-70.
23. Ranieri VM, D'Ambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. Eur Respir J 1996; 9:1283-92.
24. Keith RL, Pierson DJ. Complications of mechanical ventilation. A bedside approach. Clin Chest Med 1996; 17:439-51.
25. Ranieri VM, Mascia L, Petruzzelli V, Bruno F, Brienza A, Giuliani R. Inspiratory effort and measurement of dynamic intrinsic PEEP in COPD patients: effects of ventilator triggering systems. Intensive Care Med 1995; 21:896-903.
26. Decramer M. Hyperinflation and respiratory muscle interaction. Eur Respir J 1997; 10:934-41.
27. Wrigge H, Putensen C. What is the "best PEEP" in chronic obstructive pulmonary disease? Intensive Care Med 2000; 26:1167-9.
28. Barach A. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br J Dis Chest 1968; 62:36-40.

29. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. Chest 1992; 101:75-8.
30. Ingram R, Schilder D. Effect of pursed lips expiration on the pulmonary pressure-volume relationship in obstructive lung disease. Am J Respir Crit Care Med 1967; 96:381-388.
31. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970; 28:784-9.
32. Thomam R, Stoker G, Ross J. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966; 93:100-106.
33. van den Berg B, Stam H, Bogaard JM. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 1991; 4:561-7.
34. van den Berg B, Aerts JGJV, Bogaard JM. Effect of continuous positive airway pressure (CPAP) in patients with chronic obstructive pulmonary disease (COPD) depending on intrinsic PEEP levels. Acta Anaesthesiol Scand 1995; 39:1097-102.
35. Marini JJ. Should PEEP be used in airflow obstruction?. Am Rev Respir Dis 1989; 140:1-3.
36. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 1988; 65:1488-99.
37. Gültuna I, Huygen PE, Ince C, Strijdhorst H, Bogaard JM, Bruining HA. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Intensive Care Med 1996; 22:539-45.
38. van Rooyen W. Respiratory and hemodynamic effects of dimished expiratory flow during artificial ventilation. Thesis; Rotterdam, The Netherlands: Erasmus University Rotterdam, 1986.
39. Aerts JGJV, van den Berg B, Bogaard JM. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10:550-6.

CHAPTER 2

MECHANISMS, DETECTION AND INFLUENCING OF FLOW LIMITATION IN PATIENTS WITH COPD DURING MECHANICAL VENTILATION.



"3-Zuid Beademing", department of Intensive Care

MECHANISMS

AIRWAYS COMPRESSION AND FLOW LIMITATION

Already in the 19th century, it was recognised that the increased expiratory airways resistance could be very disabling to patients with severe airway disease, since increased effort in breathing only resulted in a limited increase in ventilation[1]. In 1892, Einthoven was the first to hypothesise that in these patients during forced expiration flow limitation occurred due to compression of the intrathoracic airways[2]. In the 50's Fry and Hyatt showed the presence of flow limitation during forced expiration[3-6]. In the same decade, Dayman described the important role of the elastic recoil pressure of the lung in this process[7].

As we know now, COPD is pathologically characterised by destruction of alveolar walls, resulting in abnormal and permanent enlargement of air spaces and loss of lung elasticity[8]. Furthermore an increased resistance is found which is related to both inflammatory processes as well as to the diminished elastic support[9]. The combination of these features is the basis for airways compression with consequently flow limitation, as found in patients with COPD.

One of the ways to describe airways compression is the equal pressure point concept[10]. This concept is based on the theory that during expiration a point exists in the intrathoracic airways, at which the intraluminal pressure (i.e. the pressure within the airways) is equal to the extraluminal pressure (i.e. the pressure surrounding the airways; the intrapleural pressure). Airways compression develops if the extraluminal pressure exceeds the intraluminal pressure.

Equal Pressure Point: intraluminal pressure = extraluminal pressure
Airways compression: intraluminal pressure < extraluminal pressure

During expiration a pressure gradient exists within the airways; in the bronchioli intraluminal pressure approaches alveolar pressure (Palv) and it decreases to atmospheric pressure at the mouth. The alveolar pressure is the driving pressure which causes gas to flow through the airways from alveoli to

mouth. The alveolar pressure can be regarded as the sum of pleural pressure (Ppl) and elastic recoil pressure of the lungs ($P_{L,el}$).

$$Palv = Ppl + P_{L,el}$$

The pleural pressure is equal to the extraluminal pressure and is determined by the pressure exerted by the thoracic wall and the respiratory muscles.
During relaxed expiration, Ppl is normally negative in sign in relation to mouth atmospheric pressure, however, during rapid and forced expiration Ppl is positive in sign, due to the inward force exerted by the respiratory muscles. During relaxed expiration a positive Ppl can only be present if the thoracic wall directs an inward force. This occurs during expiration at lung volumes in the range of the upper 40% of vital capacity[11] (Figure 1). In patients with COPD this is common because of the combination of an elevated elastic equilibrium volume and dynamic hyperinflation (see later).

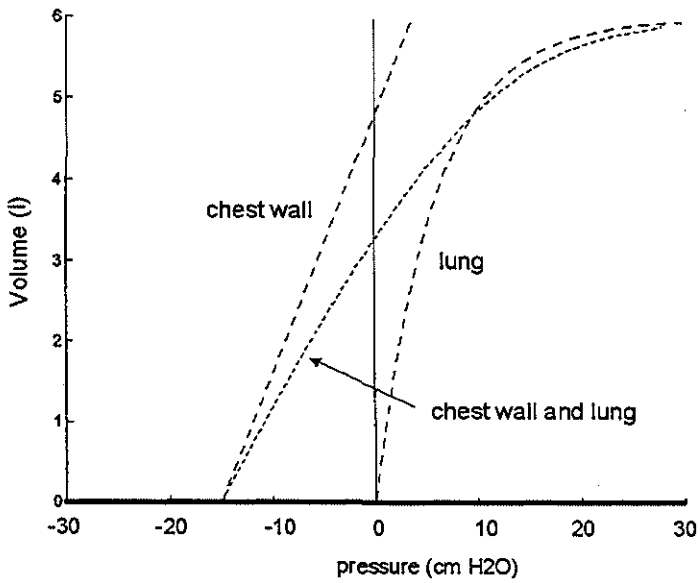


Figure 1. Pressure volume diagram for chest wall and lung. The volume at elastic equilibrium (VEE) is given by the intersection of the pressure-volume curve of chest wall and lung and the volume axis.

As Palv is the total pressure drop from alveoli to mouth, it follows that the pressure drop from the alveoli to some point within the airway must equal

$P_{L,el}$. At this point the pressure within the airways is equal to Ppl, i.e. the equal pressure point. In this concept, $P_{L,el}$ is considered the driving pressure from alveoli to EPP and Ppl is the remaining driving pressure from EPP to mouth. Upstream from the EPP, intraluminal pressures exceed Ppl, and since extraluminal pressures are equal to or little less than Ppl, the airway is distended. Downstream from the EPP, the airways will be compressed since intraluminal pressure decreases towards the mouth, while the extraluminal pressure only minimally decreases.

upstream :	intraluminal pressure > extraluminal pressure
EPP:	intraluminal pressure = extraluminal pressure
downstream:	intraluminal pressure < extraluminal pressure

In healthy subjects during relaxed expiration no airways compression develops, while Ppl is negative and no EPP occurs in the airways[10]. Once Ppl increases above atmospheric, the EPP starts to be present at the thorax aperture. If Ppl increases further (e.g. in forced expiration), the EPP will move upstream into the intrathoracic deformable airways and airways compression can occur.
In contrast to healthy subjects, in patients with COPD, airways compression can even be found during relaxed expiration. This can be explained by two factors influencing each other: a positive Ppl during relaxed expiration and a decreased $P_{L,el}$ in these patients. During relaxed expiration, Ppl is determined by the recoil pressure of the thoracic wall. In case of hyperinflation Ppl is directed inward. Furthermore, in patients with COPD, the diminished elastic recoil pressure of the lungs results in an EPP more peripherally, i.e. in the more collapsible airways.

Flow limitation is a consequence of airways compression. Flow limitation can be defined as an unaltered flow at increasing driving pressure at a certain lung volume.
Two discrete physical phenomena appeared to be associated with flow limitation; wave-speed -and viscous flow limitation[12-14]. Wave speed limitation occurs when in an airway the flow velocity becomes equal to the propagation velocity of a pressure pulse, and is determined by cross-sectional area and elastic properties of the airway wall. This mechanism is present during the

initial phase of forced expiration. In the later part of forced expiration, at low lung volumes, and most likely during tidal breathing in patients with COPD, flow limitation can described as viscous flow limitation.

DYNAMIC HYPERINFLATION AND INTRINSIC POSITIVE END EXPIRATORY PRESSURE

Flow limitation is considered a major contributor to the development of dynamic hyperinflation and intrinsic positive end expiratory pressure (iPEEP). In healthy adults breathing at normal rates, functional residual capacity (FRC) is defined by the point of zero net static recoil pressure of the respiratory system, at which the inward elastic recoil forces of the lung equal the opposite outward recoil forces of the chest wall, in that case the FRC equals VEE[15]. In patients with COPD, the elastic equilibrium volume is elevated, as the elastic recoil pressure of the lung is decreased and the chest wall compliance is within normal limits[16]. This is called static hyperinflation. Furthermore, in patients with flow limitation, the lung may not empty completely prior to the next inspiration, in that case expiration is terminated at a volume above the static relaxation volume. This is called dynamic hyperinflation[17-20]. Because of the combination of an elevated elastic equilibrium volume and dynamic hyperinflation, the thoracic wall exerts an inward force, resulting in a positive intra pleural pressure throughout expiration, causing further airways compression, flow limitation and dynamic hyperinflation. This results in progressive increases in lung volumes[17].
Dynamic hyperinflation also increases with larger minute volumes, decreased expiratory time (insufficient time for complete exhalation), increased airway resistance and higher lung compliance[17, 20, 21].

IPEEP refers to the state of elevated elastic recoil pressure of the respiratory system at end-expiration that occurs in the dynamically hyperinflated lung[17, 22, 23] . This means that at end-expiration a pressure gradient still exists between alveoli and airway opening (figure 2). This elevated end-expiratory alveolar pressure has also been called auto-PEEP or occult-PEEP[19, 20]. This designation has been derived from ventilator terminology: the ventilator can impose a positive pressure at the airway opening at end-expiration (extrinsic PEEP). In the situation of iPEEP or auto-PEEP, the positive end-expiratory

pressure is not imposed by the ventilator, but is the result of disturbed respiratory mechanics of the patient self (auto/intrinsic). The term "occult" PEEP is used because during uninterrupted breathing iPEEP was not detected at the airway opening.

Although iPEEP can occur in spontaneously breathing patients, high levels of iPEEP are predominantly found during ventilatory support. The level of iPEEP is determined by the rate of lung emptying (expiratory time constant), tidal volume and expiratory time[21]. Spontaneously breathing patients will adjust their breathing pattern in order to obtain the lowest intrinsic PEEP level. In patients on controlled mechanical ventilation, both expiration time and tidal volume are imposed by the ventilator. When mechanical ventilation is applied aiming at normoventilation (a normal PaCO2), this may result in high iPEEP.

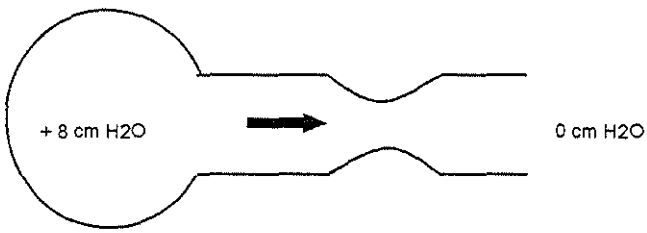


Figure 2. A schematic example of an alveolus and airway with dynamic airways compression. Positive end-expiratory pressure (PEEPi); at end-expiration a pressure gradient still exists between alveoli and airway

COMPLICATIONS OF DYNAMIC HYPERINFLATION AND IPEEP

Dynamic hyperinflation and iPEEP may have deleterious effects. In patients on controlled mechanical ventilation iPEEP may cause cardiovascular compromise and barotrauma, while in spontaneously breathing patients it may substantially increase the work of breathing. Furthermore gas-exchange may be impaired due to increased dead space ventilation[24].

Cardiovascular compromise

With hyperinflation, intrathoracic pressure is increased, venous return is impaired and the right ventricle and pulmonary veins are mechanically compressed[17, 25, 26]. As a consequence left ventricular preload and cardiac output are reduced. Furthermore central venous and pulmonary artery occlusion pressures are elevated as a result of the increased intrathoracic pressure. Dynamic hyperinflation may even result in pulseless electrical activity (PEA). Several case reports exist of patients with COPD who develop PEA and do not respond to resuscitation, but pick up a pulse after

resuscitation efforts have been discontinued[27-31]. In these patients, discontinuation of mechanical ventilation allowed full exhalation, resulting in a decrease in intrathoracic pressures, with consequently enhanced venous return and restoration of cardiac output[19].

Barotrauma

Dynamic hyperinflation causes overdistention of the already fragile lung parenchyma in COPD. This may lead to alveolar disruption and extra-alveolar air, which may dissect into the pulmonary interstitium, via the bronchovascular sheath into the mediastinum[32]. Also alveolar disruption at the visceral pleura can develop resulting in pneumothorax.

Work of breathing

The presence of iPEEP is associated with a significant increase in the work of breathing (WOB). IPEEP acts as an inspiratory threshold; the patient must first generate enough pressure to overcome PEEPi before inspiratory flow can be initiated. At the same time, respiratory muscle efficiency is decreased due to hyperinflation[33-35]. This discrepancy between workload and capacity often results in difficult weaning from the ventilator.

Gas exchange

The ventilation-perfusion imbalance is the main determinant of the abnormal gas exchange in patients with COPD[24, 36, 37]. In patients with severe COPD also a reduced diffusion capacity for CO can be found, attributed partly to reduced alveolo-capillary surface area and also to the reduced alveolar PO_2 in lung regions with low a ventilation/perfusion ratio[36] .

DETECTION

Because of the severely hampered respiratory mechanics, patients with COPD are at risk of complicated mechanical ventilation, difficult weaning and chronic ventilator dependency. Therefore, monitoring of respiratory mechanics in the patients is crucial. By gaining insight in the patient's respiratory condition

and patient-ventilator interaction, ventilator settings and medical treatment can be optimised, resulting in a more favourable outcome.

DETECTION OF HYPERINFLATION AND IPEEP

The presence of hyperinflation and iPEEP should be suspected in all patients with COPD undergoing mechanical ventilation. Clinical circumstances in which iPEEP should be suspected are the presence of unexplained tachycardia, hypotension or PEA, especially at the onset of mechanical ventilation[17]. During support ventilation, the presence of iPEEP should be suspected when the patient's inspiratory efforts do not trigger airflow from the ventilator every time (missed inspiratory efforts).

In the current generation of mechanical ventilators, respiratory variables such as flow, volume and pressure are often displayed on a screen. The presence of iPEEP can be assumed either by inspection of the tidal flow versus time record, if the expiratory flow remains above zero until the onset of the next inflation or by inspection of the tidal expiratory flow-volume loop, if the terminal part of expiration is truncated (figure 3).

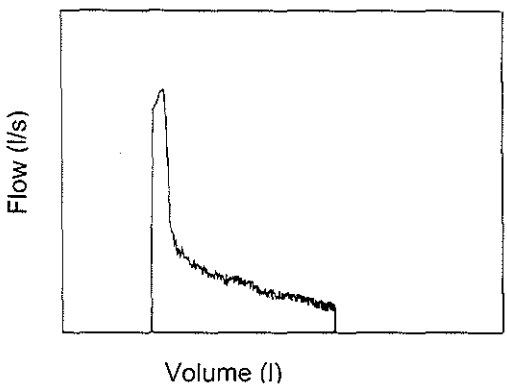


Figure 3. An expiratory flow-volume curve of a patient with COPD. The presence of iPEEP can be suspected by the truncated terminal part of the flow-volume curve.

Besides the above mentioned qualitative methods, hyperinflation and iPEEP can also be quantified. The absolute end expiratory volume, composing of FRC and end-expiratory volume above FRC (ΔEEV), can be measured using the dilution method[38]. However, this method provides only total volume levels and does not give absolute FRC or ΔEEV. In patients with COPD, this method requires very long wash-in periods, in view of the airways compression and is therefore less suitable in these patients. An easy method to assess the end-

expiratory lung volume above FRC is the technique of prolonged expiration[26]. By prolonging passive expiration, the respiratory system is allowed to reach it's relaxation volume. The difference in expired volumes between tidal breathing and prolonged passive expiration is the dynamic hyperinflated volume or ΔEEV (end-expiratory volume above FRC) (figure 4).

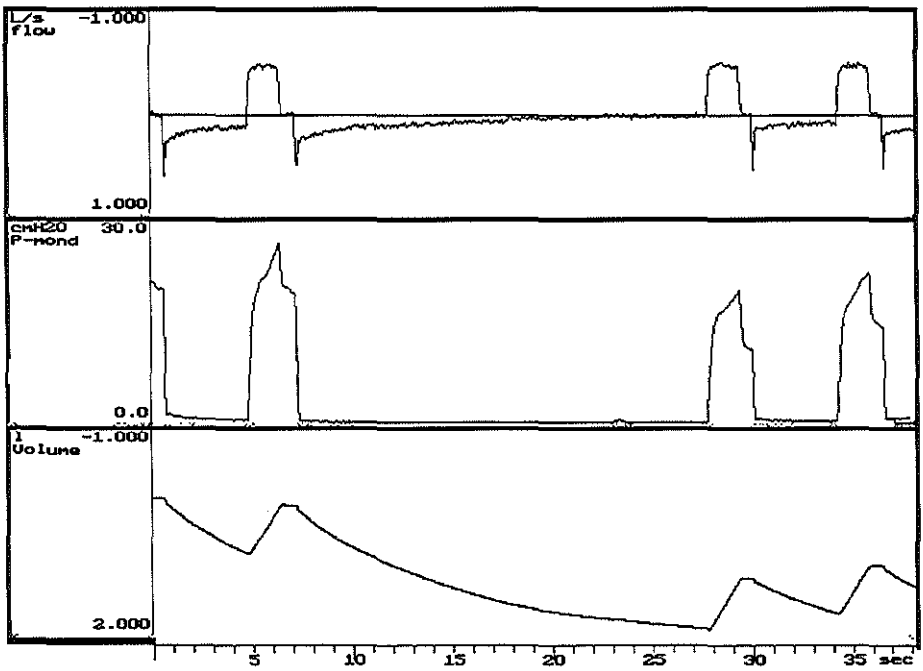


Figure 4. The technique of prolonged expiration to assess the end-expiratory volume above FRC (ΔEEV). The difference in expired volumes between tidal breathing and prolonged passive expiration is the ΔEEV.

The presence of iPEEP can be determined both during static and dynamic conditions. The static iPEEP is measured while occluding the airway opening at end-expiration[19-21]. Most modern ventilators are equipped with an end-expiratory occlusion button to perform this manoeuvre. The method is based on the assumption that during occlusion of the airway, equilibration of the pressures within the respiratory system will occur and consequently the pressure measured at airway opening will reflect the end-expiratory alveolar pressure. If iPEEP is present, after end-expiratory airway occlusion the pressure at the airway opening increases till an apparent plateau is reached,

usually within 3-5 sec. The plateau pressure reflects total PEEP being the sum of iPEEP and extrinsic PEEP (figure 5). In case no ventilator PEEP is applied the plateau pressure is almost equal to the static iPEEP (a low level of ePEEP remains due to the pressure gradient over the ventilator circuit and the expiratory valve of the ventilator). If the patient interferes with muscle activity, the end-expiratory occlusion measurement is difficult to interpret[39]. Measurements in sedated or paralysed patients are, therefore, more reliable.

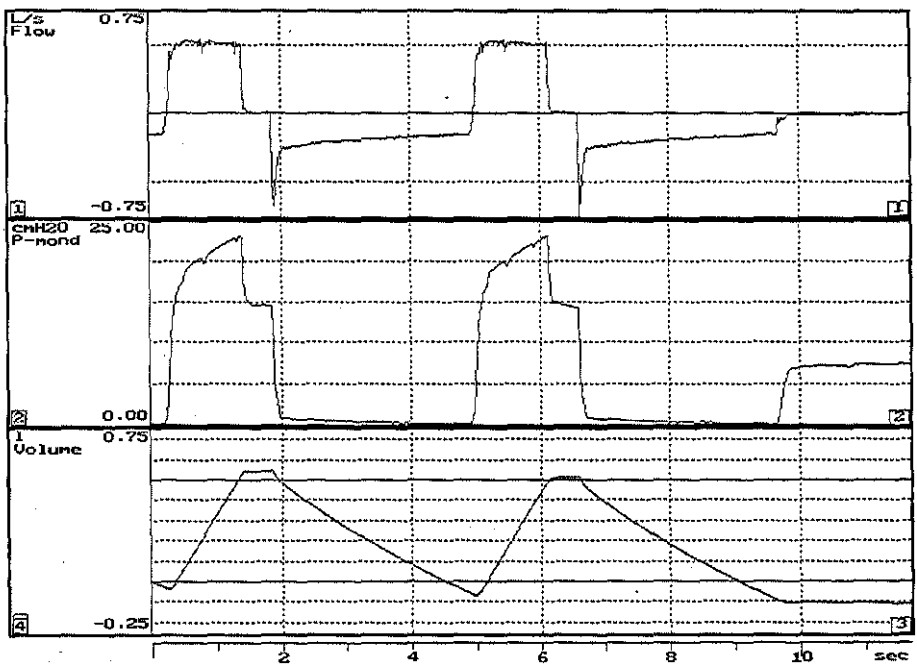


Figure 5. Measurement of static iPEEP. By occlusion of the airway at end-expiration a plateau in pressure is observed, which represents the total PEEP.

The dynamic iPEEP can be determined during uninterrupted breathing from recordings of airway pressure and flow against time. When iPEEP is present, the airway opening pressure will rise to a level equal to iPEEP before the inspiratory flow starts[22, 40, 41]. The difference between the end-expiratory airway pressure and the pressure at the onset of the inspiratory flow is referred to as dynamic iPEEP. To obtain reliable measurements, the patients need to be sedated or paralysed.

During spontaneous breathing, dynamic iPEEP can be measured using an esophageal balloon[42, 43]. The decrease in oesophageal pressure generated prior to the initiation of inspiratory flow represents the pressure needed to overcome the iPEEP (figure 6). This measurement is suitable for spontaneously breathing patients. However, abdominal muscle contraction may result in overestimation of iPEEP.

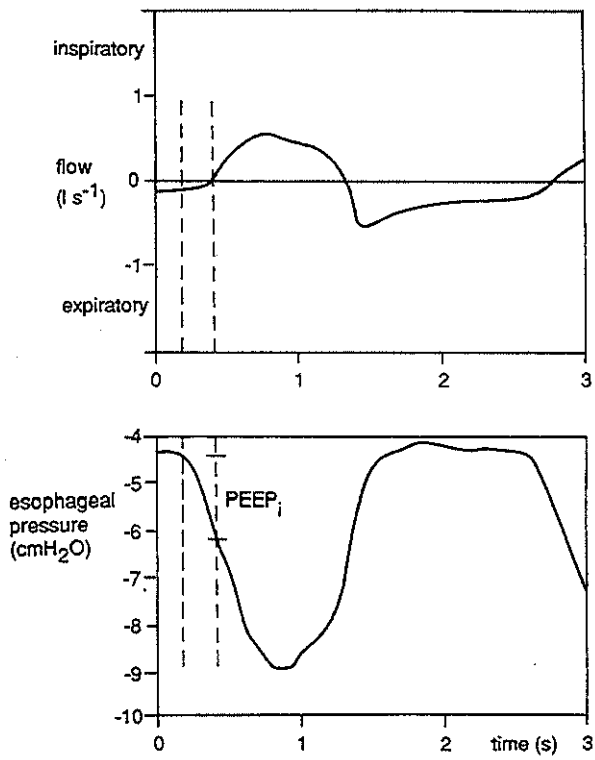


Figure 6. Determination of dynamic iPEEP in spontaneously breathing patients. Simultaneous recording of airflow and esophageal pressure. (with permission from B. van den Berg, Weaning from the ventilator in patients with respiratory failure, thesis)

Compared to static iPEEP levels, lower values of dynamic iPEEP are found. Dynamic iPEEP stems from the fastest emptying lung units and therefore reflects the lowest regional iPEEP. In the presence of heterogeneous mechanical properties of the lung, such as in COPD, it therefore gives an underestimation of the average iPEEP, which is represented by the static iPEEP[41].

Iso-volume pressure flow relationships (IVPF)

Several methods have been proposed to detect flow limitation in mechanically ventilated patients. A number of these methods is based on the principle of altering the driving pressure and observing flow, which is derived from the very first method to detect flow limitation in spontaneously breathing patients as described by Fry and Hyatt[3-5]. In 1954 Fry and Hyatt measured expiratory flows at the same lung volume (isovolume) while the expiratory force of the subject was varied, resulting in different driving pressures. Using the flow results at different isovolumes and at different driving pressures, they constructed iso-volume pressure flow curves. Flow limitation was defined as an unchanged flow at an increasing driving pressure (i.e. the pressure gradient between alveoli and airway opening) at a certain lung volume.

This method has been adapted for the detection of flow limitation in mechanically ventilated patients. As patients' co-operation is minimal during mechanical ventilation, forced expiratory manoeuvres are not feasible. However, altering the driving pressure during ventilatory support can be achieved by either decreasing the driving pressure by application of external resistances, or increasing the driving pressure by removal of external resistances (e.g. PEEP, expiratory circuit) or by application of negative pressure. Several studies have used application of various resistances to decrease driving pressure[44-46].

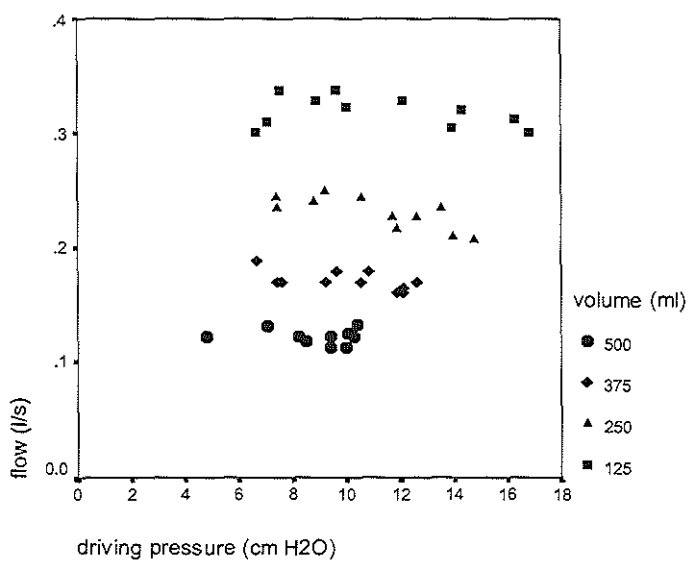


Figure 7.
Iso-volume pressure-flow relationship (IVPF) obtained during mechanical ventilation. By application of various levels of external resistance during expiration, the driving pressure is decreased. Volume is expressed as ml exhaled from start of expiration.

In absence of flow limitation during a passive expiration, the decrease in driving pressure from alveoli to the mouth will cause a decrease in flow. In contrast, in patients with flow limitation, application of a resistance will not decrease flow[4,18,46]. IVPF-relationships can be computed by plotting expiratory flow against corresponding values of driving pressure for iso-volume levels (figure 7). A plateau in the IVPF-relationships indicates flow limitation[4,18,46]. An alternative method to evaluate the effect of application of a resistance on iso-volume flow is by means of flow-volume curves; by superimposing the flow-volume curve recorded during application of a resistance on the flow-volume curve during unimpeded expiration[45]. Flow limitation is considered present if during application of the resistance no decrease in flow is found compared to unimpeded expiration, at unchanged end-expiratory lung volumes.

The mechanism of increasing the driving pressure for the detection of flow limitation has been implemented in various forms. The easiest method is the removal of PEEP, because this requires the least equipment[47]. However, PEEP is not applied in every patient. Another method based on the same principle is bypassing the expiratory circuit of the ventilator, however, this method was found intrinsically unreliable[48]. A third and frequently used method is the application of a negative expiratory pressure (NEP)[48]. Although "negative pressure" doesnot exist, the term is used to indicate a pressure difference in regard to mouth pressure, in this case the pressure at the mouth is decreased. In this thesis the term "negative pressure" is used to indicate a lowering of the pressure at the mouth. The NEP method consists of applying a negative pressure at the mouth during tidal expiration and comparing the

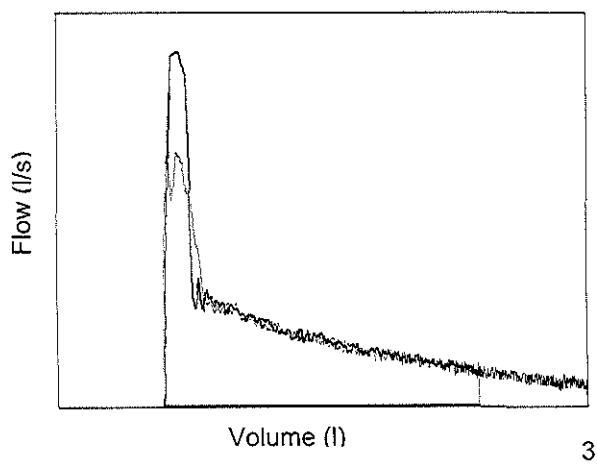


Figure 8. Expiratory flow-volume curve of a NEP breath (--) and the preceding control breath (–) in a patient with flow limitation.

ensuing flow-volume curve with that of the previous breath. In patients who are not flow limited, application of NEP will increase flow, while in flow limited patients no increase in flow will be elicited (figure 8).

Interrupter technique

Another method to detect flow limitation during mechanical ventilation, is the interrupter technique[45, 49-52]. Flow limitation is considered present when after a brief occlusion of the airway, a spike flow superimposed on the on going mouth flow is detected. During an interruption, a compressed airway or flow limiting segment will be abolished, after opening of the interrupter valve flow limitation will re-appear, resulting in an overshoot in expiratory flow (figure 9).

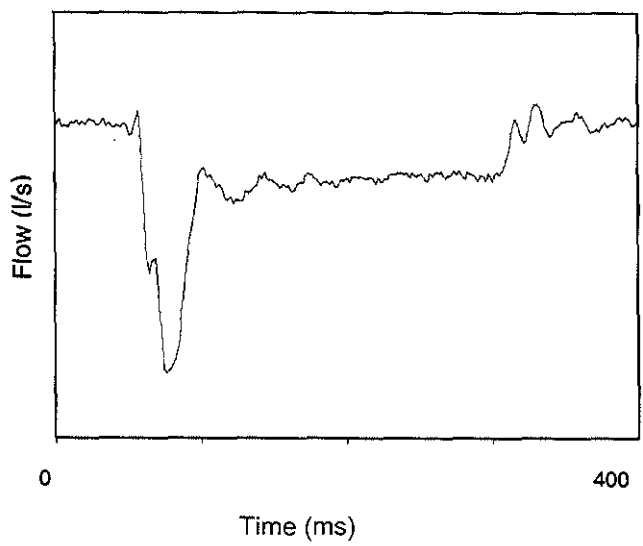


Figure 9. After a short occlusion of the valve, a flow spike is observed superimposed on the on going mouth flow.

Forced oscillation method

The forced oscillation technique can also be used to detect flow limitation in mechanically ventilated patients[53, 54]. The method is based on the application of a small pressure oscillation (~ 1 cm H2O) at the mouth by means of an external generator and on the recording of the oscillation pressure and flow[55]. Amplitude and phase differences between pressure and flow than enable the

calculation of a frequency dependent imaginary and real component of the respiratory system, considered as imput impedance. In the presence of expiratory flow limitation, during inspiration the real (Re) and imaginary (Im) part of impedance mainly reflect lung and chest wall properties. During expiration, in the presence of an increase in peripheral airway resistance, the impedance measured mainly reflects the shunt pathway, composed of central airway wall resistance and compliance. Large differences between inspiratory and expiratory Im values are indicative for the presence of expiratory flow limitation, even more than phasic variations of Re.

The flow-volume curve

In non intubated patients the maximal expiratory flow-volume (MEFV) curve is the mainstay for detection of flow limitation. As most mechanically ventilated patients are unable to perform forced manoeuvres, flow-volume relationships have been studied during tidal breathing in these patients[21, 45-47, 56, 57]. In general, expiratory flow limitation is suspected if a downward concavity in the flow-volume curve is observed. However, the interpretation of the shape of the flow volume curve has mostly been qualitative and therefore often subjective [58]. Attempts have been made to obtain quantitative data from the expiratory flow-volume relationship[56, 59].

The last decade increasing attention has been paid to the measurements of respiratory mechanics in patients on ventilatory support. In this context the flow-volume curve as a tool to describe respiratory mechanics during expiration is appealing[17, 56, 60-63]. Already in 1954, it was suggested that flow-volume curves of passive expiration could be used to assess the mechanical properties of the lung and chest wall[64]. In fact, the ventilator dependent patient is in an ideal condition to determine respiratory mechanics; the influence of the compliant upper airways is eliminated by the presence of the endotracheal tube and respiratory muscles are relaxed during most of the expiration[63]. The expiratory flow is driven by the elastic recoil built up in the respiratory system during the preceding mechanical inflation and the resistance is the opposing force. As a consequence, expiration is mainly determined by the patient's respiratory mechanics, though the additional flow resistance due to the endotracheal tube and ventilator equipment should be taken into account. However, until now, the assessment of respiratory

mechanics during relaxed expiration with simple tools in clinical settings has yielded limited results.

INFLUENCING

PURSED LIP BREATHING

It is well known that some patients with COPD relief dyspnea by pursing their lips during expiration. Several studies have suggested that pursed lip breathing decreases airways compression[65-69]. Patients were also found to decrease respiratory rate and to increase tidal volume during pursed lip breathing[65-69]. Prevention of airways compression by pursed lip breathing has been explained in terms of a positive pressure imposed at the mouth, ultimately causein a retardation of the flow in the peripheral airways. The EPP then moves more downstream to the non collapsible airways. However, intubated patients are unable to exert pursed lip breathing due to the presence of a tube.

CPAP

Already in 1934, Barach described a patient with COPD who clearly relieved dyspnea by exhaling against partially closed lips[70]. This inspired him to develop a continuous positive pressure breathing (CPPB) technique for patients with COPD. He showed roentgenographically that this technique increased the width of the branches of the bronchial tree in these patients[71]. The CPPB technique used by Barach is comparable to continuous positive airway pressure (CPAP) devices used nowadays. CPAP can be described as a system imposing a continuous positive pressure at the airway opening during spontaneous breathing[42, 43, 72]. CPAP differs from pursed lip breathing in that it acts as a threshold resistor; only one set-pressure level is applied. In contrast, pursed lip breathing probably gradually decreases the airway opening pressure and retards the flow. CPAP can be applied both in intubated patients as well as in patients on non invasive ventilation via a mask[73, 74]. In patients with COPD, CPAP reduces the inspiratory work of breathing by counterbalancing the iPEEP at end-expiration[43, 72, 75]. The level of CPAP should be adjusted to the prevailing level of iPEEP. Using a level of CPAP lower than the iPEEP will decrease work of breathing, but will not affect lung

emptying or end-expiratory lung volumes[46]. In order to affect lung emptying, CPAP-levels exceeding the intrinsic PEEP should be applied, which will inevitably increase hyperinflation[46, 76]

EXTERNAL PEEP

In the setting of mechanical ventilation positive expiratory airway pressure is known as PEEP. In clinical practice external PEEP (ePEEP) is frequently used in mechanically ventilated patients with COPD. In most modern ventilators application of ePEEP acts as a threshold resistor; one set-pressure level is applied. By administering ePEEP, iPEEP is counterbalanced, resulting in decreased work of breathing[43, 57, 77-80]. However, ePEEP should be titrated carefully in order to avoid further hyperinflation. In clinical studies no effect of ePEEP on airways compression and lung emptying could be established[46, 78, 81, 82]. Only when a level of ePEEP was applied that did increase hyperinflation, an effect on expiratory flow was found[57]. This can be explained by the waterfall analogy [20] (figure 11).

Airflow limitation occurs at a critical closing point in the airways, at which there is a back-up of pressure (iPEEP) that is analogous to the crest of a waterfall. Pressure drops across the critical closing point as water drops down the face of the waterfall. Airway pressure at the mouth is represented by the water downstream of the waterfall. If the water level downstream rises it will not affect the water level at the crest of the waterfall until the level down stream rises higher than the waterfall itself. Therefore, adding an ePEEP level below the iPEEP will not affect lung emptying, lung volume or gas-exchange. Higher levels of ePEEP will have an effect on lung emptying but will also cause an increase in end-expiratory lung volume. Until now, only one study reported a positive effect of an ePEEP smaller than iPEEP on gas exchange[37]. It is therefore reasonable to state that the effect of ePEEP lays in reducing the work of breathing during support and spontaneous ventilation[17].

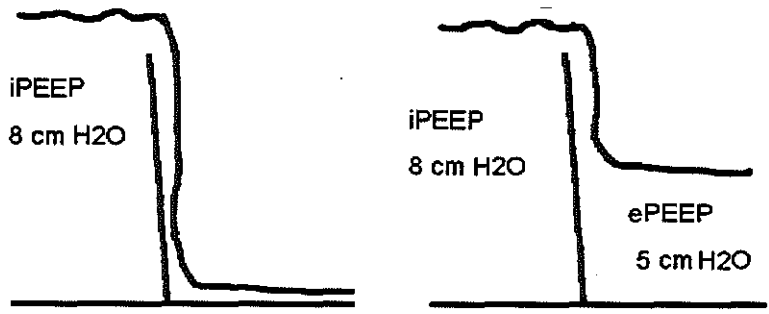


Figure 11. Airflow limitation occurs at a critical closing point in the airways, at which there is a back-up of pressure (iPEEP) that is analogous to the crest of a waterfall. Pressure drops across the critical closing point as water drops down the face of the waterfall. Airway pressure at the mouth is represented by the water downstream of the waterfall. If the water level downstream rises it will not affect the water level at the crest of the waterfall until the level down stream rises higher than the waterfall itself. Therefore, adding an ePEEP level below the iPEEP will not affect lung emptying.

FLOW RETARD

An other expiratory pressure regulation method, more close to pursed lip breathing, is the diminished early expiratory flow (DEEF). In 1968 Abboud et al showed that expiratory retard increased efficiency of breathing (i.e. the lowest work of breathing needed to obtain a normal PaCO2)[83]. In 1972, the mechanism of flow retard was adapted for mechanically ventilated patients; a resistance mechanism was incorporated in the Siemens Servo 900-B ventilator[84]. However, in mechanically ventilated patients with COPD, DEEF did not affect arterial blood-gases[85]. The effect of DEEF on respiratory mechanics was not assessed in that study.

EXPIRATORY RESISTANCE

In a preliminary study, Aerts et al. showed that application of an external resistance decreased effective airway resistance during expiration in mechanically ventilated patients with COPD[44]. This decrease in effective resistance was caused by a reduction of airways compression and an increase in iso-volume flow at unchanged end-expiratory lung volume. No effects on gas exchange could be established.

REFERENCES

1. Hutchinson J. On the capacity of the lungs and on the respiratory function with view of establishing a precise and easy method of detecting diseases by spirometer. Trans. Med. Soc. London. 1846; 29:137-252.
2. Einthoven W. Ueber die wirkung der bronchialmuskeln nach einer neuen methode untersucht, und ueber asthma nervosum. Pflugers Archiv 1892; 51:367-444.
3. Fry D, Ebert R, Stead W, Brown C. The mechanics of pulmonary ventilation in normal subjects and in subjects with emphysema. Am J Med 1954; 16:80-97.
4. Fry D, Hyatt R. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. Am J Med 1960; 24:672-689.
5. Hyatt R. The interrelationships of pressure, flow and volume during various respiratory maneuvres in normal and emphysematous patients. Am Rev Resp Dis 1961; 83:676-683.
6. Hyatt R, Schilder D, Fry D. Relationship between maximum expiratory flow and degree of lung inflation. J Appl Physiol 1958; 13:331-336.
7. Dayman H. Mechanics of airflow in health and in emphysema. J Clin Invest 1951; 30:1175-1190.
8. Barnes P. Managing Chronic Obstructive Pulmonary Disease: Science Press Limited, London, UK, 1999.
9. West J. Pulmonary pathophysiology - the essentials. Balttimore, U.S.A.: The Williams & Wilkins Company, 1977:59-91.
10. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 1967; 22:95-108.
11. Mead J, Agostoni E. Dynamics of breathing. Handbook of physiology. Vol. 1. Washington DC: American Physiological Society, 1964:411-476.
12. Brackel H. Bronchial mechanics in healthy subjects and patients with long lasting asthma. Thesis; Erasmus University, Rotterdam, The Netherlands, 2000.
13. Wilson T. The wave speed limit on expiratory flow. In: Dekker M (ed). Respiration Physiology, lung biology in health and disease. 1989:139-166.
14. Wilson T, Rodarte J, JP B. Wave-speed and viscous flow-limitation. In: Fishman A, Macklem PT, Mead J (eds). Handbook of Physiology , section 3: the Respiratory System. Vol. 3. Bethesda: Waverly Press, 1986:55-61.
15. Vinegar A, Sinnett EE, Leith DE. Dynamic mechanisms determine functional residual capacity in mice, Mus musculus. J Appl Physiol 1979; 46:867-871.

16. Sharp J, Lith P, Nuchprayoon C, Briney R, Johmson F. The thorax in chronic obstructive lung disease. Am J Med 1968; 44:39-64.
17. Gladwin MT, Pierson DJ. Mechanical ventilation of the patient with severe chronic obstructive pulmonary disease. Intensive Care Med 1998; 24:898-910.
18. Kimball WR, Leith DE, Robins AG. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am Rev Respir Dis 1982; 126:991-995.
19. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. Am Rev Respir Dis 1982; 126:166-170.
20. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. Chest 1989; 96:449-451.
21. Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med 1995; 21:522-36.
22. Rossi A, Gottfried SB, Zocchi L, et al. Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. Am Rev Respir Dis 1985; 131:672-7.
23. Ranieri VM, Grasso S, Fiore T, Giuliani R. Auto-positive end-expiratory pressure and dynamic hyperinflation. Clin Chest Med 1996; 17:379-94.
24. Wrigge H, Putensen C. What is the "best PEEP" in chronic obstructive pulmonary disease? Intensive Care Med 2000; 26:1167-1169.
25. Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. Eur Respir J 1996; 9:1283-1292.
26. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989; 140:5-9.
27. Kollef MH. Lung hyperinflation caused by inappropriate ventilation resulting in electromechanical dissociation: a case report. Heart Lung 1992; 21:74-77.
28. Lapinsky SE, Leung RS. Auto-PEEP and electromechanical dissociation. N Engl J Med 1996; 335:674.
29. Martens P, Vandekerckhove Y, Mullie A. Restoration of spontaneous circulation after cessation of cardiopulmonary resuscitation. Lancet 1993; 341:841.
30. Myles PS, Madder H, Morgan EB. Intraoperative cardiac arrest after unrecognized dynamic hyperinflation. Br J Anaesth 1995; 74:340-342.
31. Rogers PL, Schlichtig R, Miro A, Pinsky M. Auto-PEEP during CPR. An "occult" cause of electromechanical dissociation? Chest 1991; 99:492-4933.

32. Keith RL, Pierson DJ. Complications of mechanical ventilation. A bedside approach. Clin Chest Med 1996; 17:439-451.
33. Decramer M. Hyperinflation and respiratory muscle interaction. Eur Respir J 1997; 10:934-941.
34. Gibson GJ. Pulmonary hyperinflation a clinical overview. Eur Respir J 1996; 9:2640-2649.
35. Vassilakopoulos T, Zakynthinos S, Roussos C. Respiratory muscles and weaning failure. Eur Respir J 1996; 9:2383-400.
36. Calverley P, Rennard S, Agusti A, et al. Current and future management of acute exacerbations of chronic obstructive pulmonary disease. Eur Respir Rev 1999; 9:195-205.
37. Rossi A, Santos C, Roca J, Torres A, Felez MA, Rodriguez-Roisin R. Effects of PEEP on VA/Q mismatching in ventilated patients with chronic airflow obstruction. Am J Respir Crit Care Med 1994; 149:1077-1084.
38. Suter PM, Schlobohm RM. Determination of functional residual capacity during mechanical ventilation. Anesthesiology 1974; 41:605-607.
39. Ranieri VM, Mascia L, Petruzzelli V, Bruno F, Brienza A, Giuliani R. Inspiratory effort and measurement of dynamic intrinsic PEEP in COPD patients: effects of ventilator triggering systems. Intensive Care Med 1995; 21:896-903.
40. Guerin C, Tantucci C. Respiratory mechanics in intensive care units. Eur Respir Monograph. 1999; 4:255-278.
41. Maltais F, Reissmann H, Navalesi P, et al. Comparison of static and dynamic measurements of intrinsic PEEP in mechanically ventilated patients. Am J Respir Crit Care Med 1994; 150:1318-1324.
42. Aerts JG, van den Berg B, Bogaard JM. Ventilator-CPAP with the Siemens Servo 900C compared with continuous flow-CPAP in intubated patients: effect on work of breathing. Anaesth Intensive Care 1997; 25:487-492.
43. Petrof BJ, Legare M, Goldberg P, Milic-Emili J, Gottfried SB. CPAP reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe COPD. Am Rev Respir Dis 1990; 141:281-289.
44. Aerts JG, van den Berg B, Bogaard JM. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10:550-556.
45. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 1985; 131:414-420.
46. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989; 139:621-626.

47. Rossi A, Brandolese R, Milic-Emili J, Gottfried SB. The role of PEEP in patients with chronic obstructive pulmonary disease during assisted ventilation. Eur Respir J 1990; 3:818-822.
48. Valta P, Corbeil C, Lavoie A, et al. Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 1994; 150:1311-1317.
49. Hage R, Aerts JG, Verbraak AF, van den Berg B, Bogaard JM. Detection of flow limitation during tidal breathing by the interruptor technique. Eur Respir J 1995; 8:1910-1914.
50. Reinoso MA, Gracey DR, Hubmayr RD. Interrupter mechanics of patients admitted to a chronic ventilator dependency unit. Am Rev Respir Dis 1993; 148:127-131.
51. Ohya N, Huang J, Fukunaga T, Toga H. Mouth pressure curve on abrupt interruption of airflow during forced expiration. J Appl Physiol 1989; 66:509-17.
52. Ohya N, Huang J, Fukunaga T, Toga H. Airway pressure-volume curve estimated by flow interruption during forced expiration. J Appl Physiol 1989; 67:2631-2638.
53. Peslin R, Felicio da Silva J, Duvivier C, Chabot F. Respiratory mechanics studied by forced oscillations during artificial ventilation. Eur Respir J 1993; 6:772-784.
54. Vassiliou M, Peslin R, Saunier C, Duvivier C. Expiratory flow limitation during mechanical ventilation detected by the forced oscillation method. Eur Respir J 1996; 9:779-786.
55. Navajas D, Farre D. Oscillation mechanics. Eur Respir Monograph 1999; 4:112-140.
56. Aerts JGJV, van den Berg B, Lourens MS, Bogaard JM. Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiol Scand 1999; 43:322-327.
57. van den Berg B, Stam H, Bogaard JM. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 1991; 4:561-567.
58. Baydur A, Milic-Emili J. Expiratory flow limitation during spontaneous breathing: comparison of patients with restrictive and obstructive respiratory disorders. Chest 1997; 112:1017-1023.
59. Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A. Simple method to measure total expiratory time constant based on the passive expiratory flow-volume curve. Crit Care Med 1995; 23:1117-1122.
60. Guttmann J, Eberhard L, Fabry B, et al. Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 1995; 8:114-120.

61. Jubran A. Monitoring patient mechanics during mechanical ventilation. Crit Care Clin 1998; 14:629-653.
62. Rossi A, Polese G, Milic Emili J. Monitoring respiratory mechanics in ventilator-dependent patients. In: Tobin M, ed. Principles and Practise of Intensive Care Monitoring. New York: McGraw-Hill, 1998:553-596.
63. Rossi A, Polese G. As simple as possible, but not simpler. Intensive Care Med 2000; 26:1591-1594.
64. Comroe J, Nisell O, Nimms R. A simple method for concurrent measurement of compliance and resistance to breathing in anaethetized anaimals and man. J Appl Physiol 1954; 7:225-228.
65. Barach A. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br J Dis Chest 1968; 62:36-40.
66. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. Chest 1992; 101:75-78.
67. Ingram R, Schilder D. Effect of pursed lips expiration on the pulmonary pressure-volume relationship in obstructive lung disease. Am J Respir Crit Care Med 1967; 96:381-388.
68. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970; 28:784-789.
69. Thoman R, Stoker G, Ross J. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966; 93:100-106.
70. Barach A, Bickerman H, Petty T. Perspective in pressure breathing. Respir Care 1975; 20:627-642.
71. Barach A, Swenson P. Effects of breathing gases under positive pressure onlumens of small and medium sized bronchi. Archiv Int Med 1939; 63:946-948.
72. van den Berg B, Aerts JGJV, Bogaard JM. Effect of continuous positive airway pressure (CPAP) in patients with chronic obstructive pulmonary disease (COPD) depending on intrinsic PEEP levels. Acta Anaesthesiol Scand 1995; 39:1097-102.
73. Petrof BJ, Kimoff RJ, Levy RD, Cosio MG, Gottfried SB. Nasal continuous positive airway pressure facilitates respiratory muscle function during sleep in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 1991; 143:928-935.
74. Goldberg P, Reissmann H, Maltais F, Ranieri M, Gottfried SB. Efficacy of noninvasive CPAP in COPD with acute respiratory failure. Eur Respir J 1995; 8:1894-1900.

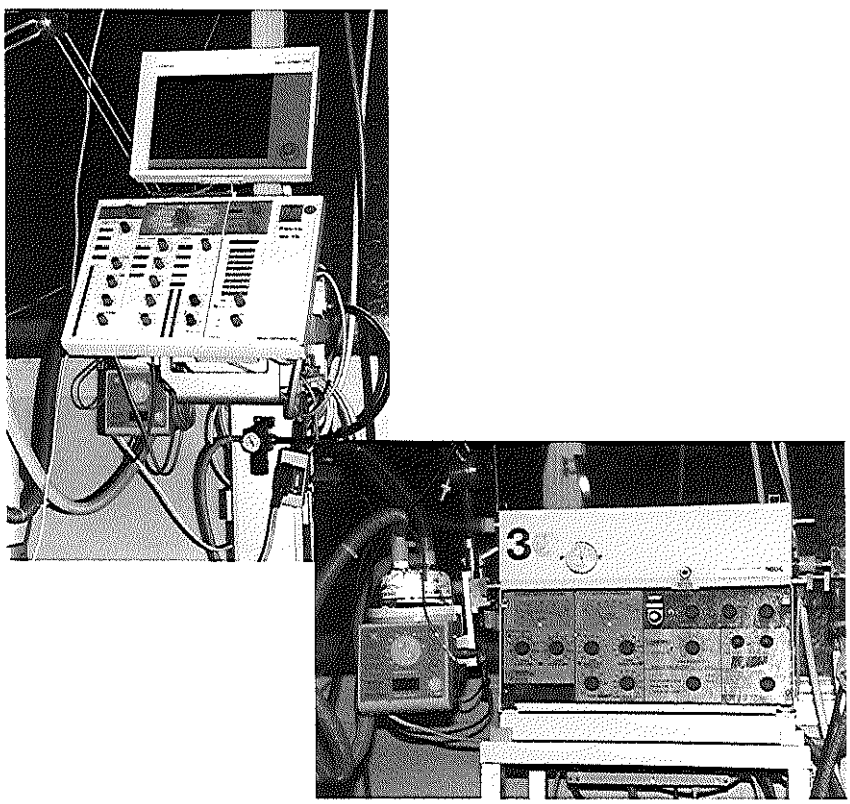
75. Aerts JGJV, van den Berg B, Verbraak AF, Bogaard JM. Elastic work of breathing during continuous positive airway pressure in intubated patients with chronic obstructive pulmonary disease (theoretical analysis and experimental validation). Acta Anaesthesiol Scand 1997; 41:607-613.
76. Aerts J. Controlled expiration in patients with chronic obstructive pulmonary disease on ventilatory support. Thesis; Erasmus University Rotterdam, The Netherlands 1996.
77. Appendini L, Purro A, Gudjonsdottir M, et al. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. Am J Respir Crit Care Med 1999; 159:1510-1517.
78. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 1988; 65:1488-1499.
79. Sydow M, Denecke T, Zinserling J, Zielmann S, Crozier TA, Burchardi H. Determination of intrinsic PEEP during mechanical ventilation. Validation of a new optional method of measurement provided by the EVITA mechanical ventilator. Anaesthesist 1994; 43:115-120.
80. Guerin C, Milic Emili J, Fournier G. Effect of PEEP on work of breathing in mechanically ventilated COPD patients. Intensive Care Med 2000; 26:1207-1214.
81. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 1993; 147:5-13.
82. Georgopoulos D, Giannouli E, Patakas D. Effects of extrinsic positive end-expiratory pressure on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation. Intensive Care Med 1993; 19:197-203.
83. Abboud R, Beidas-Jubran N, Feisal K, Fuleihan F. The effect of added expiratory obstruction on gas exchange in chronic airways obstruction. Br J Dis Chest 1968; 62:36-40.
84. Ingelstedt S, Jonson B, Nordstrom L, Olsson SG. A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiol Scand 1972; 47:7-27.
85. Gultuna I, Huygen PE, Ince C, Strijdhorst H, Bogaard JM, Bruining HA. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Intensive Care Med 1996; 22:539-545.

CHAPTER 3

FLOW-VOLUME CURVES AS MEASUREMENT OF RESPIRATORY MECHANICS DURING VENTILATORY SUPPORT: THE EFFECT OF THE EXHALATION VALVE.

M.S. Lourens
B. van den Berg
H.C. Hoogsteden
J.M. Bogaard

Intensive Care Medicine 1999;25:799-804



Mechanical ventilators Servo 300 and 900 C

ABSTRACT

Objective: To assess the feasibility of expiratory flow-volume curves as measurement of respiratory mechanics during ventilatory support: to what extent is the shape of the curve affected by the exhalation valve of the ventilator?

Design: prospective, comparative study

Setting: Medical Intensive Care Unit of a University Hospital.

Patients: 28 Consecutive patients, with various conditions, mechanically ventilated with both the Siemens Servo 900c and 300 ventilator, were studied under sedation and paralysis.

Interventions: The ventilator circuit was intermittently disconnected from the ventilator at end-inspiration in order to obtain flow-volume curves with and without the exhalation valve in place.

Measurements and results: Peakflows (PEF) and slopes of the flow-volume curve during the last 50% of expired volume (SF50) were obtained both with and without the exhalation valve in place. The exhalation valve caused a significant reduction in peakflow of 0.30 l/s (from 1.27 to 0.97 l/s) with the Siemens Servo 900C ventilator and of 0.42 l/s (from 1.36 to 0.94 l/s) with the Siemens Servo 300 ventilator ($p<0.001$). The SF50 was not affected.

Conclusion: In mechanically ventilated patients, the exhalation valve causes a significant reduction in peakflow, but does not affect the slope of the flow-volume curve during the last 50% of expired volume. This study further suggests that the second part of the expiratory flow-volume curve can be used to estimate patients' respiratory mechanics during ventilatory support.

INTRODUCTION

The importance of monitoring respiratory mechanics in patients on ventilatory support is generally accepted. In the current generation of mechanical ventilators, respiratory variables as flow, volume and pressure are displayed on a screen on-line. Also, pressure-volume and flow-volume relationships are easily visualized. The flow-volume curve provides an easy way to obtain information on conditions such as COPD, intrinsic PEEP, airway secretions, obstruction of the ventilator circuits and the expiratory time constant [1-6]. In a previous study, we showed that the relaxed expiratory flow-volume curve can be used to assess airflow obstruction in mechanically ventilated patients with COPD [7]. When the expiratory flow-volume curve is used to estimate the patient's respiratory mechanics, it is important to establish to what extent external elements affect the shape of the flow-volume curve. The endotracheal tube has been recognized as a major resistive element [8,9]. In the ventilatory circuit, the exhalation valve is considered the principal resistance [10]. The resistance of exhalation valves has been investigated predominantly under experimental conditions using test lungs [11,12]. In this study we examined, in patients on ventilatory support, expiratory flow-volume curves obtained both with and without the exhalation valve of the ventilator in place. We also compared two different ventilators.

PATIENTS AND METHODS

PATIENTS

Twenty-eight consecutive patients admitted to the medical intensive care unit of the Erasmus Medical Centre Rotterdam were studied. The patients were included if they met the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube with an inner diameter exceeding 7 mm, a ventilator-PEEP level <10 cm H20 and the absence of air leaks. The patients were mechanically ventilated for various medical conditions: patients' characteristics are given in table 1. Prior to mechanical ventilation, the patients with COPD (n=9) had a mean FEV1 of 31% of predicted (range 19-45%). Twenty-three patients had been intubated with an endotracheal tube

(inner diameter range 7.5-9 mm), 5 patients with a tracheostomy tube (inner diameter range 7-8.5 mm).

Patient	Age	Diagnosis	Sex	Days MV	Apache II
1	47	Interstitial pneumonia	M	2	15
2	66	Bacterial pneumonia	M	2	20
3	66	Drug induced lung injury	M	2	18
4	43	Post TIPS procedure	M	6	10
5	52	Post TIPS procedure	M	2	19
6	69	Guillain Barré syndrome	F	1	9
7	46	Aspiration pneumonia	F	2	15
8	51	Cyto Megalo Virus pneumonia	M	7	21
9	49	Interstitial lung disease	F	17	14
10	61	Congestive heart failure	M	7	10
11	43	Pleural empyema	M	2	8
12	77	Congestive heart failure	F	2	17
13	47	Bacterial pneumonia	M	4	11
14	81	Bacterial pneumonia	F	2	10
15	42	Porphyria acuta	M	100	1
16	81	Aspiration pneumonia	F	15	10
17	66	Congestive heart failure	M	6	19
18	71	Muscle weakness	F	5	11
19	43	Tetraplegia	M	180	5
20	65	COPD	M	1	18
21	72	COPD	F	3 yrs	10
22	78	COPD	M	1	24
23	78	COPD	M	1	12
24	81	COPD	M	2	14
25	76	COPD	M	2	11
26	56	COPD	M	1	17
27	71	COPD, pneumonia	F	2	13
28	74	COPD	F	5	12

Table 1. Patient characteristics. Days MV = days on mechanical ventilation. Apache II = Apache II score on day of measurement. TIPS = Transjugular Intrahepatic Portosystemic Shunt. COPD = Chronic Obstructive Pulmonary Disease.

In all patients, measurements were obtained while using a Siemens Servo 900C ventilator (Siemens-Elema, Solna, Sweden). In 23 patients, the study was repeated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden) applying the same ventilator settings. Ventilator settings were set by the primary physician and remained unchanged during the study, except that if present, ventilator-PEEP was removed. The volume-controlled mode was used in 21 patients, while the pressure controlled mode was used in 7 patients. The average minute volume was 10 l/min (6-15 l/min) . The average respiratory rate was 15 breaths per minute (10-30 breaths/min). At volume-controlled ventilation, the ratio between inspiratory and expiratory time was 35 : 65 in all patients. At pressure-controlled ventilation, this ratio was 50 : 50. During the study all patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, Holland) and paralysed with vecuronium (Organon Teknika B.V., Boxtel, Holland). Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

INTERVENTIONS AND RESPIRATORY MEASUREMENTS

A heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal tube to measure flow. Volume was obtained by computerized integration of the flow signal. Data were stored and analyzed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sample frequency of 100 Hz.

Expiratory flow-volume curves were obtained both with and without the exhalation valve of the ventilator in place. To obtain measurements without the exhalation valve in place, the expiratory line of the ventilator circuit was disconnected from the ventilator at an end-inspiratory pause. Subsequently the patient was allowed to expire till no flow was detected. By disconnecting the tubings at the ventilator side, not only the exhalation valve, but the total expiratory circuit inside the ventilator, including the flow transducer and connecting tubings, was bypassed during expiration. For reasons of simplicity the expiratory circuit inside the ventilator is referred to as exhalation valve. All measurements were obtained in triplicate.

ANALYSIS OF THE FLOW-VOLUME CURVE

In order to describe the relevant components of the flow-volume curve relationship, we determined the peakflow (PEF) and the angle of the slope of the flow-volume curve during the last 50% of expired volume (SF50, in degrees). In formula:

$$SF50 = \text{arctg} \left[\frac{(V'50,ex - V'end,ex)}{Vt50} \right]$$

V'50,ex = the flow at 50% of exhaled volume (l/s)
V'end,ex = the flow at end-expiration (l/s)
Vt50 = 50% of expiratory tidal volume (l)
arctg = arctangens (s^{-1})

The flow-volume curves of two consecutive breaths, the first with and the second without the exhalation valve in place, were compared, using PEF and SF50 determined at corresponding volume range. The average of three measurements was calculated.

DATA ANALYSIS

Student's t-test was used. Results are considered significantly different when $p < 0.05$. According to Bland and Altman mean differences between SF50 with valve and SF50 without valve were plotted against the mean values of SF50 with valve and SF50 without valve; limits of agreement were estimated as ± 2SD of the differences [13].

RESULTS

The results of the study are shown in table 2. For both types of ventilators studied, the presence of the exhalation valve was associated with a significant decrease in peakflow (both $p < 0.001$). In contrast, the SF50 remained unchanged by the exhalation valve of both ventilators ($p = 0.68$ and $p = 0.063$, for the Servo 900C and 300 ventilator respectively). No significant differences were found in instantaneous flows with and without valve at both mid- and end-expiration. The average change in SF50 was 0.2° (SD 2.7) for the Servo 900C ventilator and 0.9° (SD 2.2) for the Servo 300 ventilator. In figure 1, the differences between SF50 with valve and SF50 without valve are plotted against their means. Mean difference and limits of agreement are indicated. In this figure, a slight SF50 dependent systematic deviation is observed. In patients with higher SF50's removal of the valve tends to increase the SF50 , while in contrast in patients with lower SF50's removal of the valve tends to decrease the SF50. In patients with COPD the mean SF50 was 21° (SD 11°), while in patients with other pathology the mean SF50 was 50 ° (SD 12°). Examples of expiratory flow-volume curves of a patient with a low SF50 and a patient with a high SF50 with and without exhalation valve are shown in figure 2.

	Servo ventilator 900C		Servo ventilator 300	
Exhalation valve	With valve	Without valve	With valve	Without valve
Peakflow mean (l/s)	0.97	1.27*	0.94	1.36*
Standard deviation	0.23	.30	0.22	0.41
Range	0.60 – 1.60	0.74 – 1.80	0.45 – 1.32	0.65 – 2.16
SF50 mean (°)	40	40	44	45
Standard deviation	18	19	15	16
Range	9 – 68	8 - 72	15 – 68	12 – 70

Table 2. Results. * significant difference between peakflow with and without the valve of the ventilator in place $p < 0.001$ for both ventilators.

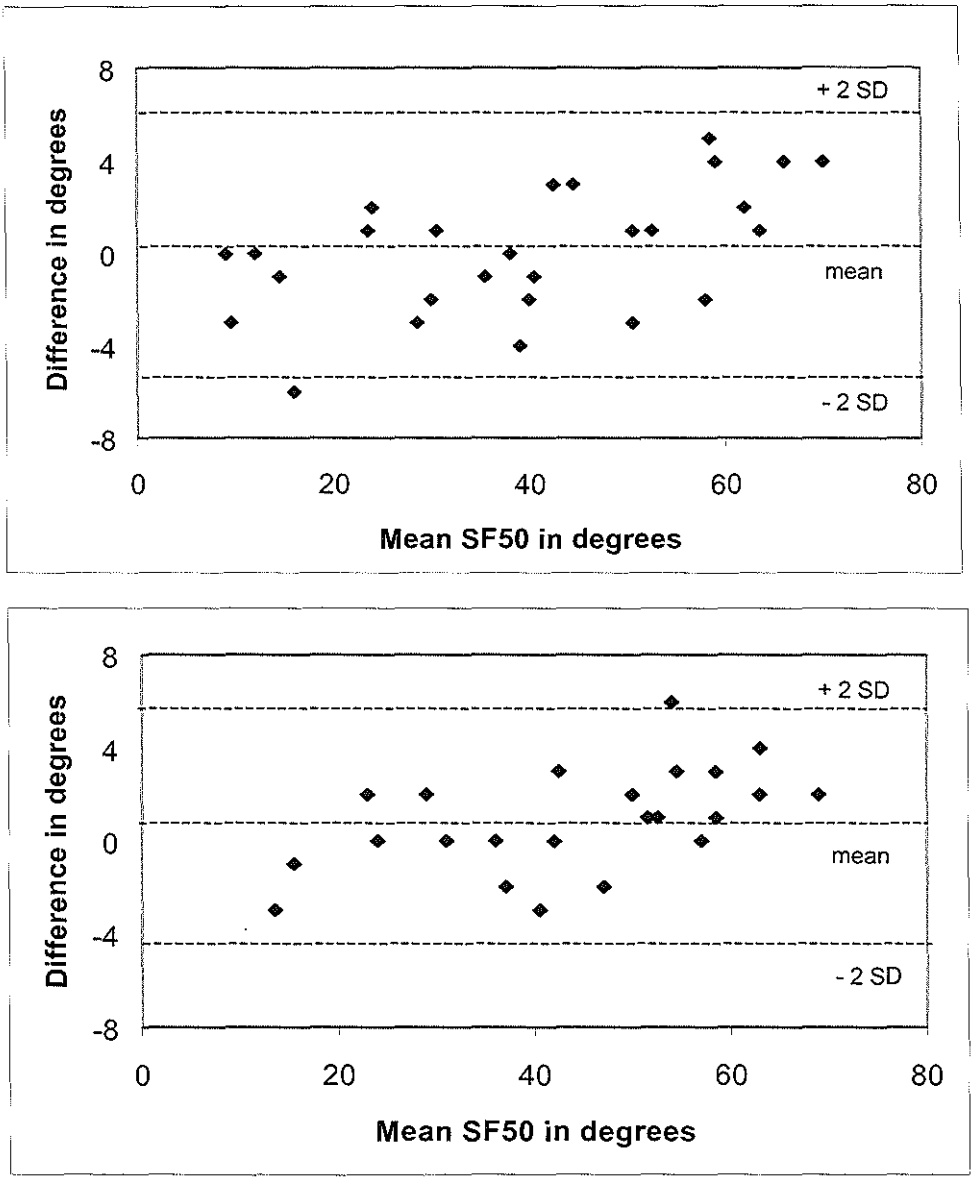


Figure 1. Bland and Altman analysis of difference (SF50 without exhalation valve minus SF50 with exhalation valve) plotted against the mean of SF50 with and without exhalation valve. The upper figure displays the results of the Servo 900C ventilator, the lower figure the Servo 300 ventilator.

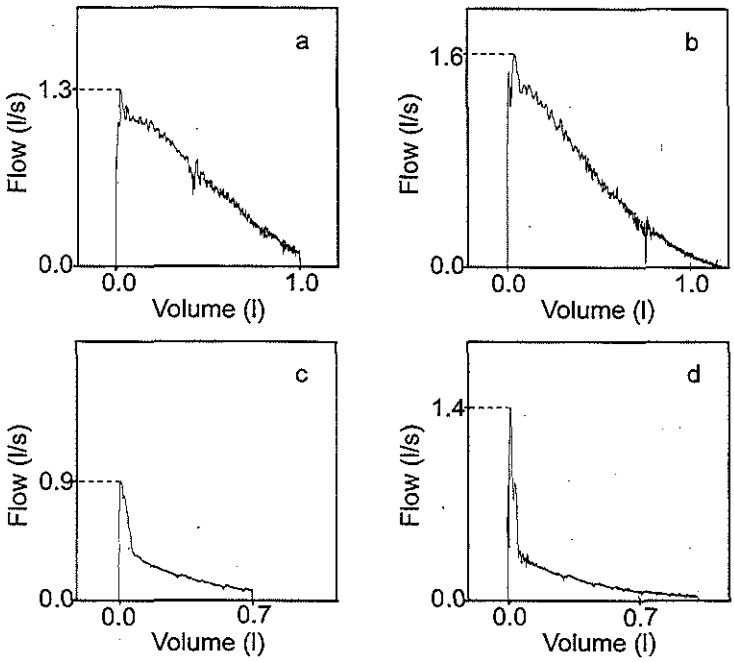


Figure 2.
Flow-volume curves of a patient with a high SF50 (a and b) and of a patient with a low SF50 (c and d), with exhalation valve (a and c) and without exhalation valve (b and d).

DISCUSSION

This study shows that in mechanically ventilated patients the exhalation valve of the ventilator decreases the peakflow but does not appreciably affect the slope of the flow-volume curve during the second half of expiration. This study further suggests that the second part of the expiratory flow-volume curve can be used to estimate patients' respiratory mechanics during ventilatory support.
The passive expiration can be described as an early rapid component, which reflects resistive behaviour of predominantly extrathoracic resistive elements and a consecutive slower component, mainly reflecting viscous and elastic properties of lung, chest wall and the endotracheal tube [6,14,15]. In the expiratory flow-volume curve, the transition between both components has been referred to as the inflection point, defined as the point of maximum slope following the peak expiratory flow [6]. In order to describe both components of the flow-volume curve relationship, we determined the peakflow (PEF) and the slope of the flow-volume curve during the second half of expiration (SF50).
The concept of the SF50 is based on a mono-exponential lung emptying pattern, assuming a constant elastance and resistance. In patients with diseased lungs and mechanical in-homogeneity, however, this assumption can

not be fulfilled. Chelucci et al. described the time course of volume change during passive expiration by a two compartment model [14,16]. Emptying of the first compartment, representing about 80% of total exhaled volume, lasted for approximately 1.5 s. For emptying of the second compartment 8 s expiration time was allowed. As our study was performed during uninterrupted mechanical ventilation with an average expiration time of about 2 s, the two compartments-model cannot be applied. Also, in the present study the analysed part of the flow-volume curves approached linearity. Application of a two compartment model would introduce unacceptable inaccuracy. It has been shown that the use of a linear model was acceptable when the expired airflow pattern was analysed in spontaneously breathing patients [17,18]. In patients with varying pathology this should be considered as an effective single compartment behaviour, covering peripheral airways obstruction, visco-elastic properties and unequal ventilation.

We used the SF50 instead of the respiratory time constant (τ), calculated as the quotient of the volume change and the corresponding flow difference. Since both the SF50 and the τ are calculated from the same variables, it is clear that they are closely related: SF50 is equal to arctangents τ^{-1}. The inverse exponential relationship explains that at low flows minor alterations in flow lead to large changes in τ, but only minimally affect the SF50. In a patient with severe COPD, a minor change in SF50 of 3 degrees from 11 to 8 corresponds to a change in time constant from 5.1 s to 7.1 s. An equal change in SF50 from 53 to 50, however, does not affect the time constant. Therefore, in patients with COPD, the SF50 represents a better way to describe the slope as these minor changes in flow are clinically irrelevant.

In a previous study, the SF50 was found to discriminate between patients with COPD and patients with other pathology. In the patients with COPD, a linear relationship was established between the SF50 and the FEV1 assessed in the period prior to ventilatory support [7]. In the present study, a mean SF50 of 21° (SD 11°) was found in the patients with COPD, while the mean SF50 was 50° (SD 12°) in the patients with other pathology.

Our results show that the exhalation valve decreases the peakflow significantly, emphasizing the influence of the flow resistance of the valve [12]. Brunner et al. calculated the expiratory time constant from peakflow and expiratory tidal volume [5]. A disadvantage of their method is that it is less

applicable in patients with COPD. In patients with COPD, the contribution of the peakflow to the exhalation is minimal and the rate of lung emptying is determined by the slope of the flow-volume curve beyond the inflection point (figure 2). Therefore, this part of the flow-volume curve seems more informative .

In our study, the exhalation valve did not appreciably affect the slope of the flow volume curve of the last 50% of expired volume. This was verified for a wide range of slopes from patients with various medical conditions. Our results are not in agreement with the findings of Guttmann et al., who describe a higher time constant when the ventilator equipment was included compared to the value without the ventilator equipment [6]. In their study, the effects of both exhalation valve and ventilator tubing were assessed. In order to determine the resistance of the ventilator tubings used in our study, we assessed the relationship between resistive pressure and airflow for these tubings . For highest flow at mid expiration found in our patients (0.71 l/s) the resistive pressure was 0.4 cm H_2O. Therefore, the resistance of the tubings may be considered negligible. In contrast to our study, Guttmann only included patients with ARDS, which are characterized by low 'internal' resistances and steep slopes. In those patients, the effect of the exhalation valve can be explained by the proportionally greater contribution of the valve to the sum of internal and external resistances.

Bypassing the expiratory circuit during exhalation has been used to detect flow limitation [19]. According to that approach, no change in SF50 after removal of the valve is expected, in case of flow-limitation. In contrast, the SF50 would increase in patients without flow limitation. As can be seen in figure 1, removal of the valve tends to decrease the SF50 in the patients with lower SF50's and to increase the SF50 in the patients with higher SF50's. However, these changes are small and it is not possible to discriminate between patients with and without flow limitation. The decrease in SF50 after removal of the valve, in patients with COPD, can be explained if the exhalation valve is considered as an external resistor. In mechanically ventilated patients with severe COPD even during relaxed expiration flow limitation develops [1,2,7,20]. Application of an external resistor can counteract airway compression and reduce flow limitation [1,2,20]. As a consequence a steeper slope is found.

The design of the study precluded removal of the endotracheal tube since all patients were on controlled ventilation with sedation and paralysis. The tube-

resistance at the flows at mid expiration, was calculated for each patient, using resistive pressure and flow-characteristics assessed for the same kind of tubes as used in this study [2]. The average resistive pressure at mid expiratory flow was 0.7 cm H_2O (SD 0.4) in the group of COPD patients and 2.5 cm H_2O (SD1.5) in the patients with other pathology. To estimate the effect of the endotracheal tube on the results of our study, we recalculated the SF50 for the theoretical condition of absence of the endotracheal tube for the two patients with the highest and the lowest flow at mid expiration. For the patient with the highest flow (0.71 l/s), the SF50 of the theoretical curve was 65° against 61° of the flow-volume curve with the endotracheal tube. In the patient with the lowest flow (0.16 l/s) the SF50's remained equal: 12° for both conditions. Therefore, we conclude that in patients with COPD, the tube resistance does not appreciably influence the SF50 due to the low flow rates at the second half of expiration. In patients with higher SF50 these values can be an underestimation of the SF50 without the endotracheal tube.

Flow dynamics of exhalation valves are determined by their physical properties. In this study, the Siemens Servo 900C and 300 ventilator, both equipped with scissor valves, were compared. The scissor valve contains a narrow tube of silicone rubber, the inner diameter of this tube measures 8 mm in the Servo 900C ventilator valve and 10 mm in the Servo 300 ventilator valve [12]. We assessed the resistance of the entire expiratory circuit within the ventilator and found that the resistive-pressure - flow characteristics were comparable for both ventilators: 4.3 and 4.7 cm H_2O/l/s for the 900C and 300 ventilator respectively.

In summary, in mechanically ventilated patients the exhalation valve affects the flow-volume curve by causing a significant decrease in peakflow. The slope of the flow-volume curve during the last 50 % of expired volume, however, is not affected. In patients with COPD, the presence of the endotracheal tube does not appreciably affect the SF50. In patients with higher SF50's, the endotracheal tube can cause a slight underestimation of the SF50. No difference was found between the two types of Servo ventilators studied. This study suggests that in mechanically ventilated patients expiratory flow-volume curves can be used to estimate patients' respiratory mechanics at the bedside.

REFERENCES

1. Gottfried SB, Rossi A, Higgs BD, Calverley PMA, Zocchi L, Bozic C, Milic-Emili J (1985) Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 131:414-420.
2. Van den Berg B, Stam H, Bogaard JM (1991) Effect of PEEP on respiratory mechanics in patients with COPD. Eur Respir J 4:561-567.
3. Peslin R, Felicio da Silva J, Chabot F, Duvivier C (1992) Respiratory Mechanics studied by multiple regression in unsedated ventilated patients. Eur Respir J 5:871-878.
4. Jubran A, Tobin MJ (1994) Use of flow-volume curves in detecting secretions in ventilator-dependent patients. Am J Respir Crit Care Med 150:766-769.
5. Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A (1995) Simple method to measure total expiratory time constant based on the passive expiratory flow-volume curve. Crit Care Med 23:1117-1122.
6. Guttmann J, Eberhard L, Fabry B, Bertschmann W, Zeravik J, Adolph M, Eckhart J, Wolff G (1995) Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 8:114-120.
7. Aerts JGVJ, Van den Berg B, Lourens MS, Bogaard JM (1999) Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiol Scand 43:322-327.
8. Fiastro JF, Habib MP, Quan SF (1988) Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 93:499-505.
9. Fabry B, Haberthür C, Zappe D, Guttmann J, Kuhlen R, Stocker R (1997) Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilatory demands during inspiratory pressure support and automatic tube compensation. Intensive Care Med 23:545-552.
10. Nott MR (1977) Expiratory resistances and airway pressure. Proc Royal Soc Med 70:784-788.
11. Marini JJ, Culver BC, Kirke W (1985) Flow resistance of exhalation valves and positive end-expiratory pressure devices used in mechanical ventilation. Am Rev Respir Dis 131:850-854.
12. Kayaleh RA, Wilson AF (1988) Mechanisms of expiratory valves resistance. Am Rev Respir Dis 137:1390-1394.
13. Bland JM, Altman DG (1986) Statistical methods for the assessing agreement between two methods of clinical measurement. Lancet 8:307-310.

14. Chelucci GL, Brunet F, Dall'Ava-Santucci J, Dhainaut JF, Paccaly D, Armaganidis A, Milic-Emili J, Lockhart A (1991) A single compartment model cannot describe passive expiration in intubated, paralyzed humans. Eur Respir J 4:458-464.
15. Bates JHT, Decramer M, Chartrand D, Zin WA, Boddener A, Milic-Emili J (1985) Volume – time profile during relaxed expiration in the normal dog. J Appl Physiol 59:732-737.
16. Chelucci GL, Dall' Ava-Santucci J, Dhainaut J-F, Chelucci A, Allegra A, Paccaly D, Brunet F, Milic-Emili J, Lockhart A (1993) Modelling of passive expiration in patients with adult respiratory distress syndrome. Eur Respir J 6:785-790.
17. Williams EM, Madgwick RG, Morris MJ (1998) Tidal expired airflow patterns in adults with airway obstruction. Eur Respir J 12:1118-1123.
18. Morris MJ, Madgwick RG, Collyer I, Denby F, Lane DJ (1998) Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. Eur Respir J 12:1113-1117.
19. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chassé M, Braidy J, Milic-Emili J (1994) detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 150:1311-1307.
20. Aerts JGVJ, Van den Berg B, Bogaard JM (1997) Controlled expiration in mechanically ventilated patients with chronic obstructive pulmonary disease. Eur Respir J 10:550-556.

CHAPTER 4

EXPIRATORY TIME CONSTANTS IN MECHANICALLY VENTILATED PATIENTS WITH AND WITHOUT COPD.

Marlies S. Lourens
Bart van den Berg
Joachim G.J.V. Aerts
Anton F.M. Verbraak
Henk C. Hoogsteden
Jan M. Bogaard.

Intensive Care Medicine 2000;26:1612-1618

"3-Zuid Beademing", the Intensive Care Unit

ABSTRACT

Objective: In mechanically ventilated patients the expiratory time constant provides information about the respiratory mechanics and the actual time needed for complete expiration. As an easy method to determine the time constant, the ratio of exhaled tidal volume to peak expiratory flow has been proposed. This assumes a single compartment model for the whole expiration. Since the latter has to be questioned in patients with COPD, we compared time constants calculated from various parts of expiration and related these to time constants assessed with the interrupter method.

Design: prospective study

Setting: a medical intensive care unit in a university hospital

Patients: 38 Patients (18 severe COPD, 8 mild COPD, 12 other pathology) were studied during mechanical ventilation under sedation and paralysis.

Measurements and Results: Time constants determined from flow-volume curves at 100%, the last 75, 50 and 25 % of expired tidal volume, were compared to time constants obtained from interrupter measurements. Furthermore, the time constants were related to the actual time needed for complete expiration and to the patient's pulmonary condition. The time constant determined from the last 75% of the expiratory flow-volume curve (RCfv75) was in closest agreement with the time constant obtained from the interrupter measurement, gave an accurate estimation of the actual time needed for complete expiration and was discriminative for the severity of COPD.

Conclusions: In mechanically ventilated patients with and without COPD, a time constant can well be calculated from the expiratory flow-volume curve for the last 75% of tidal volume, gives a good estimation of respiratory mechanics and is easy to obtain at the bedside.

INTRODUCTION

In Chronic Obstructive Pulmonary Disease (COPD) acute respiratory failure is a common and in many cases life-threatening complication, requiring ventilatory support. Mechanically ventilated patients with COPD are at risk of difficult weaning and chronic ventilatory dependency. Monitoring respiratory mechanics in these patients is a prerequisite to assess the patient's pulmonary condition, to detect poor patient-ventilator interaction and consequently optimise ventilator settings. By appropriately setting the ventilator, hyperinflation, intrinsic PEEP and consequently work of breathing can be minimised resulting in a more favourable outcome.

Many studies have addressed the issue of the mechanical properties of the respiratory system during lung inflation. The assessment of respiratory mechanics during relaxed expiration with simple tools, in clinical settings, has been rather unsuccessful.

The expiratory time constant provides information on the mechanical properties of the respiratory system, is a measure of lung emptying and can be used to predict the minimal time needed for complete exhalation [1,2]. A generally accepted way to determine the expiratory time constant is by multiplying compliance and resistance assessed with the interrupter method [3-5]. However, this method interferes with the relaxed expiration and is not considered a simple tool for bedside use. A more easy way to determine the expiratory time constant is based on the slope of the relaxed expiratory flow-volume curve [1,2,6-11]. Brunner et al. proposed to determine the expiratory time constant as the ratio of exhaled tidal volume to peak expiratory flow [1]. This approach assumes a single compartment model for the whole expiration, i.e. a single compartment emptying itself through a constant resistance. This has to be questioned in patients with COPD in view of the presence of ventilatory inhomogeneity and expiratory flow-limitation [12]. However, a linear relationship between flow and volume has been described for the later part of expiration in patients with airway obstruction [7,13-15]. Because this linear relationship is inherent in a one compartment model, we hypothesise that an effective time constant can more appropriately be calculated from the later part of expiration in these patients.

The purpose of this study was to assess the applicability of the expiratory time constant determined from the expiratory flow-volume curve at different

percentages of exhaled volume in mechanically ventilated patients both with and without COPD. These time constants were compared to reference time constants obtained from values of compliance and resistance determined with the interrupter method. To evaluate the clinical value of the time constants, we related them to the actual time needed for complete expiration to functional residual capacity and to the presence and severity of airflow obstruction.

PATIENTS AND METHODS

PATIENTS

The study was conducted in 38 patients admitted to the respiratory intensive care unit. Patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube with an inner diameter ≥ 7 mm, a ventilator-PEEP level < 10 cm H_2O, respiratory rate ≤ 20 breaths per minute and absence of air leaks. Twenty-six patients had a history of COPD. Amongst these, 18 patients suffered from severe COPD and required ventilatory support for respiratory failure due to acute exacerbation of COPD. All these patients fulfilled the criteria of severe COPD according to the ERS consensus: a clinical diagnosis of COPD and previous spirometric data showing an FEV_1 < 50 % of predicted (mean 30% of predicted) [16]. The remaining 8 patients had a history of moderate COPD and a previous FEV_1 between 50 and 70 % of predicted (mean 59%) [16]. These patients were ventilated for other conditions than COPD. In 12 patients, underlying diseases included a variety of medical conditions all complicated by respiratory failure and ventilator dependency. Thirty patients were intubated with an endotracheal tube (inner diameter range 7.5- 9 mm), 8 patients with a tracheostomy tube (inner diameter range 7 – 8.5 mm). All patients were ventilated with a Siemens Servo 900C ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study, except that if present, ventilator-PEEP was removed. In 32 patients, the volume-controlled mode was used, in 6 patients the pressure-controlled mode. The average minute volume was 9.7 l/min, ranging from 6 l to 17.5 l per minute. The average respiratory rate was 16 breaths per minute, ranging from 10 to 20 breaths per minute. At volume-controlled ventilation, the ratio between inspiratory and expiratory time was 35 : 65. In the pressure-controlled mode,

the ratio between inspiratory and expiratory time was 50 : 50. During the study all patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, Holland) and paralysed with vecuronium (Organon Teknika B.V., Boxtel, Holland). Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

RESPIRATORY MEASUREMENTS

A heated pneumotachometer (Lilly, Jaeger, Würzburg, Germany) was connected to the endotracheal tube to measure flow. Volume was obtained by computerised integration of the flow signal. Airway opening pressure was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). Data were stored and analysed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sample frequency of 100 Hz.

ANALYSIS OF THE FLOW-VOLUME CURVE

The time constant was obtained by calculating the quotient of exhaled volume and the corresponding change in flow at different values of exhaled volume. Time constants were calculated for 100 % (RCfv100), the last 75 % (RCfv75), 50 % (RCfv50) and 25 % (RCfv25) of exhaled volume. In formula for the RCfv50:

$$RCfv50 = \frac{0.5*Vt}{(V'50,ex - V'end,ex)}$$

RCfv50 = time constant obtained from flow-volume curve for last 50% of exhaled tidal volume (s)
0.5*Vt = 50% of expiratory tidal volume (l)
V'50,ex = flow at 50% of exhaled volume (l/s)
V'end,ex = flow at end-expiration (l/s)

For the calculation of the RCfv100 the peakflow was considered as 100% flow-level (fig.1).

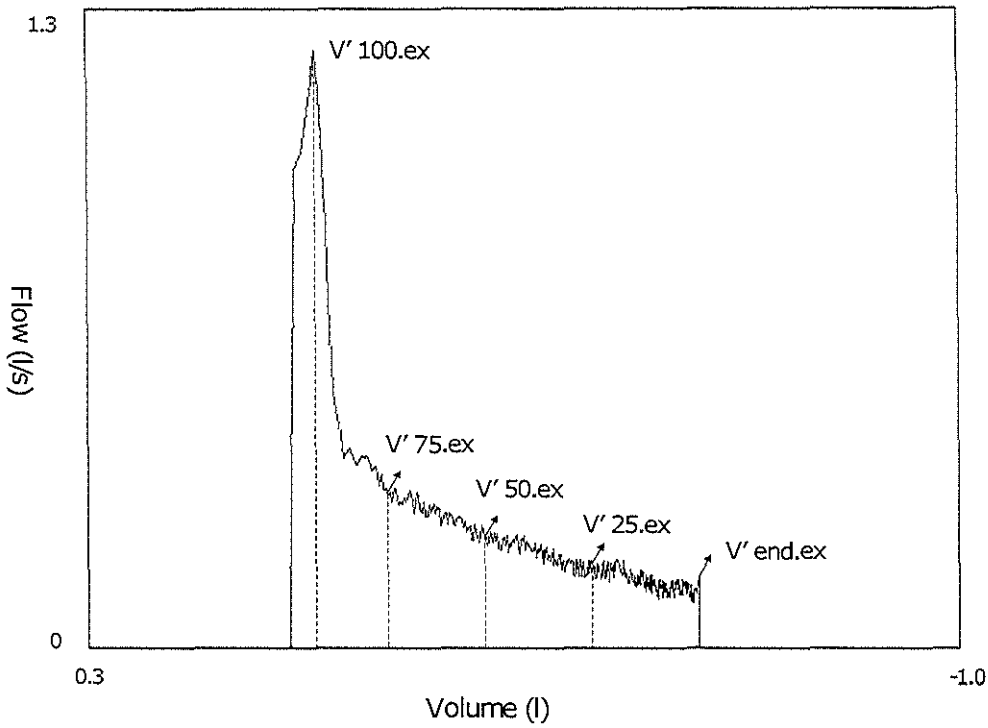


Figure 1. Flow -volume curve of a patient with COPD. V'100,ex, V'75,ex, V'50ex, V'25,ex and V'end,ex are indicated.

To compare our time constants with the method proposed by Brunner et al, the time constant was also calculated as the ratio of exhaled volume and peakflow (RCfvp) [1]. To estimate the actual time needed for lung emptying, the expiratory line of the ventilator circuit was disconnected from the ventilator at end-inspiratory pause and the patient was allowed to expire completely (n=27). Taking into account the noise in the flow recording, expiration was considered complete when the flow was $\leq$ 0.04 l/s. The time needed for complete expiration was measured (tact). All measurements were performed in triplicate and the average was calculated.

INTERRUPTER MEASUREMENTS

A pneumatic interrupter installed distal to the pneumotachometer in the ventilator circuit, was used for repeated occlusions of the upper airway during expiration. The valve was computer-controlled. Opening and closing of the valve was alternated at a cycle time of 500 ms. The interrupter procedure was performed throughout the expiration. Pressure and flow signals were stored on a computer for subsequent analysis. Values of the post-interruption plateau in tracheal pressure, of preceding flow and of corresponding volume were obtained for all subsequent occlusions during one expiration. Volume-pressure (V/P) and pressure-flow (P/V') curves were plotted from these values. Using a least squares linear regression method, a line was fit through the data from the second interruption till a volume was expired equal to the pre-set tidal volume. Compliance and resistance were determined for this tidal volume range from the slope of the V/P and P/V' curve, respectively. During flow limitation the resistance behaviour is complex and resistance has to be considered as effective resistance. The time constant (RCint) was calculated by multiplying compliance- and resistance-values. All measurements were performed in triplicate and the average was calculated.

DATA ANALYSIS

Time constants obtained from the flow-volume curve and from the interrupter method were compared using the method of Bland and Altman for assessing agreement between two methods of clinical measurement [17]. Differences between RCint and RCfv were plotted against the means of the corresponding values of RCint and RCfv, limits of agreement were estimated as $\pm$ 2 sd of the differences.

To assess the differences in time constants between the groups of mild COPD, severe COPD and other pathology, Kruskal-Wallis test was performed. A p-value <0.05 was considered significant.

To evaluate the sensitivity and specificity of the time constant as measure for COPD, receiver operating characteristic (ROC) curves were computed for the time constants obtained with the interrupter and flow-volume method at different percentages of exhaled volume [18,19]. An $FEV_1 < 70\%$ of predicted prior to ventilatory support was used as standard for discrimination between patients with other pathology and COPD (moderate and severe). The area

under the ROC curve represents the combined sensitivity and specificity behaviour of the used index.

The time constants obtained from flow-volume curves were correlated with the actual time needed for complete expiration. According to the concept of a single compartment model, passive lung emptying is described by the following exponential equation: $V(t) = V(0) * e^{(-t/\tau)}$ with V(0) and V(t) as respectively the lung volume at the start (time t=0) and at t (time=t) seconds from the onset of expiration and τ as the expiratory time constant [7-10]. According to this equation, 3 times the time constant is needed to achieve exhalation down to 5% of the initial volume. The time constants determined from the flow-volume curve were multiplied by 3 and correlated to 95% of the actual time needed for complete expiration, using Pearson's correlation. To show the relationship between RCfv and Tact the Bland and Altman method was used. The differences between 3*RCfv and Tact were plotted against their means. Limits of agreement were estimated as ± 2 sd of the differences.

RESULTS

In all patients, both relationships between volume and pressure and between pressure and flow obtained from interrupter measurements were found to be approximately linear for the volumes studied ($r^2 = 0.99$, sd 0.01 and $r^2 = 0.97$, sd 0.02, respectively).

The values of the time constants obtained from flow-volume curves and interrupter measurements are shown in table 1. Comparing the time constants of the 3 patient groups within one method, significant differences were found between the groups of moderate and severe COPD and between the groups of severe COPD and other pathology for the RCint, RCfv75 RCfv50 and RCfv25 (all $p<0.001$). The difference found between the group of moderate COPD and the group of other pathology was only significant for the RCint ($p=0.034$) and the RCfv75 ($p=0.017$).

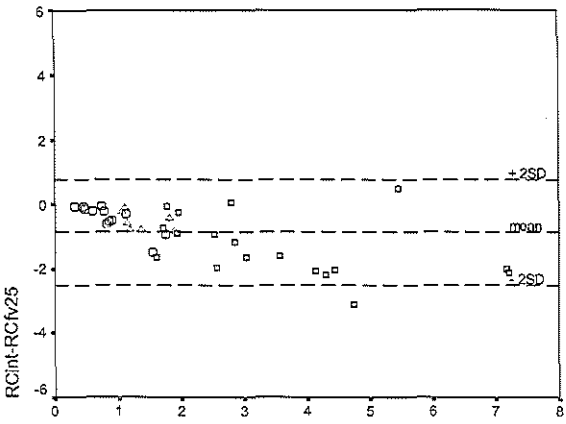
		severe COPD		moderate COPD		other pathology	
Rcint	mean (sd)	2.88	(1.61)*	1.02	(0.40)**	0.65	(0.28)
Rcfvp	mean (sd)	0.75	(0.20)	0.70	(0.19)	0.60	(0.10)
RCfv100	mean (sd)	0.85	(0.18)	0.79	(0.22)	0.63	(0.12)
RCfv75	mean (sd)	2.84	(1.53)*	1.05	(0.32)**	0.72	(0.18)
RCfv50	mean (sd)	3.42	(1.61)*	1.05	(0.32)**	0.84	(0.39)
RCfv25	mean (sd)	4.20	(1.99)*	1.47	(0.57)	1.06	(0.63)

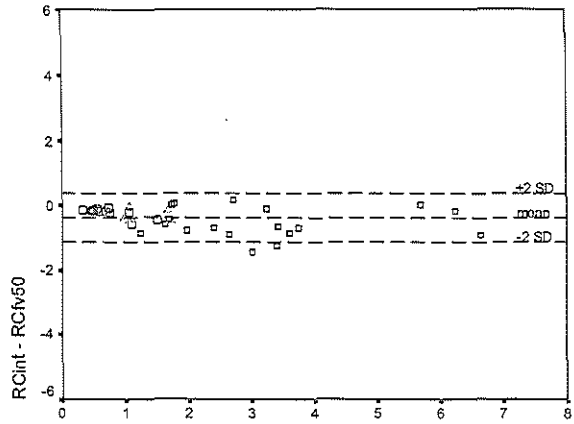
Table 1. Time constants obtained from flow-volume curves and interrupter measurements. For abbreviations and definitions see text.
* significant difference between time constants of severe and moderate COPD
** significant difference between time constants of moderate COPD and other pathology

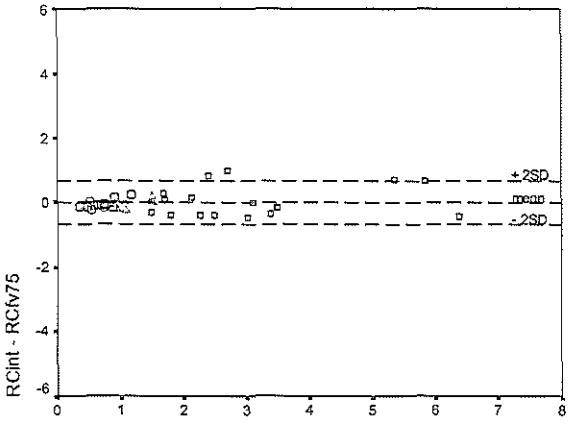
The agreement between the time constants obtained from flow-volume curves and interrupter measurements is shown in Bland and Altman analyses (figure 2). The differences between RCint and RCfv are plotted against their means. Mean difference and limits of agreement are indicated.

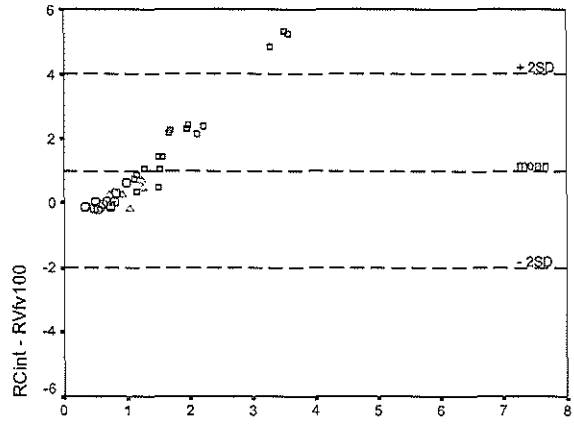
ROC-curves were computed for all time constants. The area under the curve was for the RCint 0.93 , for the RCfvp 0.75, for the RCfv100 0.82, for the RCfv75 0.94, for the RCfv50 0.92 and for the RCfv25 0.89. The RCfv75 with a cut-off level of 0.82 combines the highest sensitivity (0.96) and specificity (0.83) as measure of airways obstruction.

The mean difference between actual times needed for complete expiration and 3*RCfv was for the RCint 0.5 s (sd 2.8), for the RCfvp 2.9 s (sd 4.2), for the RCfv100 2.8 s (sd 4.2), for the RCfv75 0.4 s (sd 2.4), for the RCfv50 -0.5 s (sd 3.1) and for the RCfv25 -1.6 s (sd 3.6). Pearson's test yielded the following correlations between Tact and the respective time constants: RCint: 0.81 ($p<0.001$), RCfvp: 0.26 ($p>0.1$), RCfv100: 0.38 ($p=0.052$), RCfv75: 0.85 ($p<0.001$), RCfv50: 0.79 ($p<0.001$) and RCfv25: 0.82 ($p<0.001$). In figure 3, the Bland and Altman plot of 3*RCfv75 and Tact is shown.









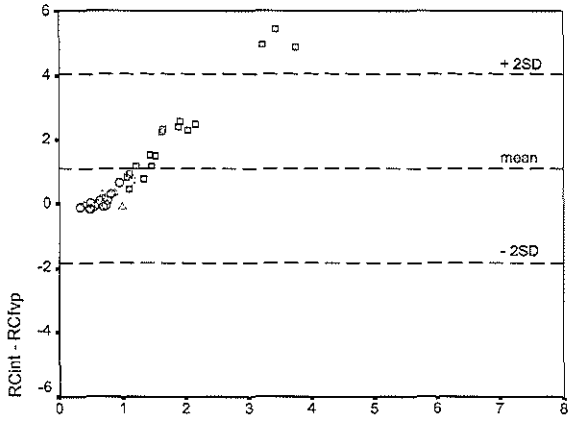


Figure 2. Bland and Altman analyses of differences (RCint - RCfv) plotted against the means of RCint and RCfv. Mean and standard deviations are indicated. □ = patients with severe COPD, Δ = patients with moderate COPD and O = patients with other pathology.

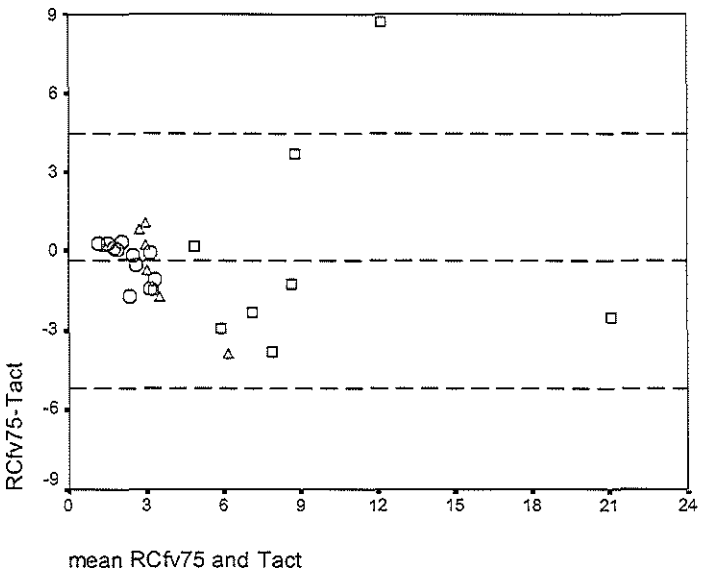


Figure 3. Bland and Altman analysis of the differences between 3 * the time constant obtained from the last 75% of tidal volume of the flow-volume curve (3*RCfv75) and the time needed for complete exhalation (Tact) against the means of 3*RCfv75 and Tact, in seconds. Mean and standard deviations are indicated. □ = patients with severe COPD, Δ = patients with moderate COPD and O = patients with other pathology.

DISCUSSION

This study demonstrates that in mechanically ventilated patients with and without COPD the expiratory time constant determined from the expiratory flow-volume curve for the last 75% of tidal volume is in closest agreement with the time constant obtained with interrupter measurements. The RCfv75 is a good prognosticator for the actual time needed for complete exhalation and is discriminative for the severity of COPD.

In the present study, time constants obtained from the flow-volume curves and time constant obtained with the interrupter technique were compared. The interrupter method is based on the assumption that a rapid equilibration occurs between alveolar and airway opening pressures during a brief period of airway occlusion [3-5]. In this study, the airways were occluded intermittently for 250 ms. In COPD patients with airway obstruction, pressure equilibration may be delayed because of regional differences in mechanical properties within the

lungs [3,4]. However, we observed pressure plateau's during airway closure within 250 ms in all patients. This is comparable to the findings of others, describing a plateau in airway opening pressure within 300 ms during expiratory interruptions [3]. In the present study the presence of an endotracheal tube or a tracheal cannula eliminated the influence of the upper airway. Therefore no delay in pressure equilibration occurred related to the compliance of the extrathoracic airways [20].

On the other hand the presence of the endotracheal tube might have influenced the time constant. The design of the study precluded removal of the endotracheal tube since all patients were on controlled ventilation with sedation and paralysis. However a previous study showed that in patients with COPD the presence of the endotracheal tube did not appreciably affect the slope of the later part of the expiratory flow-volume curve, due to the low flow-rates in these patients [21]. In the patient group with other pathology the average flow rate during expiration is usually higher. The endotracheal tube can cause a minor decrease in flow in these patients, resulting in a slightly higher time constant [21]. With respect to the exhalation valve of the ventilator, it has been described that this valve significantly decreases the peakflow , but does not affect the slope of the flow-volume curve during the later part of expiration [21].

The passive expiratory flow-volume relationship can be divided in an early rapid component, which reflects resistive behaviour of predominantly extrathoracic resistive elements and a consecutive slower component, mainly reflecting viscous and elastic properties of the lungs and chest wall [2,22,23]. The transition point between these components has been referred to as the inflection point, determined as the point of maximum slope following the peak expiratory flow [2]. In this study we found that the time constants calculated from the part of the flow-volume curve beyond the inflection point more closely approached the values determined with the interrupter method, especially in patients with COPD. The RCfv75 and RCfv50 were found to be in good agreement with the RCint. The results of the RCfv25 were less favourable, this is most likely due to an increase in the noise-signal ratio, because of the low flow rates at end-expiration. The RCfv100 and RCfvp gave a systematic underestimation of the time constant particularly in patients with COPD. In these patients the peakflow only minimally contributes to the exhalation and the rate of lungemptying is predominantly determined by the slope of the flow-

volume curve beyond the inflection point (figure1). Therefore, the method to determine the time constant as the ratio of exhaled volume to peakflow, proposed by Brunner et al, is less appropriate in COPD patients [1]. As the part of the expiratory flow-volume relationship beyond the inflection point approaches linearity, both in patients with COPD and with other pathology, it is more suitable for calculation of the time constant. This linearity has also been described by others [7,13-15]. We chose to use the RCfv75 instead of the RCfv50 for several reasons: the RCfv75 was in closest agreement with the RCint, it was the best discriminator for the severity of COPD and it represented a greater part of the expiratory flow-volume curve.

This is in agreement with the findings of Galbusera et al, who also studied expiratory time constants during mechanical ventilation at different percentages of exhaled volume [11]. However, in their calculation of the time constant the end-expiratory flow is not taken into account. In mechanically ventilated patients with flow limitation, expiration is usually terminated before the end-expiratory flow reaches zero l/s. Therefore, the end-expiratory flow should also be included in the calculation.

The present study shows that the time needed for complete expiration was approximately three times the calculated time constant for all patient groups, in which the RCfv75 correlated best with the Tact. This indicates that the time constant can be a useful tool in setting the ventilator. Recently, the expiratory time constant determined over the last 75% of expiratory tidal volume has even been implemented in the software of the Hamilton ventilator "Galileo" (Hamilton Medical AG, Rhäzüns, Switzerland), giving information about the suitable respiratory rate. In patients with severe COPD, however, it may be impossible to set the expiratory time at three times the time constant in view of the minimum respiratory rate required for sufficient ventilation. In these patients the time constant is informative on the patient's pulmonary condition and can be used to optimise patient-ventilator interaction.

The time constant was found to discriminate between patients with and without COPD. These findings are in line with previous studies, in which the time constant and the FEV1 were closely related both in spontaneously breathing and in mechanically ventilated patients with COPD [7,14].

The present study was performed in paralysed patients. During paralysis exhalation is passively driven by the elastic recoil of the total respiratory system. In mechanically ventilated patients without paralysis, muscle activity

may interfere during expiration. Several studies have described the presence of inspiratory muscle activity during the first part of expiration opposing emptying of the lungs [24-26]. It has however been shown in spontaneously breathing patients with COPD that the measured flow-volume relationship closely followed the course of the flow-volume curve predicted on the basis of the passive time constant during late expiration [24]. Another study reported activity of the diaphragm for only the first 50% of expiration [26]. In patients with COPD an even faster decline in inspiratory muscle activity has been described during expiration [27,28]. Therefore it is likely that a time constant can be determined from the later part of expiration in mechanically ventilated patients without paralysis. Further studies are required to validate the feasibility of the expiratory time constant in non paralysed patients.

In conclusion, in mechanically ventilated patients an expiratory time constant can best be calculated from expiratory flow-volume curve for the last 75% of exhaled tidal volume. Both in patients with COPD and in patients with other pathology, RCfv75's are in good agreement with time constants assessed with interrupter measurements. Furthermore, the RCfv75 is found to be a good prognosticator for the actual time needed for complete expiration and to be an indicator of the severity of COPD. Thus, a time constant calculated from the last 75% of the expiratory flow-volume curve is an easy method to assess respiratory mechanics at the bedside in artificially ventilated patients.

REFERENCES

1 Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A (1995) Simple method to measure total expiratory time constant based on the passive flow-volume curve. Crit Care Med 23:1117-1122.

2 Guttmann J, Eberhard L, Fabry B, Bertschmann W, Zeravik J, Adolph M, Eckart J, Wolff G (1995) Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 8:114-120.

3 Gottfried SB, Higgs BD, Rossi A, Carli F, Mengeot PM, Calverly PMA, Zocchi L, Milic-Emili J (1985) Interrupter technique for measurement of respiratory mechanics in anesthetized humans. J Appl Physiol 59(2):647-652.

4 Gottfried SB, Rossi A, Higgs BD, Calverly PMA, Zocchi L, Bozic C, Milic-Emili J (1985) Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 131:414-420.

5 Reinoso MA, Gracey DR, Hubmayr RD (1993) Interrupter mechanics of patients admitted to a chronic ventilator dependency unit. Am Rev Respir Dis 148:127-131.

6 McIlroy MB, Tierney DF, Nadel JA (1963) A new method for measurement of compliance and resistance of lungs and thorax. J Appl Physiol 18:424-427.

7 Aerts JGJV, Berg van den B, Lourens MS, Bogaard JM (1999) Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaest Scand 43:322-327.

8 Zin WA, Böddener A, Silva PRM, Pinto TMP, Milic-Emili J (1986) Active and passive respiratory mechanics in anesthetized dogs. J Appl Physiol 61:1647-1655.

9 Zin WA, Pengelly LD, Milic-Emili J (1982) Single-breath method for measurement of respiratory mechanics in anesthetized animals. J Appl Physiol 52:1266-1271.

10 Behrakis PK, Higgs D, Baydur A, Zin WA, Milic-Emili J (1983) Respiratory mechanics during halothane anesthesia and anesthesia-paralysis in humans. J Appl Physiol 55:1085-1092.

11 Galbusera C, Cortis G, Olivei M, Tosi PF, Via G, Ciccone R, Verde G, Iotti G, Braschi A (1999) Breath-by-breath evaluation of the expiratory time constant during mechanical ventilation. Am Rev Respir Crit Care Med 159(3):A366.

12 Peslin R, Felicio da Silva J, Chabot F, Divivier C (1992) Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients. Eur Respir J 5:871-878.

13 Rossi A, Polesi G, Brandi G, Conti G (1995) Intrinsic positive end-expiratory pressure (PEEP). Intensive Care Med 21:522-536.

14 Morris MJ, Madgewick RG, Collyer I, Denby F, Lane DJ (1998) Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. Eur Respir J 12:1113-1117.

15 Williams EM, Madgewick RG, Morris MJ (1998) Tidal expired airflow patterns in adults with airway obstruction. Eur Respir J 12:1118-1123.

16 Siafakas NM, Vermeire P, Pride P, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J (1995) Optimal assessment and management of chronic obstructive pulmonary disease. Eur Respir J 8:1398-1420.

17 Bland JM, Altman DG (1986) Statistical method for assessing agreement between two methods of clinical measurement. Lancet 8:307-310.

18 Mc Neil B, Keeler E, Adelstein SJ (1975) Primer on certain elements of medical decision making. N Engl J Med 293:211-215.

19 Zweig MH, Campbell G (1993) Receiver-operating characteristics (ROC) plots: a fundamental evaluation tool in clinical medicine. Clinical Chemistry 39: 561-577.

20 Jaeger MJ (1982) The effect of the cheeks and the compliance of alveolar gas on the measurement of respiratory variables. Respir Physiol 47:325-340.

21 Lourens MS, Berg van den B, Hoogsteden HC, Bogaard JM (1999) Flow-volume curves as measure of respiratory mechanics during ventilatory support: the effect of the exhalation valve. Intensive Care Med 25:799-804.

22 Chelucci GL, Brunet F, Dall'Ava-Santucii J, Dhainaut JF, Paccaly D, Armaganidis A, Milic-Emili J, Lockhart A (1991) A single compartment model cannot describe passive expiration in intubated, paralysed humans. Eur Respir J 4:458-464.

23 Bates JHT, Decramer M, Chartrand D, Zin WA, Boddener A, Milic-Emili J (1985) Volume-time profile during relaxed expiration in the normal dog. J Appl Physiol 59:732-737.

24 Shee CD, Ploy-song-sang Y, Milic-Emili J (1985) Decay of inspiratory muscle pressure during expiration in conscious humans. J Apppl Physiol 58:1859-1865.

25 Agostoni A, Citterio G, D'Angelo E (1979) Decay rate of inspiratory muscle pressure pressure during expiration in man. Respir Physiol 36:269-285.

26 Agostoni A, Citterio G (1979) Relative decay rate of inspiratory muscle pressure during expiration in man. Respir Physiol 38:335-346.

27 Morris MJ, Madgwick RG, Frew AJ, Lane DJ (1990) Breathing muscle activity during expiration in patients with chronic airflow obstruction. Eur Respir J 3:901-909.

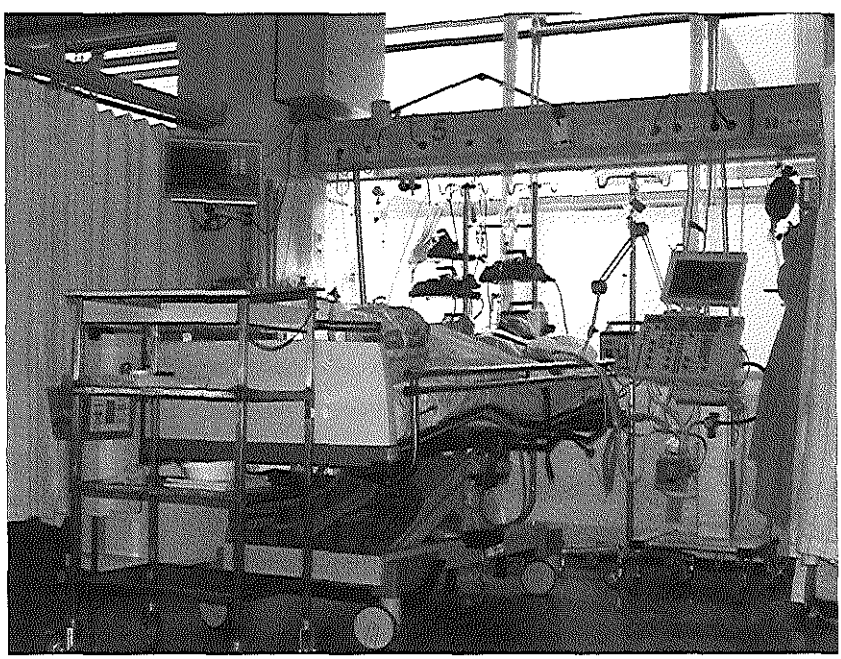
28 Citterio G, Agostoni E, Del Santo A, Marazzini L (1981) Decay of inspiratory muscle activity in chronic airway obstruction. J Appl Physiol 51:1388-1397.

CHAPTER 5

EXPIRATORY TIME CONSTANTS IN PATIENTS WITH COPD DURING CONTROLLED AND SUPPORT MECHANICAL VENTILATION.

M.S. Lourens
B. van den Berg
J.G.J.V. Aerts
H.C. Hoogsteden
J.M. Bogaard

Submitted for publication



At the bedside

ABSTRACT

Objective: In patients with COPD mechanical ventilation is often hampered by disturbed respiratory mechanics. Therefore, monitoring of respiratory mechanics is essential to adjust ventilator settings. In sedated and paralysed patients, the expiratory time constant was shown to be a good parameter of respiratory mechanics. We investigated the applicability of this time constant in the daily situation of ventilatory support without muscle relaxants.
Design: Prospective study
Setting: A medical intensive care unit in a university hospital
Patients: 26 mechanically ventilated patients with COPD
Measurements: 19 patients were studied in the volume controlled mode with and without sedation and paralysis. 10 patients were studied in the volume controlled mode and the pressure support mode. Expiratory time constants were determined for the last 75% of exhaled volume. Time constants obtained during the three modes of ventilation were compared.
Results: Close agreement was found between expiratory time constants determined during controlled mechanical ventilation with and without muscle relaxants; the mean difference was 0.06 s (SD 0.25 s). Between time constants determined during pressure support ventilation and time constants determined during controlled ventilation less agreement was found; the mean difference was -0.18 s (SD 0.89 s)
Conclusions: This study indicates that the determination of expiratory time constants is feasible in patients with COPD who are mechanically ventilated without muscle relaxant. Expiratory time constants may be used for estimating respiratory mechanics at the bedside and adjusting ventilator settings in patients with COPD on ventilatory support without paralysis.

INTRODUCTION

In patients with severe chronic obstructive pulmonary disease (COPD) acute respiratory failure is a common, and in many cases life threatening, event requiring ventilatory support. When mechanical ventilation has been instituted, these patients are at risk of difficult weaning and chronic ventilator dependency. The importance of monitoring respiratory mechanics in these patients is generally accepted. By gaining insight in the patient's respiratory condition and patient-ventilator interaction, medical treatment and ventilator settings can be optimised, resulting in a more favourable outcome.

The past years various techniques have been developed to quantify respiratory mechanics in artificially ventilated patients (1-3). However, most of these techniques were focused on the inspiration and the data obtained are severely affected by ventilatory modes and settings (4). In contrast, expiration is far less influenced by the ventilator.

In a recent study, we showed that an expiratory time constant determined from the last 75% of the expiratory flow-volume curve gave a good estimation of respiratory mechanics at the bedside in mechanically ventilated patients (5). That study was performed in patients mechanically ventilated under sedation and paralysis. In that situation expiration is determined by the elastic recoil of the respiratory system (the driving force) and the resistance of respiratory system and tube (the opposing force). In daily routine, muscle relaxants are seldom used in mechanically ventilated patients. During mechanical ventilation applied without muscle relaxants, muscle activity may interfere during expiration. In patients with COPD, the patient-ventilator interaction is cumbersome and monitoring respiratory mechanics crucial. Therefore, it is of clinical importance to investigate if the applicability of the expiratory time constant, as previously described during sedation and paralysis, can be extrapolated to the daily situation of ventilatory support without muscle relaxants.

The purpose of this study is to assess the feasibility of an expiratory time constant in non-paralysed patients with COPD. We compared time constants obtained during controlled mechanical ventilation with and without muscle relaxants and during pressure support ventilation.

PATIENTS AND METHODS

PATIENTS

26 patients with COPD admitted to the respiratory intensive care unit were studied. The patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube, a ventilator-PEEP level < 10 cm H_2O and absence of air leaks. All patients had a history of severe COPD according to the ERS consensus (6). 19 patients of these patients had undergone pulmonary function tests within a year before the period of mechanical ventilation. The average FEV_1 as percentage of predicted was 35 % (SD 8%). In 23 patients the negative expiratory pressure (NEP) method was used to assess the presence of flow limitation during mechanical ventilation (7). In 21 patients flow limitation was found, the mean flow portion (expressed as percentage of expiratory tidal volume in which no increase in flow was caused by the NEP) was 89% (SD 6 %). Patient characteristics and medical conditions leading to mechanical ventilation are shown in table 1.

23 patients were intubated with an oro- tracheal tube (inner diameter range 7.5- 9 mm), 2 patients with a naso-tracheal tube (inner diameter 7.0 and 7.5 mm) and one patient with a tracheostomy tube (inner diameter 8.0 mm). All patients were ventilated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden).

16 patients were studied under sedation in the volume controlled mode both with and without paralysis. All measurements in these patients were performed within an hour. 10 patients were studied without paralysis both in the volume controlled mode and in the pressure support mode. 3 of the latter patients were also studied in the volume controlled mode under sedation and paralysis. The time between the measurements in the volume controlled mode and the pressure support mode varied from 2 hours till 24 hours. In the volume controlled mode, ventilator settings were kept as set by the primary physician, with the exception that ventilator-PEEP was removed. The average minute volume was 8.6 l/min ranging from 7 to 12.5 l/min. The average respiratory rate was 13 breaths per minute, ranging from 9 to 20 breaths per minute. The ratio between inspiratory and expiratory time was 35 : 65. In the pressure support mode, the setting of the inspiratory pressure level (IPL) was adjusted to maintain acceptable tidal volume and respiratory frequency. The average

IPL above PEEP was 13 cm H2O, ranging from 10 to 20 cm H2O. The average PEEP was 5 cm H2O, ranging from 0 to 8 cm H2O.
For sedation midazolam (Roche Nederland B.V., Mijdrecht, Holland) was used and for paralysis vecuronium (Organon Teknika B.V., Boxtel, Holland). Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

RESPIRATORY MEASUREMENTS

Two measuring devices were used. The first was a respiratory mechanics monitoring system (RMMS) developed in our hospital, the second was a commercially available system (Novametrix, Cosmo Plus, Medical Systems inc., Wallingford, USA). Both measurement systems were randomly used, but in each patient only one system was employed. Earlier investigations have shown that measurements with both systems yielded identical results.
The RMMS comprised of a heated pneumotachometer (Lilly, Jaeger, Würzburg, Germany) which was connected to the endotracheal tube to measure flow. Volume was obtained by computerised integration of the flow signal. Airway opening pressure was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). Data were stored and analysed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sample frequency of 100 Hz.
With the Novametrix system flow was measured by a disposable fixed orifice differential flow sensor (Novametrix Medical Systems Inc., Wallingford CT, USA), connected to the endotracheal tube. Volume was obtained by computerised integration of the flow signal. Pressure was measured by a differential pressure transducer referenced to atmosphere (Novametrix Medical Systems Inc., Wallingford CT). Data were stored at a sample frequency of 100 Hz (Novametrix, Cosmo Plus, Medical Systems inc., Wallingford, USA) and analysed using a personal computer.

Patient	Age (years)	Sex	Diagnosis	NEP (FLP)	FEV1 (%pred)
1	78	M	Exacerbation COPD	86	47
2	55	F	Exacerbation COPD	96	32
3	80	M	COPD, pneumonia	92	
4	70	M	COPD, cerebral bleeding	97	
5	69	M	Exacerbation COPD	86	27
6	55	F	Exacerbation COPD	90	29
7	61	M	COPD, pneumonia	0	21
8	58	M	Exacerbation COPD	92	37
9	76	F	Exacerbation COPD	95	
10	78	M	Exacerbation COPD	92	37
11	57	M	COPD, pneumonia	87	41
12	85	F	COPD, gastro-intestinal bleeding	92	
13	87	M	COPD, lung cancer	77	
14	81	M	Exacerbation COPD	0	30
15	65	F	Exacerbation COPD	92	37
16	73	F	Exacerbation COPD	*	34
17	70	M	Exacerbation COPD	84	47
18	74	M	Exacerbation COPD	94	33
19	71	F	COPD, pneumonia	*	31
20	74	M	COPD, contusio cerebri	82	35
21	67	M	COPD, pulmonary bleeding	95	43
22	67	M	Exacerbation COPD	82	31
23	65	M	COPD, gastro-intestinal bleeding	77	
24	80	F	COPD, pneumonia	94	
25	60	F	Exacerbation COPD	97	21
26	70	F	Exacerbation COPD	*	50

Table 1. Patient characteristics. NEP = negative expiratory pressure, expressed as FLP = flow limited portion of exhaled tidal volume (%) . FEV1= forced expiratory volume in one second, expressed as percentage of predicted. * in these patients no NEP was applied.

ANALYSIS OF THE FLOW-VOLUME CURVE

In all modes of mechanical ventilation flow–volume loops were recorded. Expiratory time constants were obtained by calculating the quotient of exhaled volume and the corresponding change in flow for the last 75% of exhaled volume (Fig. 1) (5).
In formula for the RC75:

$$RC75 = \frac{0.75*Vt}{(V'75,ex - V'end,ex)}$$

RC75 = time constant obtained from flow-volume curve for last 75% of exhaled tidal volume (s)
0.75*Vt = 75% of expiratory tidal volume (l)
V'75,ex = flow at 75% of exhaled volume (l/s)
V'end,ex = flow at end-expiration (l/s)

All measurements were performed in duplicate and the average was calculated.

DATA ANALYSIS

Time constants obtained during controlled mechanical ventilation with sedation and paralysis (RCvc+) were compared to time constants obtained during controlled mechanical ventilation without sedation and paralysis (RCvc-), using the method of Bland and Altman for assessing agreement between two methods of clinical measurement (8). Differences between RCvc+ and RCvc- were plotted against the means of the corresponding values of RCvc+ and RCvc-, limits of agreement were estimated as ± 2 sd of the differences. The same Bland and Altman analysis was used for the comparison of time constants obtained during controlled mechanical ventilation (RCvc-) and time constants obtained during pressure support ventilation (RCps).

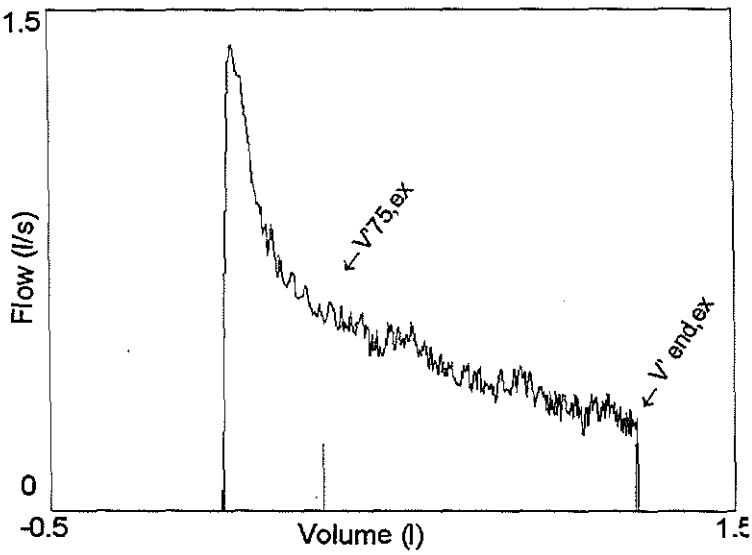


Figure 1.
Flow -volume curve of a patient with COPD. V'75,ex and V'end,ex are indicated.

RESULTS

The values of the time constants for the individual patients during the three ways of mechanical ventilation are shown in table 2.

The agreement between the time constants obtained during controlled mechanical ventilation with sedation and paralysis (RCvc+) and the time constants obtained without sedation and paralysis (RCvc-) is shown in a Bland and Altman analysis (Fig. 2). The differences between RCvc+ and RCvc- are plotted against their means. The mean difference was 0.06 s (SD 0.25 s).

Figure 3 shows the results of the Bland and Altman analysis comparing time constants obtained during volume controlled mechanical ventilation without sedation and paralysis and the time constants obtained during pressure support ventilation (RCps). The differences between RCps and RCvc- are plotted against their means. The mean difference was -0.18 s (SD 0.89 s).

In both cases, no dependency of bias on the absolute value of RC could be detected (fig. 2 and 3). Because the differences increased with the absolute value of RC, the differences in RC were also calculated in terms of percentage of the mean. For the difference between RCvc+ and RCvc- the mean difference was 2.5 % (SD 9.8%). For the comparison of RCps and RCvc- this value was -11.9 % (SD 38.7%).

Patient	RCvc+ (s)	RCvc- (s)	RCps (s)
1	1.7	2.0	
2	3.5	3.4	
3	2.6	2.5	
4	2.6	2.6	
5	3.7	4.1	
6	2.0	2.1	
7	1.3	1.3	
8	1.7	1.7	
9	2.4	2.3	
10	2.5	2.3	
11	1.5	1.5	
12	1.5	1.6	
13	2.4	2.4	
14	1.5	1.6	
15	1.7	1.7	
16	0.9	0.9	
17	3.0	2.3	2.6
18	4.0	3.3	2.0
19	1.4	1.2	2.2
20		2.6	2.6
21		4.0	4.9
22		2.7	1.5
23		1.7	1.2
24		2.2	1.4
25		4.5	5.2
26		2.7	1.9

Table 2. Time constant values for the individual patients (s).
RCvc+: time constant obtained during controlled mechanical ventilation with sedation and paralysis. RCvc-: time constant obtained during controlled mechanical ventilation without sedation and paralysis. RCps: time constant obtained during pressure support ventilation.

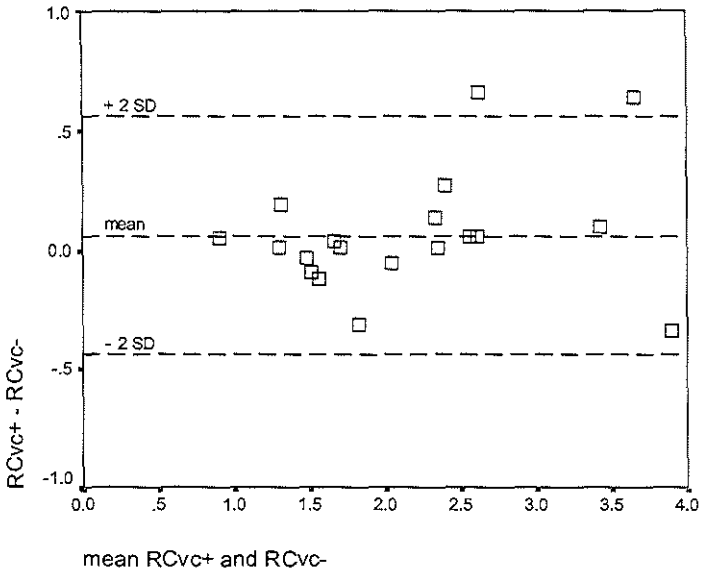


Figure 2. Bland and Altman analyses of differences (RCvc+ - RCvc-) plotted against the means of RCvc+ and RCvc-. Mean and standard deviations are indicated.

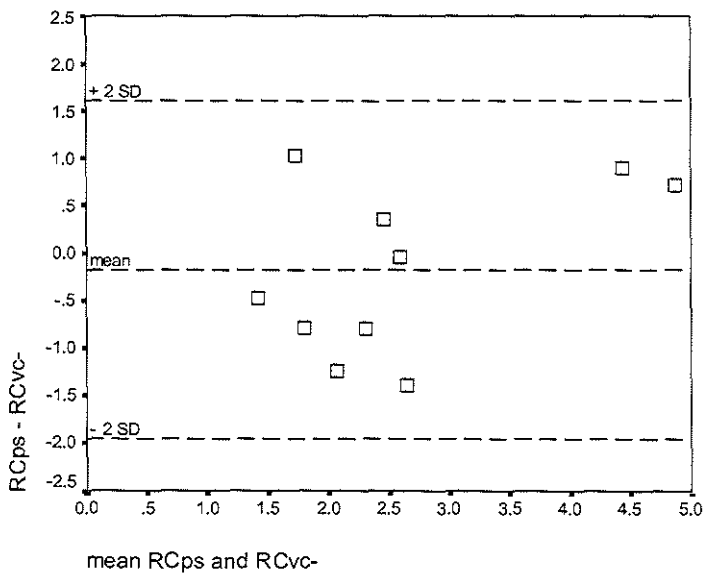


Figure 3. Bland and Altman analysis of the differences between (RCps - RCvc-) plotted against the means of RCps and RCvc- . Mean and standard deviations are indicated.

DISCUSSION

This study demonstrates that an expiratory time constant is a feasible respiratory parameter in patients with COPD, mechanically ventilated without muscle relaxants. Close agreement was found between expiratory time constants determined during controlled mechanical ventilation with and without muscle relaxants. Time constants determined during pressure support ventilation showed greater variability if compared to time constants determined during volume controlled ventilation.

During relaxed expiration, passive lung emptying has been described by a one compartment model, i.e. a single compartment emptying itself through a constant resistance (9-11). In that model the driving force is the elastic recoil of the respiratory system and the opposing force is the resistance of respiratory system. In that situation, the time decay of expired volume has been described by a mono-exponential function : $V_{(t)} = V_0 * e^{-t/\tau rs}$, with V_0 and $V_{(t)}$ as, respectively, the lung volume at the start (time = 0) and at t (time = t) s from the onset of expiration and τrs as the expiratory time constant (9, 12, 13). The expiratory time constant is the product of respiratory compliance (Crs) and resistance (Rrs). Therefore, τrs = Crs * Rrs, in which Crs is: exhaled volume (V) / change in elastic recoil pressure of the respiratory system (Pel, rs) and in which Rrs is: resistive pressure dissipated to overcome resistance (Pres) / flow (V'). As at any given time Pel,rs is equivalent to Pres, it can be derived that τrs = dV/dV', which is the slope of the linear flow volume relationship during relaxed expiration. Already in 1954 Comroe et al suggested that flow-volume curves of passive expiration could be used to assess the mechanical properties of the lung and chest wall (14).

Various methods have been proposed to quantify the relaxed flow-volume curve (9, 11, 13, 15-18). However, none of these methods has gained popularity as bedside technique. A simple method was described by Brunner et al. who proposed to determine the expiratory time constant as the ratio of exhaled tidal volume to peak expiratory flow (17). This approach assumes a single compartment model for the whole expiration, i.e. a single compartment emptying itself through a constant resistance. However, in patients with COPD this method was shown not to be of clinical significance, in view of the presence of ventilatory inhomogeneity and expiratory flow limitation (5, 19).

During mechanical ventilation, the passive expiratory flow-volume relationship can be divided into an early rapid component, which reflects resistive behaviour of predominantly extra thoracic resistive elements, and a consecutive slower component, mainly reflecting elastic and viscous properties of the lungs and chest wall (5, 20, 21). The transition point between these components has been referred to as the inflection point, determined as the point of maximum slope following the peak expiratory flow (16). Several studies described a linear relationship between flow and volume for the part of the flow volume curve beyond the inflection point, also for patients with COPD (20, 22-24). It was shown that a time constant could well be determined from this part of the expiratory flow volume curve in patients on controlled mechanical ventilation with sedation and paralysis (5). It has to be emphasised that in these patients, by the presence of viscous flow limitation over the larger part of expiration the time constant has to be defined as an "effective" time constant related to the lung emptying rate.

Also in non-intubated patients with COPD, it was shown that an average time constant could be calculated from the later part of expiratory tidal volume (22). The results of the present study are in line with the outcome of that study.

We find that during mechanical ventilation time constants determined with and without paralysis do correlate well, certainly if the volume controlled mode is considered. When measurements during mechanical ventilation with paralysis are compared to measurement obtained without paralysis, the effect of muscle activity should be taken into account. Several studies have described the presence of inspiratory muscle activity during the first part of expiration opposing emptying of the lungs (25-27). In patients without COPD, activity of the diaphragm was observed during the first 50% of expiration (25). In patients with COPD even a faster decline in inspiratory muscle activity has been described during expiration (28, 29). Furthermore, it has been shown in spontaneously breathing patients with COPD that the measured flow-volume relationship closely followed the course of the flow-volume curve predicted on the basis of the passive time constant during late expiration (27).

This is also confirmed by the present study; good agreement is found in time constants determined during volume controlled mechanical ventilation with and without muscle relaxants. During pressure support ventilation less agreement is found. We hypothesise that this is due the greater variability in breathing pattern in patients on support ventilation compared to controlled ventilation.

Furthermore, the pulmonary situation might be altered, considering the time interval between the measurements during volume controlled ventilation and pressure support ventilation.

During pressure support ventilation, the presence of missed inspiratory efforts (i.e. when the patient initiates inspiration and is not followed by the ventilator) should be taken into account . The expiratory flow volume curve is altered by these missed inspiratory efforts, however, in the majority of patients the slope of the curve remains essentially the same, and a time constant can still be calculated.

As the expiratory time constant is considered as parameter of respiratory mechanics, the presence of endotracheal tube should also be reckoned with (30). However, a previous study showed that in patients with COPD the presence of the endotracheal tube did not appreciably affect the slope of the later part of the flow volume curve (21). We hypothesise that this is because the resistance (the tube) is added downstream from the "choke point". Several studies have demonstrated that no change in iso-volume flow was found when a resistance was applied (till a critical level) in patients with expiratory flow limitation (31-35).

In conclusion, time constants determined from expiratory flow-volume curves obtained with and without paralysis during controlled mechanical ventilation are in close agreement. Time constants determined during pressure support ventilation showed greater variability if compared to time constants determined during volume controlled ventilation. This study shows that time constants are also feasible in mechanically ventilated patients without paralysis. Although these "effective" time constants might not fully reflect physiological events, they give an estimation of respiratory mechanics at the bedside and can be used to set the ventilator.

REFERENCES

1. Jubran A. Monitoring patient mechanics during mechanical ventilation. Crit Care Clin 1998: 14:629-653.
2. Rossi A, Polese G, Milic Emili J. Monitoring respiratory mechanics in ventilator-dependent patients. Principles and Practise of Intensive Care Monitoring. New York: McGraw-Hill, 1998.
3. Tobin MJ. Respiratory monitoring in the intensive care unit. Am Rev Respir Dis 1988: 138:1625-1642.
4. Rossi A, Polese G. As simple as possible, but not simpler. Intensive Care Med 2000: 26:1591-1594.
5. Lourens MS, van den Berg B, Aerts JGJV, Verbraak ATM, Hoogsteden HC, Bogaard JM. Expiratory time constants in mechanically ventilated patients with and without COPD. Intensive Care Med 2000: 26:1612-1618.
6. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995: 8:1398-1420.
7. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chasse M, Braidy J, Milic-Emili J. Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 1994: 150:1311-1317.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986: 1:307-310.
9. Zin WA, Pengelly LD, Milic-Emili J. Single-breath method for measurement of respiratory mechanics in anesthetized animals. J Appl Physiol 1982: 52:1266-1271.
10. Otis A, Fenn W, Rahn H. Mechanics of breathing in man. J Appl Physiol 1950: 2:592-607.
11. McIlroy M, Tierney D, Nadel J. A new method for measurement of compliance and resistance of lung and thorax. J Appl Physiol 1963: 17:424-427.
12. Behrakis PK, Higgs BD, Baydur A, Zin WA, Milic-Emili J. Respiratory mechanics during halothane anesthesia and anesthesia-paralysis in humans. J Appl Physiol 1983: 55:1085-1092.
13. Zin WA, Boddener A, Silva PR, Pinto TM, Milic-Emili J. Active and passive respiratory mechanics in anesthetized dogs. J Appl Physiol 1986: 61:1647-1655.
14. Comroe J, Nisell O, Nimms R. A simple method for concurrent measurement of compliance and resistance to breathing in anesthetised animals and man. J Appl Physiol 1954: 7:225-228.

15. Chelucci GL, Dall' Ava-Santucci J, Dhainaut JF, Chelucci A, Allegra A, Paccaly D, Brunet F, Milic-Emili J, Lockhart A. Modelling of passive expiration in patients with adult respiratory distress syndrome. Eur Respir J 1993: 6:785-790.
16. Guttmann J, Eberhard L, Fabry B, Bertschmann W, Zeravik J, Adolph M, Eckart J, Wolff G. Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 1995: 8:114-120.
17. Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A. Simple method to measure total expiratory time constant based on the passive expiratory flow-volume curve. Crit Care Med 1995: 23:1117-1122.
18. Chelucci GL, Brunet F, Dall'Ava-Santucci J, Dhainaut JF, Paccaly D, Armaganidis A, Milic-Emili J, Lockhart A. A single-compartment model cannot describe passive expiration in intubated, paralysed humans. Eur Respir J 1991: 4:458-464.
19. Peslin R, da Silva JF, Chabot F, Duvivier C. Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients. Eur Respir J 1992: 5:871-878.
20. Aerts JG, van den Berg B, Lourens MS, Bogaard JM. Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiol Scand 1999: 43:322-327.
21. Lourens MS, van den Berg B, Hoogsteden HC, Bogaard JM. Flow-volume curves as measurement of respiratory mechanics during ventilatory support: the effect of the exhalation valve. Intensive Care Med 1999: 25:799-804.
22. Morris MJ, Madgwick RG, Collyer I, Denby F, Lane DJ. Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. Eur Respir J 1998: 12:1113-1117.
23. Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med 1995: 21:522-536.
24. Williams EM, Madgwick RG, Morris MJ. Tidal expired airflow patterns in adults with airway obstruction. Eur Respir J 1998: 12:1118-1123.
25. Agostoni E, Citterio G. Relative decay rate of inspiratory muscle pressure and breath timing in man. Respir Physiol 1979: 38:335-346.
26. Agostoni E, Citterio G, D'Angelo E. Decay rate of inspiratory muscle pressure during expiration in man. Respir Physiol 1979: 36:269-285.
27. Shee CD, Ploy-Song-Sang Y, Milic-Emili J. Decay of inspiratory muscle pressure during expiration in conscious humans. J Appl Physiol 1985: 58:1859-1865.
28. Citterio G, Agostoni E, Del Santo A, Marazzini L. Decay of inspiratory muscle activity in chronic airway obstruction. J Appl Physiol 1981: 51:1388-1397.
29. Morris MJ, Madgwick RG, Frew AJ, Lane DJ. Breathing muscle activity during expiration in patients with chronic airflow obstruction. Eur Respir J 1990: 3:901-909.

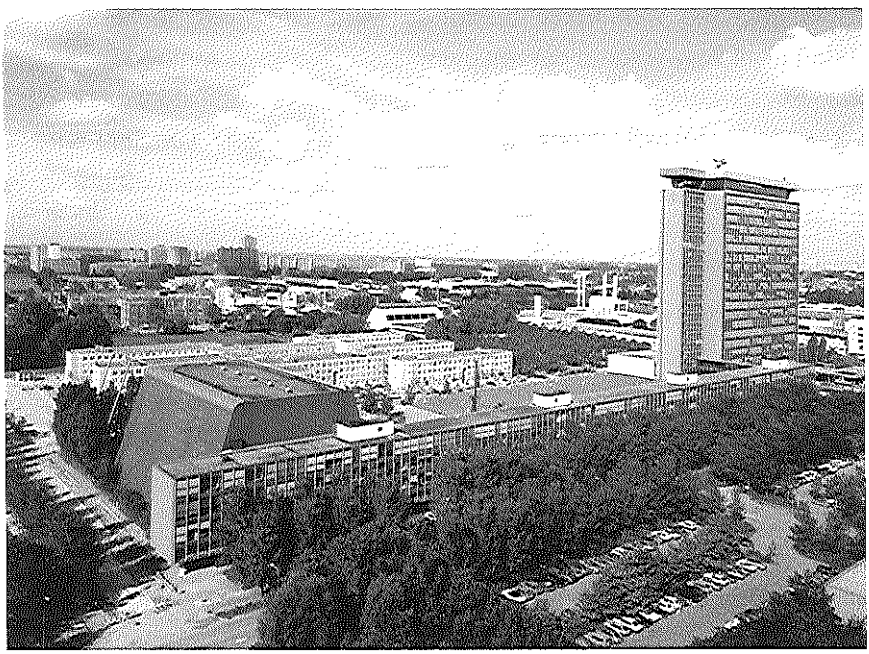
30. Conti G, De Blasi RA, Lappa A, Ferretti A, Antonelli M, Bufi M, Gasparetto A. Evaluation of respiratory system resistance in mechanically ventilated patients: the role of the endotracheal tube. Intensive Care Med 1994: 20:421-424.
31. Lourens MS, Van den Berg B, Verbraak ATM, Hoogsteden HC, Bogaard JM. Effect of series of resistance levels on flow limitation in mechanically ventilated COPD patients. Respir Physiol, in press.
32. Aerts JG, van den Berg B, Bogaard JM. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997: 10:550-556.
33. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989: 139:621-626.
34. Fry D, Hyatt R. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. Am J Med 1960: 24:672-689.
35. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol1967: 22:95-108.

CHAPTER 6

ESTIMATION OF EXPIRATORY TIME CONSTANTS VIA FUZZY CLUSTERING

Marlies S. Lourens
Lejla Alić
Bart van den Berg
Anton F.M. Verbraak
Jan M. Bogaard
Henk C. Hoogsteden
Robert Babuška

Adapted from Artificial Intelligence in Medicine 2001;21:91-105
Submitted for publication



Delft University of Technology, in collaboration with whom the fuzzy clustering study was performed.

ABSTRACT

Objective: In mechanically ventilated patients the expiratory time constant provides information about respiratory mechanics. In the present study a new method, fuzzy clustering, is proposed to determine expiratory time constants. Fuzzy clustering differs from other methods since it neither interferes with expiration nor presumes any functional relationship between the variables analysed. Furthermore, time constant behaviour during expiration can be assessed, instead of an average time constant. The time constants obtained with fuzzy clustering are compared to time constants conventionally calculated from the same expirations.

Methods: 20 mechanically ventilated patients, including 10 patients with COPD, were studied. The data of flow, volume and pressure were sampled. From these data, four local linear models were detected by fuzzy clustering. The time constants (τ) of the local linear models (clusters) were calculated by a least-squares technique. Time constant behaviour was analysed. Time constants obtained with fuzzy clustering were compared to time constants calculated from flow-volume curves using a conventional method.

Results: Fuzzy clustering revealed two patterns of expiratory time constant behaviour. In the patients with COPD an initial low time constant was found (mean τ1: 0.33 s, SD 0.21) followed by higher time constants; mean τ2: 2.00 s (SD 0.91s), mean τ3: 3.45 s (SD 1.44) and mean τ4: 5.47 s (SD 2.93). In the other patients only minor changes in time constants were found; mean τ1: 0.74 s (SD 0.30), mean τ2: 0.90 s (SD 0.23), mean τ3: 1.04 s (SD 0.42) and mean τ4: 1.74 s (SD 0.78). Both the pattern of expiratory time constants, as well as the time constants calculated from the separate clusters, were significantly different between the patients with and without COPD. Time constants obtained with fuzzy clustering for cluster 2, 3 and 4 correlated well with time constants obtained from the flow-volume curves.

Conclusions: In mechanically ventilated patients, expiratory time constant behaviour can accurately be assessed by fuzzy clustering. A good correlation was found between time constants obtained with fuzzy clustering and time constants obtained by conventional analysis. On the basis of the time constants obtained with fuzzy clustering, a clear distinction was made between patients with and without COPD.

INTRODUCTION

The importance of monitoring respiratory mechanics in patients on ventilatory support is generally accepted. Respiratory variables can be used to assess patients' pulmonary condition, to detect poor patient-ventilator interaction and consequently to optimise ventilator settings. This applies in particular to patients with COPD in whom the determination of the degree of bronchial obstruction is essential to adjust medical treatment and ventilator settings and to prognosticate weaning outcome.

For the analysis of lung emptying the expiratory time constant is an important parameter. The expiratory time constant provides information on the mechanical properties of the respiratory system and can be used to predict the minimal time needed for complete expiration[1, 2]. Several methods have been proposed to determine the expiratory time constant[2-6]. However, these methods all have disadvantages, with respect to either measurement technique or analysis. One method interferes with the expiration; thereby altering the respiratory mechanics[4, 5]. Other methods are based on qualitative and subjective pattern recognition. Again other methods assume a linear relationship between flow and volume for the whole expiration; in patients with COPD, this has to be questioned in view of the presence of ventilatory inhomogeinity and expiratory flow-limitation[3, 6]. The latter problem has been avoided by analysing only the last 75% of expiration[2]. Although that method is applicable in the majority of patients, a fair number of patient remains, in whom a time constant determined over 75% of expiration does not represent lung emptying.

In this study, a new method based on fuzzy clustering is proposed to determine expiratory time constants. Fuzzy clustering differs from other methods since it does not interfere with the expiration, nor presumes any functional relationship between the variables analysed and does not rely on subjective pattern recognition[7]. Furthermore, by fuzzy clustering the time constant behaviour over the whole expiratory phase can be estimated. Therefore, fuzzy clustering could be a valuable addition to the conventional methods describing lungemptying in mechanically ventilated patients. In this

study, time constants are assessed with fuzzy clustering and compared to time constants obtained with a conventional method.

PATIENTS AND METHODS

PARAMETER ESTIMATION BASED ON FUZZY CLUSTERING

The method is based on a straightforward extension of the classical linear single compartment model[8, 9]. This model describes the dynamic relation between the pressure P (cm H2O), the air flow-rate V' (l/s) and the volume V (l) of the lungs:

$$P = Ers\ V + Rrs\ V' + P_0 \qquad (1)$$

P is the pressure at airway opening, Ers is respiratory system elastance, Rrs is the respiratory system resistance and P0 is the offset pressure, which represents the end-expiratory pressure. During expiration V' is considered a negative value. Ers, Rrs and P0 are parameters to be estimated from data. It is well known that this linear model may yield too coarse an approximation of the given data, especially for patients with pulmonary disorders. Therefore, various modifications of equation 1 have been proposed. Amongst these are the use of different variables for inspiration and expiration and the introduction of nonlinearities by considering E and R as functions of volume or flow[8, 9]. However, the model above (1) turned out as most adequate for clinical use[9].

The method used in this paper is based on an automatic detection (localisation) of multiple local linear models[7]. Hence, no assumptions are made about the mathematical form or parameterisation of the nonlinearity. By observing the dependence of the local respiratory parameters on the location of the model in the flow–volume–pressure space, information on the condition of the respiratory system can be obtained.

The two main techniques used to obtain parameters of multiple models are *fuzzy clustering* and *linear least-squares* estimation[7,10-13]. By means of fuzzy clustering, the available data set is partitioned into fuzzy subsets that can be well approximated by local linear regression models. Parameters of these models are then estimated by least-squares techniques.

The use of clustering techniques has the advantage of revealing structures in data without relying on assumptions common to conventional statistical methods, such as the underlying statistical distribution[14].
Clustering has been successfully used in a variety of fields, including classification, image processing, pattern recognition, modelling and identification. In the medical field an increasing number of applications can be found, such as; image processing for computer-aided diagnosis[15-17], signal processing in evoked potentials estimation[18] and analysis of time series for imaging[19].

PATIENTS

Twenty patients admitted to a medical intensive care unit were studied. Patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube and absence of air leaks. Ten patients had a history of severe chronic obstructive pulmonary disease (COPD) according to the European Respiratory Society consensus; a clinical diagnosis of COPD and previous lung function data showing an forced expiratory volume in one second (FEV1) < 50% of predicted (mean 29% of predicted, range 21% - 37%)[20]. These 10 patients were ventilated because of respiratory failure due to an exacerbation of their COPD. In the other 10 patients, underlying diseases included a variety of medical conditions all complicated by respiratory failure and ventilator dependency. Patient characteristics are shown in table 1.
All patients were mechanically ventilated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study, except that if ventilator positive end expiratory pressure (PEEP) was present, it was set on 0 cm H2O. All patients were ventilated in the volume controlled mode with an average minute volume of 8.5 l/min (range 6.5 - 15.0 l/min). The average respiratory rate was 12 breaths per minute (range 8 - 20). The ratio between inspiratory and expiratory time was 35:65 in all patients. During the study the patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, The Netherlands). Informed consent was obtained from the patients or their next of kin. The measurements for this study were approved of by the local ethics committee.

Patient	Age (years)	Sex	Diagnosis	FEV1 (%pred)
COPD1	60	F	COPD	21
COPD2	80	F	COPD, pneumonia	
COPD3	37	M	COPD	37
COPD4	71	M	COPD, pneumonia	25
COPD5	41	M	COPD	10
COPD6	70	M	COPD, cerebral bleeding	
COPD7	76	F	COPD	
COPD8	74	M	COPD	33
COPD9	80	M	COPD, pneumonia	
COPD10	55	F	COPD	32
Others11	77	M	Weaning problem	
Others12	46	F	Non-Hodgekin, stomatitis	
Others13	69	F	Guillain-Barré syndrome	
Others14	61	M	Dystrophia Myotonica	73
Others15	66	M	Drug induced lung injury	
Others16	42	M	Porphyria acuta	56
Others17	44	M	Pleural empyema, mild COPD	60
Others18	65	M	Mild COPD	55
Others19	71	F	Muscle weakness, mild COPD	56
Other20	47	M	Complications bone marrow transplantation	

Table 1. Patient characteristics. FEV1= forced expired volume in 1 s (% of predicted).

RESPIRATORY MEASUREMENTS

A heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal tube to measure flow (V'). Volume (V) was obtained by computerised integration of the flow signal. Airway opening pressure (P) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). A 12-bit AD converter was used to convert signals to digital data at a sample frequency of

100 Hz. Data were stored and analysed using a personal computer. On average, 3000 samples were used for the analysis of each patient.
A minimal drift in the volume signal was observed, which was mainly caused by leakage and by the difference in temperature and relative humidity between inspiration and expiration. This drift was corrected by adding an offset signal obtained by fitting a line or a low order polynomial through the volume minima in the individual cycles.

CONVENTIONAL DETERMINATION OF THE TIME CONSTANT

The time constant (τfv) was obtained by calculating the quotient of exhaled volume and corresponding change in flow for the last 75% of exhaled volume[2].
In terms of an equation:

$$\tau fv = \frac{0.75*Vt}{(V'75,ex - V'end,ex)}$$

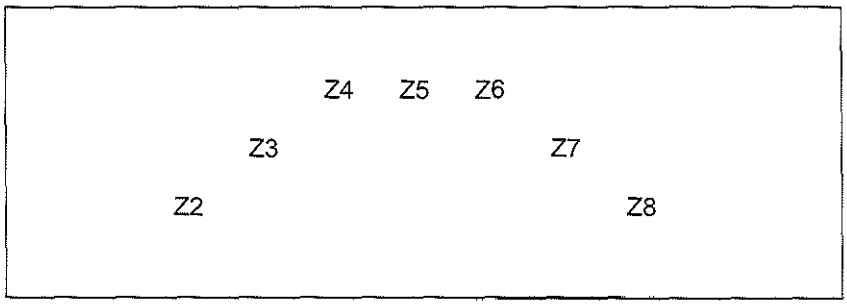
0.75*Vt = 75 % of expiratory tidal volume (l)
V'75,ex = flow at 75 % of exhaled volume (l/s)
V'end,ex = flow at end-expiration (l/s)

TIME CONSTANT ESTIMATION THROUGH FUZZY CLUSTERING

A detailed description of the underlying mathematics has been presented in a previous paper[7]. Fuzzy clustering can be applied either to the entire respiratory cycle (or several cycles) or to the inspiration and expiration separately. In this study we have restricted the analysis to the expiration phase, because in our research we are focussed on the expiratory time constant behaviour.
In our application the data are the samples of pressure, flow and volume. Taking a sample frequency of 100 Hz and an average expiratory time of 3 s, for each patient 10 sets of 300 observations (i.e 10 expirations) are obtained, which are displayed in a 3 dimensional space. From these observations a data set (Z) is extracted, which forms the basis of the analysis.

$$Z = \begin{matrix} V1 \ldots V300 \\ V'1 \ldots V'300 \\ P1 \ldots P300 \end{matrix} \qquad (2)$$

The objective is to partition the data set Z into clusters which fit the data to the underlying model (equation 1). The cluster algorithm assigns to each individual sample a membership value, which represents the position of this sample in relation to the cluster. The sum of all membership values for an individual sample is one. For instance, consider a data set Z = {Z2,...Z8]



This data set can be partitioned into two subsets, fitting lines through Z2-Z4 and Z6-Z8. Point Z5 does not fully belong to either of the clusters. The corresponding fuzzy partition of Z is :

	Z2	Z3	Z4	Z5	Z6	Z7	Z8
Cluster1	1.0	1.0	1.0	0.5	0.0	0.0	0.0
Cluster2	0.0	0.0	0.0	0.5	1.0	1.0	1.0

The first row shows the membership values of each individual sample for the first subset, the second row the membership values for the second subset. Membership degrees of Z5 indicates the fuzziness of the partition, Z5 belongs for 50% to cluster 1 and for 50% to cluster 2.

Before clustering, the number of clusters should be pre-set. As result of clustering a matrix is computed, which displays to what degree the individual data samples belong to the linear submodels (clusters). In order to derive the respiratory variables from these clusters, the tolerated "fuzziness" within the clusters should be defined, i.e. only the data samples with a membership value above a pre-set threshold are included. Assuming a local linear model (1), any

least-squares estimation method can then be applied to estimate the local E, R and Po for each cluster.

In the present study, our research is directed towards the expiratory time constant (τ = resistance * compliance = RC). As during expiration the P is zero, equation 1 becomes a first order differential equation (3), in which V and V' are transformed by differentiation into volume -and flow changes;

$$0 = 1/C * V + R * V'$$
$$V + \tau V' = 0 \qquad (3)$$

which simplifies the estimation of τ.

In the present study, we have chosen to partition the data set Z for the expiration phase into 4 clusters. Therefore, the matrix is partitioned into 4 fuzzy subsets. The data samples, belonging to the chosen clusters are used for the analysis of τ, assuming a local linear model given by equation 3. In the results section, examples are given of clustering in the expiration phase. It has to be underlined that in this analysis the non-linear behaviour in parts of expiration is captured in the trend of τ. Furthermore, this analysis enables the description of the volume dependent behaviour of τ.

STATISTICAL ANALYSIS

To assess the difference in time constants between patients with and without COPD, a Mann Whitney test was performed. A p-value < 0.05 was considered significant.

The time constants obtained with fuzzy clustering were compared to time constants obtained from flow volume curves (τfv) using Pearson correlation. A p-value <0.05 was considered significant. Mean differences of the τfv and the times constants of the clusters are calculated.

RESULTS

Figure 1 shows the clustering results of a patient with COPD and a patient with other pathology. For all patients, the time constants of each cluster and of the flow volume curve are shown in table 2. In the patients with COPD, in cluster 1 low time constants are observed with subsequently an increase in time constants in the following clusters; mean $\tau 1$ 0.33 s (SD 0.21 s), mean $\tau 2$ 2.00 s (SD 0.91s), mean $\tau 3$ 3.45 s (SD 1.44) and mean $\tau 4$ 5.47 s (SD 2.93). In the other patients only a minor change in time constants is found for cluster 2 and 3, with subsequently a slight increase in time constants in cluster 4 found; mean $\tau 1$ 0.74 s (SD 0.30), mean $\tau 2$ 0.90 s (SD 0.23), mean $\tau 3$ 1.04 s (SD 0.42) and mean $\tau 4$ 1.74 s (SD 0.78) (figure 2).
In figure 3 a representative example is shown of an expiratory flow volume curve of a patient with other pathology and a patient with COPD.
For all clusters the time constants were significantly different between the patients with and without COPD; $\tau 1$ was significantly lower in the patients with COPD ($p<0.01$), whereas $\tau 2$, $\tau 3$, $\tau 4$ were significantly higher in the patients with COPD ($p \leq 0.001$).
The correlations between the τfv and the time constants of the individual clusters were $r=0.93$ ($p<0.001$) for cluster 2, $r= 0.92$ ($p<0.001$) for cluster 3 and $r=0.75$ ($p=0.040$) for cluster 4. Cluster 1 did not correlate significantly with the τfv. The mean differences between the τfv and the time constants of the clusters were: 0.31 (sd 0.52) for $\tau 2$, -0.48 (sd 0.70) for $\tau 3$ and -1.84 (sd 2.51) for $\tau 4$.

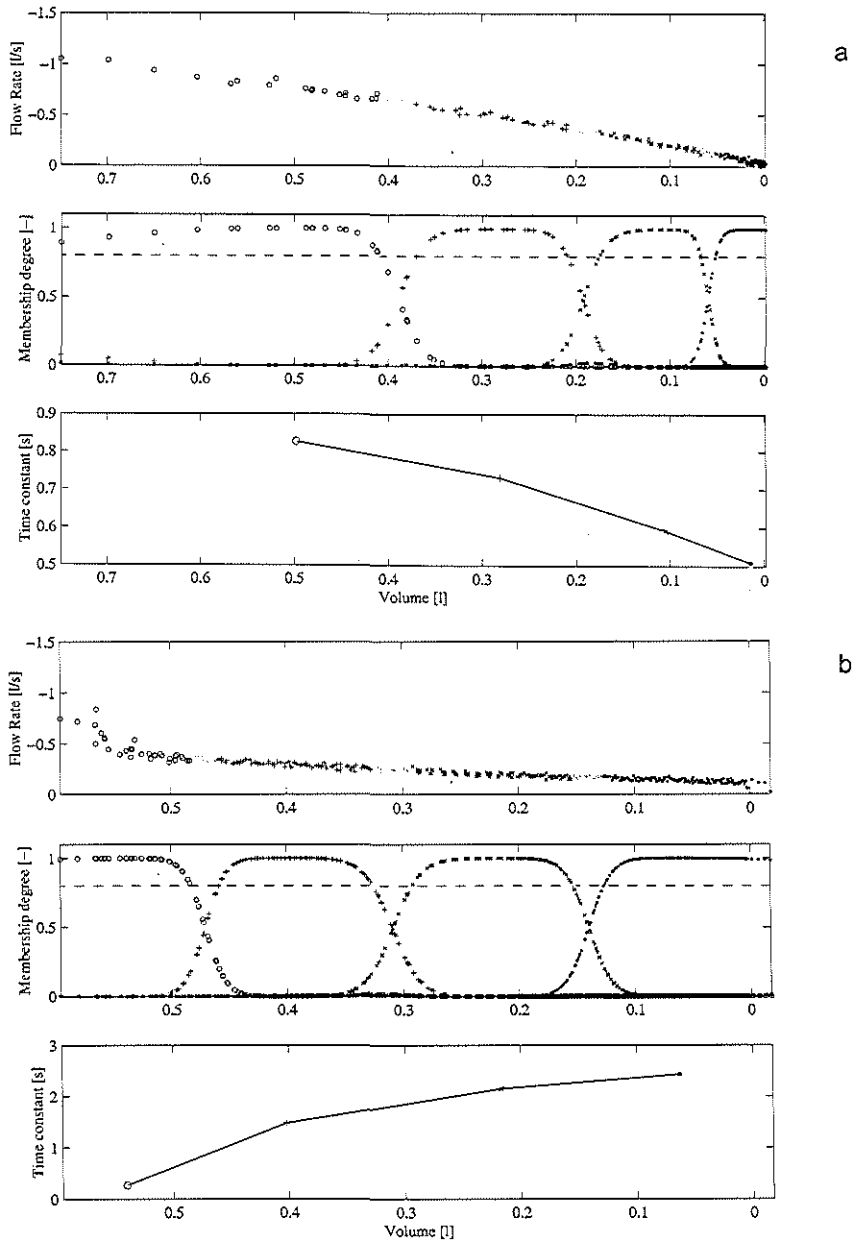


Figure 1. a) patient with other pathology. b) patient with COPD.
Top: Flow - volume data partitioned into four clusters. Middle: membership degrees of the four clusters plotted against volume. --- indicates the membership threshold value.
Bottom: the time constants of the four local models plotted against the volume coordinate of cluster centres.

	τ 1	τ 2	τ 3	τ 4	τfv
Patient	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Flow-volume
COPD1	0.22	3.59	6.75	8.04	5.14
COPD2	0.32	1.39	3.03	6.29	2.25
COPD3	0.32	1.40	2.05	2.47	2.25
COPD4	0.14	1.55	2.21	3.01	2.48
COPD5	0.15	0.84	3.36	12.34	.97
COPD6	0.51	2.42	3.77	4.93	2.61
COPD7	0.18	1.53	2.49	3.15	2.36
COPD8	0.14	2.11	2.95	5.15	1.66
COPD9	0.51	1.69	2.86	4.15	2.61
COPD10	0.77	3.49	4.98	5.17	4.01
Other11	0.60	0.51	0.42	1.60	.50
Other12	0.83	0.73	0.59	0.51	.56
Other13	1.16	0.97	0.76	1.12	.78
Other14	1.11	0.81	0.62	3.22	.90
Other15	1.09	0.88	1.03	1.13	.82
Other16	0.44	1.29	1.50	2.08	1.19
Other17	0.56	0.88	1.47	2.49	.95
Other18	0.74	1.22	1.18	1.43	1.05
Other19	0.27	0.79	1.25	1.55	1.03
Other20	0.63	0.96	1.55	2.23	1.06

Table 2. Time constants calculated with fuzzy clustering for the individual clusters

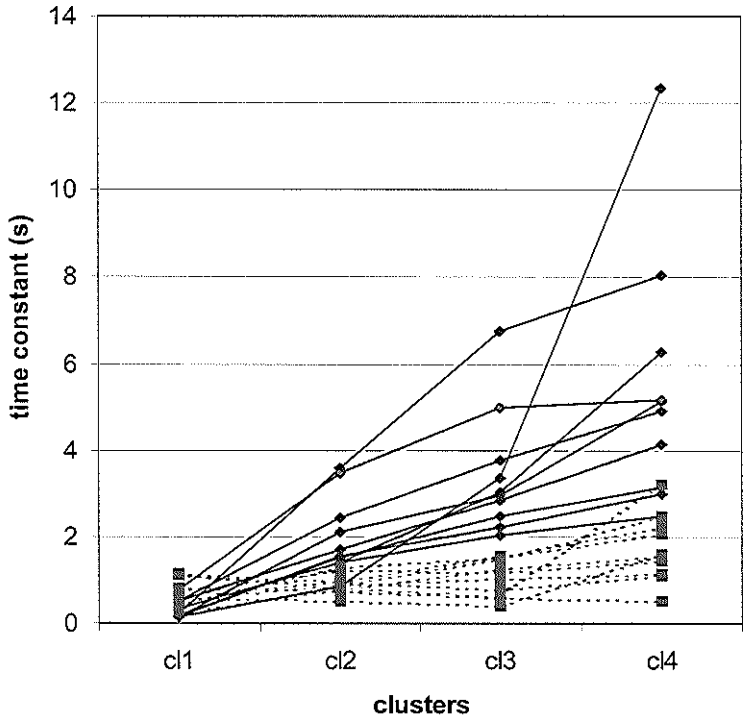


Figure 2. Time constants for each cluster for the patients with other pathology (----) and the patients with COPD (—).

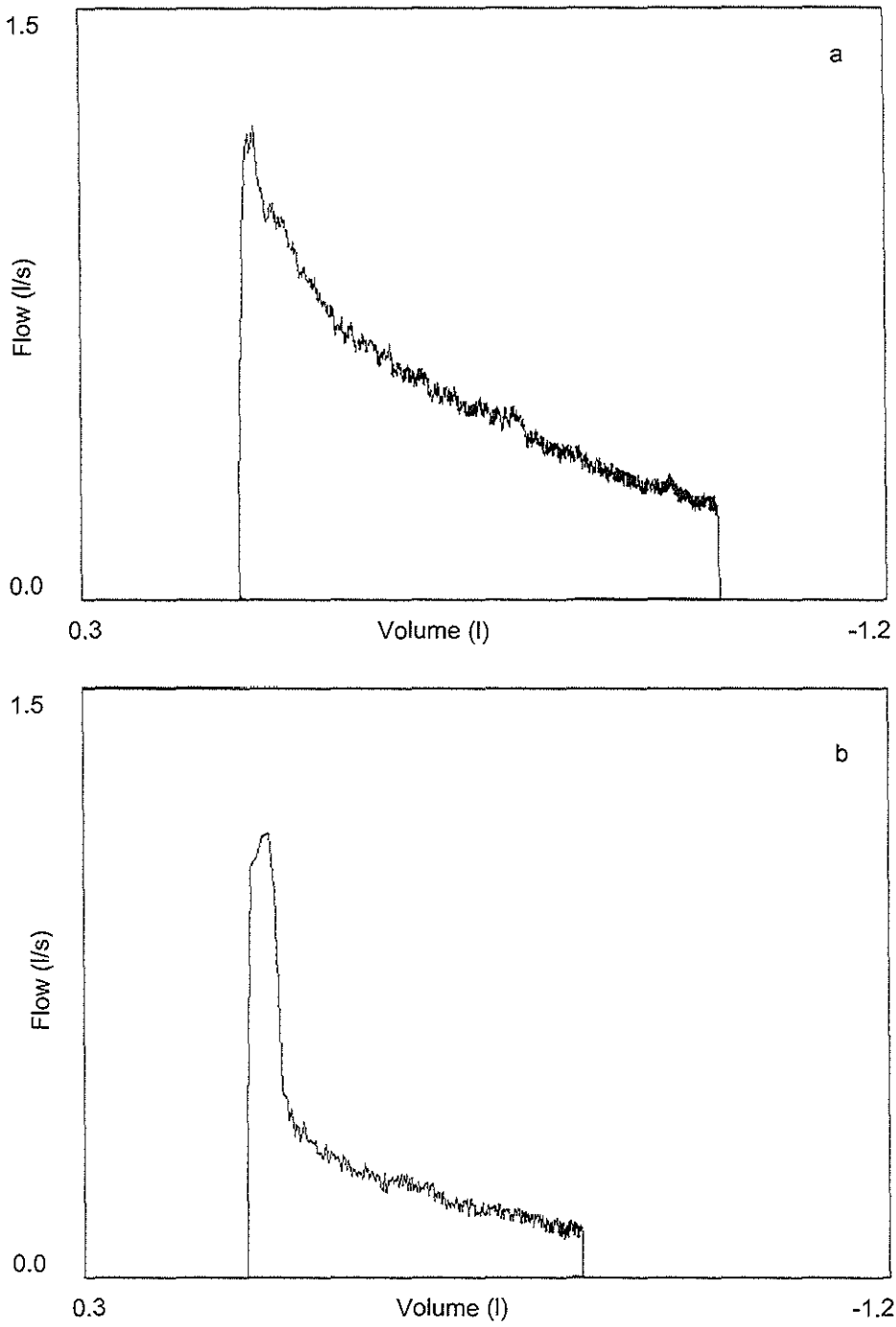


Figure 3. Expiratory flow-volume curves of a patients with other pathology (a) and of a patient with COPD (b).

DISCUSSION

This study shows that in mechanically ventilated patients with and without COPD, fuzzy clustering can be applied to assess expiratory time constants. On the basis of the expiratory time constant behaviour detected by fuzzy clustering a clear distinction can be made between patients with and without COPD. Time constants obtained with fuzzy clustering correlated well with time constants obtained from flow volume curves.

The passive expiration is determined by the mechanical properties of the respiratory system. The driving pressure is provided by the elastic recoil pressure of the total respiratory system, which is the force to overcome the expiratory resistance. Already in 1954 Brody proposed to describe expiration as a single-compartment model, i.e. a single compartment of constant compliance emptying itself through a constant resistance[21]. However, in case of lung inhomogeneity, a multi compartment model will exist. As a consequence, in patients with flow limitation the one-compartment model cannot be applied[9]. Chelucci et al. proposed a two-compartment model to describe the passive expiration, however, this was not applicable in mechanically ventilated COPD patients[22, 23].

In previous studies we have shown that the expiratory flow-volume curve provides information about mechanical properties of the respiratory system[1,2,22]. The inverse of the slope of these curves can be interpreted as a time constant, describing lung emptying. The time constant calculated from the last 75% of expiratory tidal volume was found to be most representative of respiratory mechanics during relaxed expiration[2]. This time constant represents effective single compartment behaviour, comprising peripheral airways obstruction, visco-elastic properties and unequal ventilation.

However, this time constant might not fully reflect physiological events. The 75% of exhaled volume is an artificially chosen percentage and does not always represent the pattern of lung emptying. In figure 4, an example given of an expiratory flow-volume curve of a patient (not from the present study), in whom a single time constant does not adequately reflect lungemptying.

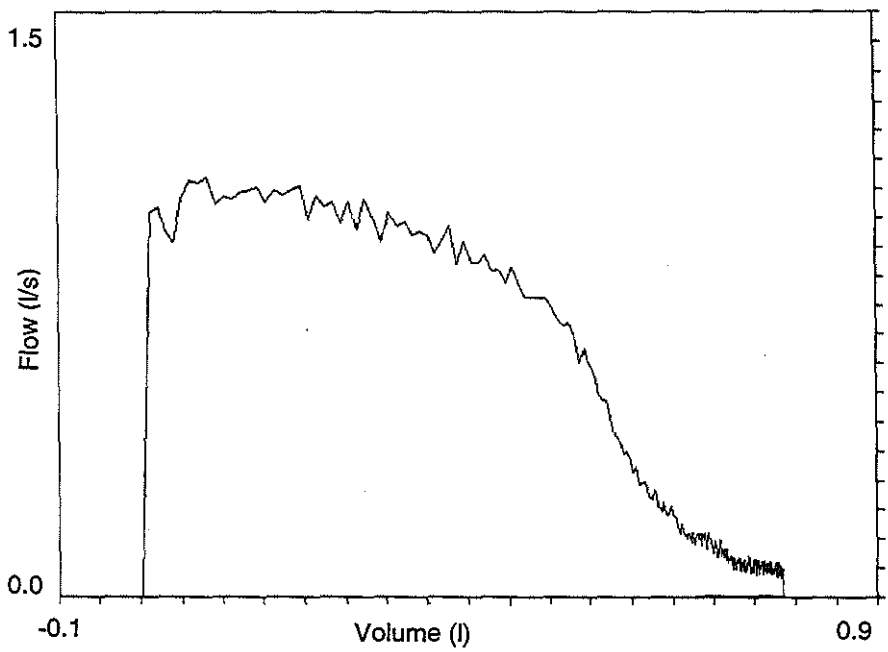


Figure 4. An example of an expiratory flow-volume curve of a patient, in whom a time constant determined from the last 75% of expired volume would not reflect lung emptying.

In this study we applied a method based on automatic detection of multiple local linear models which enables the description of time constant behaviour during expiration[7].

The advantage of this method is that it is able to describe any shape of the flow - volume relationship without presuming a functional relationship (e.g. single or two compartment model), it does not interfere with the expiration and it does not rely on subjective visual inspection.

The shape of the expiratory flow-volume curve is different between patients with and without COPD[1,2,22,24,25]. In patients with COPD a initial peakflow is observed, followed by a sudden decline in flow, resulting in a concave shape (figure 3b). This discontinuity between initial and later part of the flow volume curve, is caused by airway compression. In patients without COPD the expiratory flow-volume curve is mostly characterised by a smooth transition between the initial and later part of the curve (figure 3a). This is also reflected in figure 2, which clearly shows the distinction between the groups with and without COPD. The large changes of the time constant from cluster 1 to the

consecutive clusters in the patients with COPD is also apparent in table 2. In the patients with other pathology two patterns are observed: in patients 11 - 15 a decrease in time constant is found after cluster 1, while in patients 16-20 an slight increase is found. This might be explained by the underlying diseases. Patient 10-15 have a normal or even low lung compliance. These patients were ventilated because of muscular weakness or hypoxemic respiratory failure. Patients 16 - 20 were ventilated for various medical conditions, but 4 patients had mild COPD (FEV1 between 50% - 70% of predicted), in one patient no lung function data were available.

In figure 2, some overlap is found between the curves of patients with COPD and the patients with other pathology. This overlap is mostly found in cluster 1, which represents the early rapid phase, which is largely determined by extra-thoracic resistive elements. The overlap found is therefore not clinically relevant. In three patients a minor overlap is found at end-expiration, which is mainly caused by the relatively high time constant in cluster four of patient 14. We think that this is due to noise in the signal at end-expiration.

Not only the time constant behaviour was found to be discriminative for COPD, but also the individual cluster time constants were able to discriminate between patients with and without COPD. For cluster 1 the time constant was significantly lower in the patients with COPD, while for the clusters 2-4 it was significantly higher in the patients with COPD. These findings also represent the shape of the flow-volume curves. As shown in previous studies and mentioned above, the extrathoracic resistive elements, but also the early occurring airways compression in COPD, cause the steeper slope directly beyond the peakflow[22]. By using fuzzy clustering this part can easily be distinguished from the consecutive slower component, which is more informative on the patients respiratory mechanics[22]. Furthermore, a large difference in time constants of cluster 1 and 2 was found to be very indicative for the presence of COPD.

The time constants of the clusters 2 and 3 correlated best with the time constant derived from the flow volume curve for the last 75% of tidal volume. However, the average $\tau 2$ is slightly higher than the τfv, whereas the average $\tau 3$ is slightly lower than the τfv. This confirms the idea that the τfv gives an effective time constant representing a time constant behaviour. By using the

fuzzy clustering a better approximation of this time constant behaviour is obtained.

In this study it was chosen to use 4 clusters to describe the expiration. This is a compromise between the accuracy of the separate time constants and the number needed for a discriminatory time constant behaviour. A larger number of clusters would mean less data points in the analysis of local linear models, with consequently less accurate time constants for those regions. Four clusters proved to be sufficient to discriminate the pattern of expiration of patients with COPD from patients without COPD. Whether analyses with a larger number of clusters might have additional benefits, needs to be investigated.

In conclusion, in this study, fuzzy clustering can well be used to assess expiratory time constants in mechanically ventilated patients. Time constants obtained with fuzzy clustering correlated well with time constants obtained from the same part of the flow- volume curves by a conventional method. Besides making a distinction in patients with and without COPD, fuzzy clustering might also discriminate for other pulmonary conditions.

REFERENCES

1. Aerts JGjv, van den Berg B, Lourens MS, Bogaard JM. Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiologica Scandinavica 1999; 43:322-7.
2. Lourens MS, van den Berg B, Aerts JGJV, Verbraak AFM, Hoogsteden HC, Bogaard JM. Expiratory time constants in mechanically ventilated patients with and without COPD. Intensive Care Medicine 2000; 26:1612-1618.
3. Guttmann J, Eberhard L, Fabry B, et al. Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 1995; 8:114-20.
4. Gottfried SB, Rossi A, Calverley PM, Zocchi L, Milic-Emili J. Interrupter technique for measurement of respiratory mechanics in anesthetized cats. J Appl Physiol 1984; 56:681-90.
5. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 1985; 131:414-20.
6. Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A. Simple method to measure total expiratory time constant based on the passive expiratory flow-volume curve. Crit Care Med 1995; 23:1117-22.
7. Babuska R, Alic L, Lourens MS, Verbraak AFM, Bogaard JM. Estimation of respiratory parameters via fuzzy clustering. Artif Intell Med 2001; 21:91-105.
8. Lauzon AM, Bates JH. Estimation of time-varying respiratory mechanical parameters by recursive least squares. J Appl Physiol 1991; 71:1159-65.
9. Peslin R, da Silva JF, Chabot F, Duvivier C. Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients. Eur Respir J 1992; 5:871-8.
10. Babuska R. Fuzzy modelling for control. Boston, USA: Kluwer Academic Publishers, 1998.
11. Bezdek J. Pattern recognition with fuzzy objective function. New York, USA: Plenum Press, 1981.
12. Gustafson D, Kessel W. Fuzzy clustering with a fuzzy covariance matrix. Proc. IEEE CDC. San Diego, CA, USA, 1979:761-766.
13. Hathaway R, Bezdek J. Switching regression models and fuzzy clustering. TFS 1993; 1:195-204.
14. Bezdek J, Pal S. Fuzzy models for pattern recognition. New York, USA: IEEE Press, 1992.

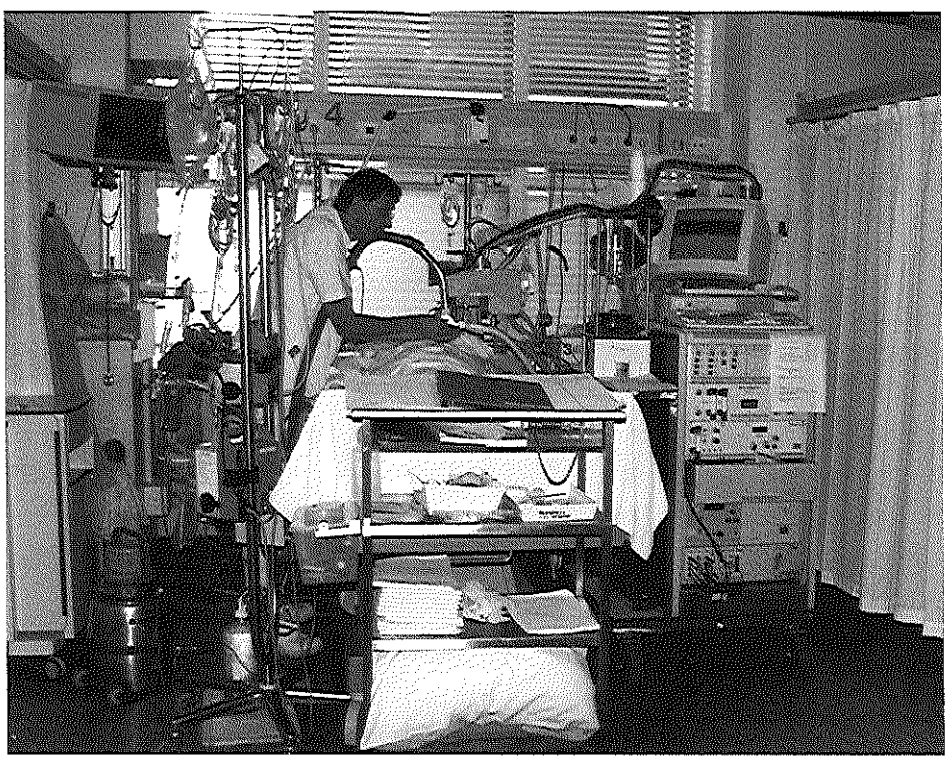
15. Kanazawa K, Kawata Y, Niki N, et al. Computer-aided diagnosis for pulmonary nodules based on helical CT images. Comput Med Imaging Graph 1998; 22:157-67.
16. Lin JS, Cheng KS, Mao CW. Multispectral magnetic resonance images segmentation using fuzzy Hopfield neural network. Int J Biomed Comput 1996; 42:205-14.
17. Tolias YA, Panas SM. A fuzzy vessel tracking algorithm for retinal images based on fuzzy clustering. IEEE Trans Med Imaging 1998; 17:263-73.
18. Zouridakis G, Jansen BH, Boutros NN. A fuzzy clustering approach to EP estimation. IEEE Trans Biomed Eng 1997; 44:673-80.
19. Mansfield JR, Sowa MG, Scarth GB, Somorjai RL, Mantsch HH. Fuzzy C-means clustering and principal component analysis of time series from near-infrared imaging of forearm ischemia. Comput Med Imaging Graph 1997; 21:299-308.
20. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995; 8:1398-420.
21. Brody A. Mechanical compliance and resistance of the lung-thorax calculated from the flow recorded during passive expiration. Am J Physiol 1954; 178:189-196.
22. Lourens MS, van den Berg B, Hoogsteden HC, Bogaard JM. Flow-volume curves as measurement of respiratory mechanics during ventilatory support: the effect of the exhalation valve. Intensive Care Med 1999; 25:799-804.
23. Chelucci GL, Brunet F, Dall'Ava-Santucci J, et al. A single-compartment model cannot describe passive expiration in intubated, paralysed humans. Eur Respir J 1991; 4:458-64.
24. Morris MJ, Lane DJ. Tidal expiratory flow patterns in airflow obstruction. Thorax 1981; 36:135-42.
25. Morris MJ, Madgwick RG, Collyer I, Denby F, Lane DJ. Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. Eur Respir J 1998; 12:1113-7.

CHAPTER 7

DETECTION OF FLOW LIMITATION IN MECHANICALLY VENTILATED PATIENTS

Marlies S. Lourens
Bart van den Berg
Henk C. Hoogsteden
Jan M. Bogaard.

Submitted for publication



Detecting flow limitation with the Nilfisk vacuum cleaner. On the right side of the bed the respiratory mechanics monitoring system.

ABSTRACT

Objective: In mechanically ventilated patients flow limitation often goes unrecognised. We compared three methods for detection of flow limitation in mechanically ventilated patients: the resistance method, the negative expiratory pressure (NEP) method and the interrupter method.
Design: prospective study
Setting: a medical intensive care unit in a university hospital
Patients: 26 patients (20 COPD, 6 other pathology), mechanically ventilated under sedation.
Measurements and Results: Respiratory mechanics were obtained during application of the three methods. For the resistance method, flow limitation was expressed as percentage of expiratory tidal volume, in which flow did not decrease (FLP-R). For the NEP method, flow limitation was expressed as percentage of expiratory tidal volume in which flow did not increase (FLP-NEP). For the interrupter method, flow limitation was expressed as area of spike-overshoot in flow after interruption. In 18 COPD patients, flow limitation was detected by all methods; mean FLP-R 76% (SD 12%), mean FLP-NEP 90% (SD 11%), mean spike area 21ml (SD 7ml). In 3 patients with other pathology, these values were respectively 20% (SD 19%), 48% (SD 21%) and 5 ml (SD 4ml). The three methods were in close agreement. In 9 patients resistance increased flow and in 6 patients NEP decreased flow compared to the unimpeded breath.
Conclusions: In mechanically ventilated patients, flow limitation can well be detected by the resistance-, NEP- and interrupter-method. However, NEP can overestimate the flow limited portion, while the resistance can underestimate the flow limited portion. The interrupter method is found less practical.

INTRODUCTION

In mechanically ventilated patients with chronic obstructive pulmonary disease respiratory mechanics may be disturbed to such extent that expiratory flow limitation occurs even during relaxed tidal breathing [1-5]. As a result dynamic hyperinflation develops, which is associated with the presence of a positive alveolar pressure at end-expiration (iPEEP). iPEEP increases work of breathing, since the pressure gradient between alveoli and mouth acts as an inspiratory threshold [4]. In addition, hyperinflation is associated with decreased efficiency of the respiratory muscles [6, 7]. Furthermore, the elevation in intra thoracic pressures leads to haemodynamic impairment [8]. The combination of these factors, often causes difficult weaning and chronic ventilator dependency [1, 4, 8, 9]. In mechanically ventilated patients expiratory flow limitation goes often unrecognised. As a result therapy as PEEP, external resistance or bronchodilators are not considered [1, 2, 10-13]
Several methods have been proposed for the detection of flow limitation during mechanical ventilation. The very first method was based on determination of iso-volume pressure-flow relationships (IVPF) [2-4]. In order to compute these relationships, driving pressure is decreased by application of an external resistance (i.e. the pressure gradient between alveoli and airway opening). In absence of flow limitation, a decrease in driving pressure will cause a decrease in flow. In contrast, in patients with flow limitation, application of a resistance will not decrease expiratory flow [2, 4, 14]. However, the construction of IVPF-curves is time consuming and not suitable for simple bed side use.
Valta et al. proposed an alternative method to detect flow limitation based on the application of negative expiratory pressure (NEP), which increases the driving pressure [5]. The method consists of applying negative pressure at the mouth during tidal breathing and comparing the ensuing flow-volume curve with that of the previous breath. In patients who are not flow limited, application of NEP will increase flow, while in flow limited patients no increase in flow will be elicited. Several studies have addressed the NEP technique for the detection of flow limitation in spontaneously breathing patients [15-18]. However, in mechanically ventilated patients NEP has never been truly validated [5].

A third method proposed for the detection of flow limitation during mechanical ventilation is based on the interrupter technique [3, 19]. Flow limitation is assumed present when after a brief occlusion of the airway, a spike flow superimposed on the ongoing mouth flow is detected. In spontaneously breathing patients this method has been quantified and validated [20]. In mechanically ventilated patients the interrupter method has only been used in a qualitative way [3, 19].
In this study, we compare three methods for the assessment of flow limitation in mechanically ventilated patients; the addition of a resistance, the application of NEP and the interrupter method.

PATIENTS AND METHODS

PATIENTS

26 patients admitted to the medical intensive care unit were studied. Patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube with an inner diameter $\geq$ 7 mm, respiratory rate $\leq$ 30 breaths per minute and absence of air leaks. 20 patients had a history of COPD according to the ERS consensus [21]. 12 of these patients had undergone pulmonary function testing within a year before or after the period of mechanical ventilation, mean FEV1 as percentage of predicted was 30 % (range 20 - 40%). In the other 6 patients, underlying diseases included a variety of medical conditions all complicated by respiratory failure and ventilator dependency. Patient characteristics are shown in table 1. 25 Patients were intubated with an endotracheal tube (inner diameter range 7.5 - 8.5 mm), 1 patient with a tracheostomy tube (inner diameter 8 mm). All patients were ventilated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study, except that if present, ventilator PEEP was removed. In 24 patients the volume controlled mode was used, in 2 patients the pressure controlled mode. The average minute volume was 9.0 l/min (range 6.5-13). The average respiratory rate was 14 breaths per minute (range 10-22). At volume controlled ventilation the ratio between inspiratory and expiratory time was 35:65, in the pressure- controlled mode this ratio was 50:50. All patients were studied in supine position and sedated with midazolam

(Roche Nederland B.V., Mijdrecht, Holland). Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

Patient	Age	Sex	Diagnosis	FEV1 (% pred.)
1	79	m	COPD, bullectomy	
2	85	f	Gastrointestinal bleeding, COPD	
3	57	m	Pneumonia, COPD	40
4	64	m	Exacerbation COPD	29
5	71	m	Legionella pneumonia, COPD	25
6	78	m	Exacerbation COPD	37
7	66	f	Exacerbation COPD	
8	58	m	Pulmonary cancer, COPD	37
9	55	f	Exacerbation COPD	29
10	69	m	Exacerbation COPD	30
11	70	m	Cerebral bleeding, COPD	
12	55	f	Exacerbation COPD	32
13	80	m	Pneumonia, COPD	
14	74	m	Exacerbation COPD	33
15	57	f	Post-surgery, COPD	
16	60	f	Exacerbation COPD	21
17	80	f	Pneumonia, COPD	
18	75	m	Gastrointestinal bleeding, COPD	
19	75	m	Exacerbation COPD	29
20	71	m	Pneumonia, COPD	20
21	49	f	Neurofibromatosis	
22	40	m	Pulmonary embolism, pneumonia	
23	62	m	Dystrophia myotonica	
24	67	f	Pneumonia	
25	49	m	M. Wegener	
26	74	m	Post-surgery	

Table 1. Patient characteristics. FEV1 = forced expiratory volume in 1 s, expressed as percentage of predicted.

RESPIRATORY MEASUREMENTS

A heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal or tracheostomy tube to measure flow. Volume was obtained by computerised integration of the flow signal. Airway opening pressure was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). Data were stored and

analysed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA) at a sample frequency of 100 Hz.

RESISTOR

An adjustable resistor was placed in the expiratory line of the ventilatory circuit [22]. The pressure at the airway opening at end-expiration and end-inspiration were obtained by application of end-expiratory and end-inspiratory occlusions respectively. To obtain the optimum level of resistance, in each patient increasing levels of resistance were applied. This was to select the resistance the would cause an appreciable change in flow, yet not to be too high, since a large resistance will decrease flow even when flow limitation is present. The highest level of resistance that did not increase end-expiratory plateau pressure, was used for further analysis.

For reasons of simplicity, we evaluated the effect of the resistor by means of flow-volume curves instead of IVPF-curves. By using this method, a comparable analysis of the resistance- and NEP-method was feasible. The flow-volume curve recorded during the highest level of resistance was superimposed on the flow volume curve during unimpeded expiration. Flow limitation was considered present if during application of the resistance in any part of the expiratory tidal volume no decrease (i.e. < 5%) in flow was found compared to the unimpeded expiration [16]. Flow limitation was expressed as percentage of expiratory tidal volume during which no decrease was found, and was called the flow limited portion (FLP-R).

NEGATIVE EXPIRATORY PRESSURE

A three way valve was connected distal to the pneumotachometer in the ventilator circuit enabling expiration at a negative pressure (-5 cm H2O) generated by a vacuum cleaner (Nilfisk, Diemen, Holland). By manually switching the valve during an end-inspiratory pause (1 s) the patient was rapidly subjected to the negative pressure and simultaneously the inspiratory and expiratory limb of the ventilator circuit were occluded. The valve was kept open for the complete expiration. All measurements were obtained in triplicate. The flow-volume curve recorded during NEP was superimposed upon the preceding breath. Flow limitation was considered present if, during NEP application, in any part of the expiratory tidal volume no increase in flow was

found compared to the preceding breath. We considered a change of less than 5% in flow consistent with flow limitation, as proposed by Jones et al. [16]. Flow-limitation was expressed as percentage of expiratory tidal volume during which no increase in flow was found, this was called the flow limited portion (FLP-NEP). The average of three measurements was calculated.

INTERRUPTER MEASUREMENT

A computer controlled 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). Opening- and closing time of the valve were each 250 ms. Ohya et al. found that a closure time of more than 100 ms yielded equal flow spikes in patients with flow limitation, indicating that within that period the expansion of the compressed airway segment has been completed [23]. The dynamic properties of the interrupter device have previously been studied using a constant flow generator. Using this technique small oscillations were detected of the same magnitude, frequency and pattern during opening and closing of the interrupter valve, for which could be corrected [20].

After an end-inspiratory hold procedure applied by the ventilator the interrupter valve was closed, the patient disconnected from the ventilator tubings and the interrupter-procedure was started. After opening of the valve, flow limitation was assumed to be present when the opening transient clearly exceeded the closing transient [19, 20]. To quantify the analysis of the data obtained with the interrupter technique the spike area was determined by back extrapolation of the flow during the interval 100 - 250 ms after reopening of the interrupter (figure 3). The first 7 interruptions were analysed.

DATA ANALYSIS

The FLP obtained with the resistances and with NEP were compared using the method of Bland and Altman for assessing agreement between two methods of clinical measurements [24]. Differences in FLP obtained with resistances and with NEP were plotted against the means of the corresponding values of FLP-R and FLP-NEP, limits of agreement were estimated as ± 2 SD of the differences. To assess agreement between NEP, resistor and interrupter method, the results were correlated using Spearman's test. A p-value of $p<0.05$ was considered significant.

RESULTS

Table 2 summarises the results obtained in the individual patients.
In the patients with COPD, the resistance method revealed flow limitation in 18 patients (mean FLP-R 76%, SD 12%). The NEP method also showed flow limitation in these 18 patients (mean FLP-NEP 90%, SD 11%). In the other 2 patients with COPD neither resistance nor NEP revealed a flow limited portion. (fig. 1 and 2). The interrupter method showed flow limitation in the same 18 patients (mean spike area 21 ml, SD 7 ml), in one of the other two patients (pt 19) a small spike (2 ml) was detected (fig. 3). In the patients without COPD, the resistance and NEP method revealed a FLP in 3 patients (mean FLP-R 20, SD 19), (mean FLP-NEP 48, SD 21). In the other 3 patients no FLP was observed. The interrupter method showed spikes in 4 patients (mean spike area 5 ml, SD 3 ml).
Application of the resistance changed flow volume curves compared to preceding breaths in various ways. In 5 patients flow was decreased for the entire exhalation. In 8 patients a decrease in peakflow was followed by unchanged flow. In 4 patients a decrease in peakflow was followed by small portion of increased flow, with subsequently unchanged flow. In 9 patients the following pattern was observed: a decrease in peakflow, subsequently a portion of unchanged flow, followed by increased flow compared to the unimpeded breath (fig.1).
Application of NEP also elicited various patterns in flow-volume curves compared to the preceding breaths. In 5 patients flow was increased for the entire exhalation. In 15 patients an increase in peakflow was followed by a portion of unchanged flow. In 6 patients the following pattern was observed: an increase in peakflow, subsequently a portion of decreased flow and ultimately unchanged flow compared to the preceding breath (fig.2).

Patient	FLP-R (% exp. tidal vol.)	FLP-NEP (% exp. tidal vol.)	Interrupter, Spike (ml)
COPD			
1	58	75	37
2	71	92	12
3	60	87	23
4	77	50	13
5	90	97	18
6	89	94	22
7	80	95	21
8	64	92	17
9	69	91	18
10	85	86	36
11	86	100	18
12	73	96	26
13	83	92	16
14	84	94	29
15	72	97	20
16	89	97	26
17	50	94	15
18	88	86	11
19	0	0	2
20	0	0	0
Other			
21	46	72	7
22	19	37	8
23	15	34	1
24	0	0	3
25	0	0	0
26	0	0	0

Table 1. The results of the three methods to detect flow limitation. FLP-R (flow limited portion resistance) indicates the percentage of expiratory tidal volume in which no decrease in flow was found when a resistance was applied. FLP-NEP (flow limited portion negative expiratory pressure) indicates the percentage of expiratory tidal volume in which no increase in flow was found when NEP was applied. The spike value indicates the spike area in ml.

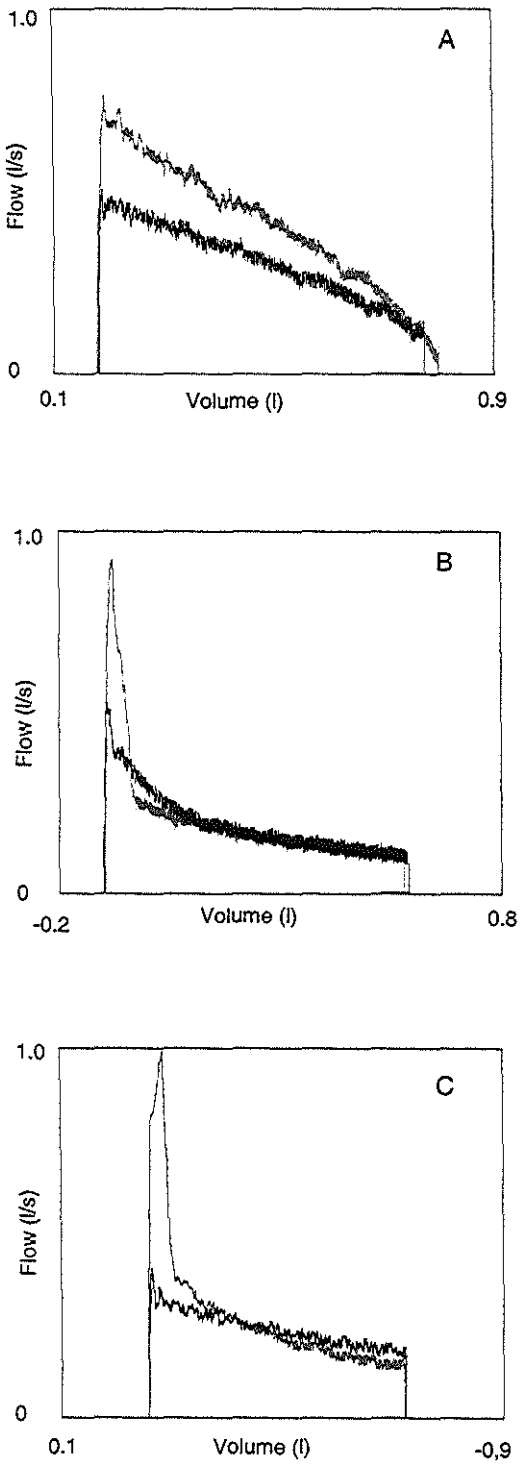
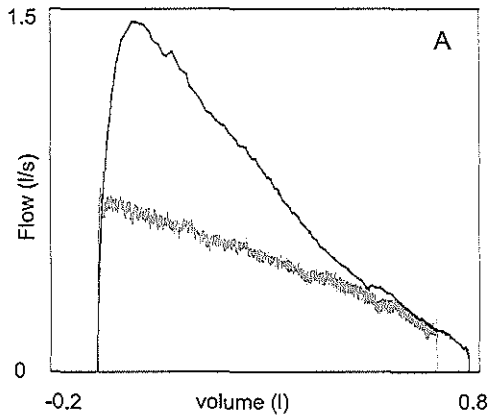
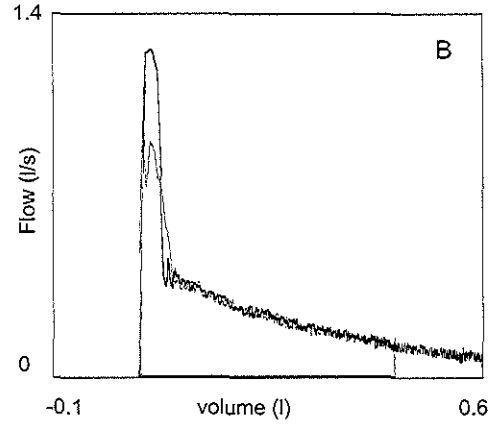


Figure 1. Flow-volume curve of breaths with resistance (—) and preceding control breaths (.....) in a patient without flow limitation (A) and in patients with flow limitation (B and C).

A) a patient with a decrease in flow during application of resistance.
B) a patient with unchanged flow during application of resistance.
C) a patient with an increase in flow during application of resistance.





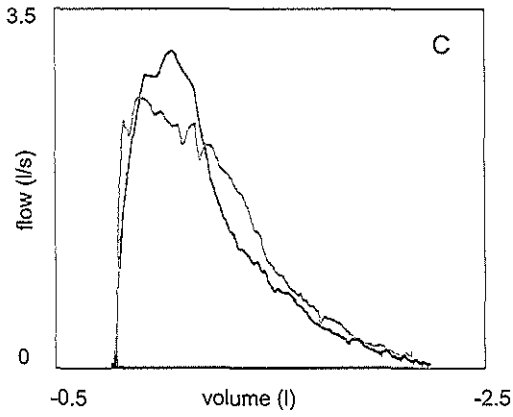


Figure 2 . Flow-volume curves of NEP breaths (▬) and preceding control breaths (▭) in a patient without flow limitation (A) and in patients with flow limitation (B and C).

A) a patient with an increase in flow during NEP

B) a patient with an unchanged flow during NEP.

C) a patient with a decrease in flow during NEP.

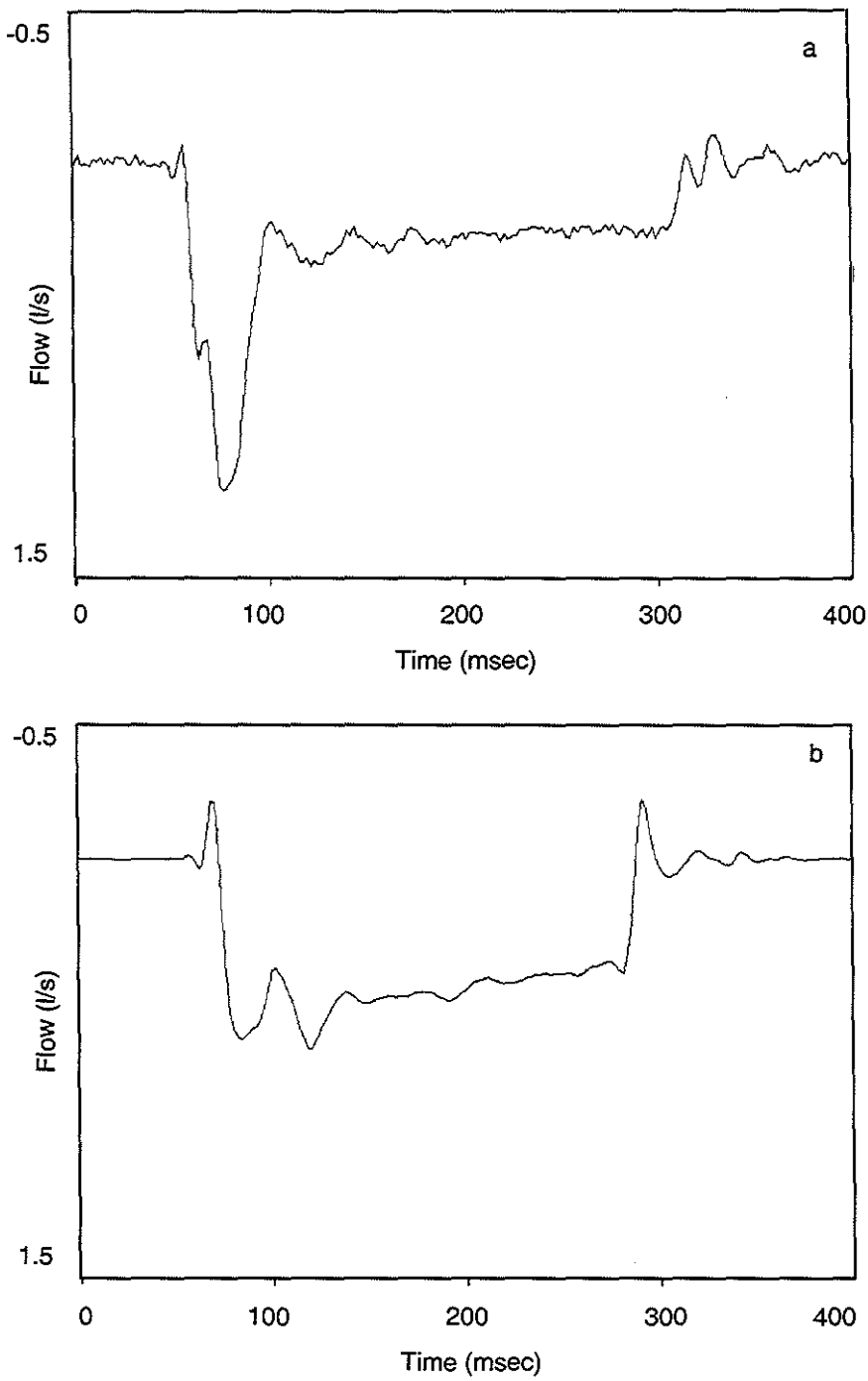


Figure 3. Representative examples of interrupter pattern of a) a patient with flow limitation and b) a patient without flow limitation.

In figure 4, the differences between FLP-NEP and FLP-R are plotted against their means. Mean differences and limits of agreement are indicated. This figure shows that in the majority of patients the FLP-NEP exceeds the FLP-R. Spearman's test showed a correlation coefficient between NEP and interrupter of 0.69 ($p<0.001$) and between resistor and interrupter method of 0.67 ($p<0.001$).

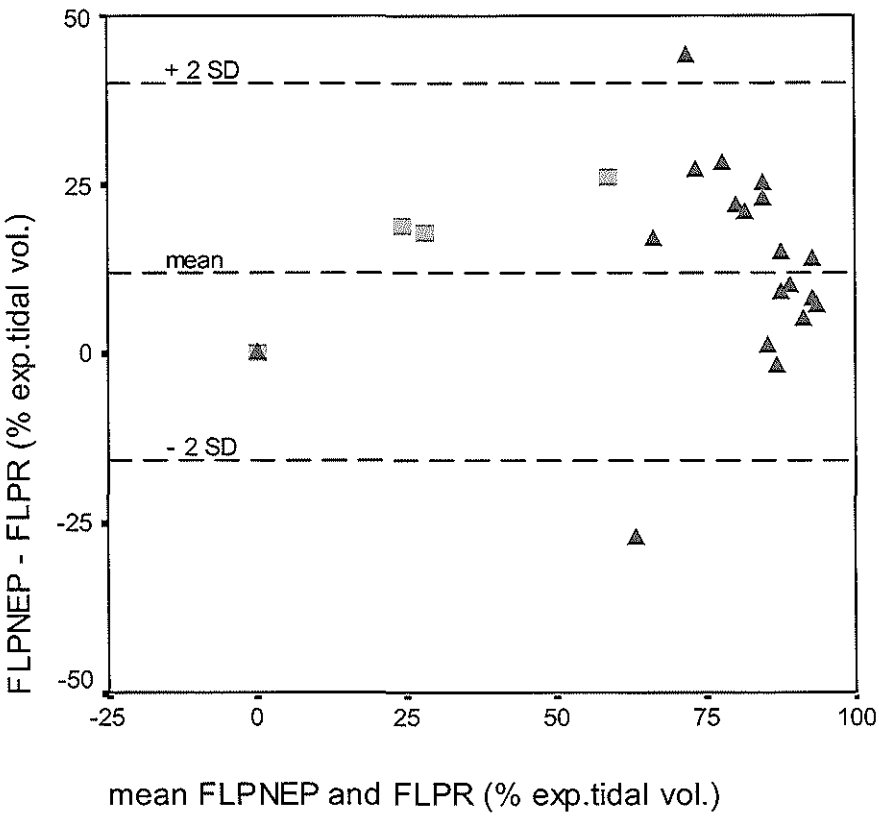


Figure 4. Bland and Altman analysis of difference (FLP-NEP - FLP-R) against the mean of FLP-NEP and FLP-R. Mean differences and limits of agreement are indicated.
▲ patients with COPD, ■ patients with other pathology.

DISCUSSION

This study shows that NEP, resistance and interrupter method are all suitable for the detection of flow limitation in mechanically ventilated patients. The results of the three methods are in close agreement. The advantages and disadvantages of the various methods will be discussed.

Flow limitation has been described both during forced and relaxed expirations; the pathogenesis was found to be fundamentally different. During forced expiration local wave speed is considered the basic mechanism of flow limitation, while during relaxed expiration flow limitation can be described as viscous flow limitation [25, 26]. By analysis of the effect of varying driving pressures on iso-volume flow, flow limitation can be assessed independent of the underlying mechanism [1, 2, 5, 14, 27].

One of the first publications on the assessment of flow limitation has been provided by Fry, who computed IVPF curves during forced expiration [14, 28]. In that study driving pressure was varied by the degree of effort the subject put in exhaling.

In mechanically ventilated patients, during relaxed expiration, various methods have been proposed for the detection of flow limitation based on the principle of altering the driving pressure. During ventilatory support, this can be achieved by either decreasing driving pressure by application of external resistances or increasing driving pressure by removal of external resistances (e.g. PEEP, expiratory circuit) or by application of negative pressure.

In this study we investigated both mechanisms: decreasing driving pressure by application of external resistances and increasing driving pressure by NEP. The third method studied was the interrupter technique, which is based on a different mechanism: the abolishment and re-establishment of the flow limiting segment by interruption of the expiratory flow.

The application of negative pressure during expiration was first described by Valta et al. [5]. They studied various methods to detect flow limitation, including the application of NEP, expiration to atmosphere (ATM) and of additional resistances in 12 mechanically ventilated patients. Although ATM is the simplest method available in the ICU, it was found to be unreliable [5]. Valta et al. reported a discrepancy between the results obtained with NEP and those with additional resistances. This discrepancy was ascribed to the unreliability to detect flow limitation by application of resistances. In our study a close

agreement between the application of NEP and of additional resistances was established. We titrated the level of resistance in the individual patient, to such extent that the highest level of resistance was applied without increasing airway pressures and end-expiratory lung-volume. In the study of Valta et al. two fixed levels of resistance were applied in all patients. In 4 patients, in whom NEP showed flow limitation, they found that application of the lower resistance caused no appreciable changes in flow (indicating flow limitation), whereas application of the higher resistance caused a decrease in flow (indicating absence of flow limitation). These findings might be explained when at the higher resistance the driving pressure decreased below the critical driving pressure. Below this critical pressure hyperinflation occurs and a decrease in iso-volume flow is found [2]. We therefore suggest to standardize the procedure by using a simple adjustable resistance and increase the level of resistance till an increase in airway pressures is found.

In the present study, we observed with the NEP technique in 6 patients a decrease in flow immediately after the peakflow (Fig. 2). In non-intubated snorers has been reported that NEP can actually decrease flow [29, 30]. This has been attributed to the more collapsible upper airways of snorers compared to non snorers. As in the present study all patients were intubated and the upper airways by-passed, the transient decrease in flow should be explained differently. During passive expiration, the expiratory flow volume curve can be divided in a rapid component, which predominantly reflects the extrathoracic resistive elements and a consecutive slower component, mainly reflecting viscous and elastic properties of the lung and chest wall [31, 32]. The transition point between these components has been referred to as inflection point [31]. Applying NEP in the early rapid phase will lead to an increase in flow, resulting in a higher but narrower peakflow and a leftward shift of the inflection point (fig. 2). Therefore, flow limitation will start at a higher lung volume, consequently in the first part immediately after the peakflow, the flow will decrease compared to the preceding control breath (fig. 2).

Application of resistances also elicited various patterns in flow volume curves. In 9 patients, the flow increased for the last part of expiration during application of the resistance (fig. 4). This is in accordance with the results of previous studies, reporting that application of a resistance can counteract airways compression and increase iso-volume flow [1, 33].

Flows could also have been affected by the length and presence of the end-inspiratory pause. Guerin et al. described that in patients with COPD iso-volume flow during expiration is affected by the presence or absence of an end-inspiratory pause [34]. They observed higher peakflows when no end-inspiratory pause was applied. It is assumed that without pause the overall elastic recoil pressure of the lung is higher than after a pause, since in the latter situation elastic energy is dissipated due to viscoelastic properties of the pulmonary tissue and / or time constant inequalities. However, in all our measurements end-inspiratory pauses are applied. In the situation of application of resistances, the expiratory pause, set at the ventilator, was exactly the same during application of the resistance and during the preceding control breath. The increase of iso-volume flow can therefore not be explained by a difference in pause. The measurement procedure with NEP was slightly different. During the normal breaths, the end-inspiratory pause was set by the ventilator and was approximately 0.5 s. During application of NEP, the end-inspiratory pause was applied manually, while at the same time the valve was switched and the patient was subjected to NEP. In this situation the end-inspiratory pause was approximately 1 s. This longer end-inspiratory pause could cause a decrease in flow. However, in that case the decrease in flow would be seen at the start of expiration, i.e. the peakflow, while in our patients the decrease in flow is observed after the peakflow (fig. 2 C).

In the present study in almost all patients the flow limited portion with NEP exceeded the flow limited portion with the resistance (fig. 4). This can be explained by taking into account the volume at which flow limitation is generated. By application of a resistance, the initial flow will be retarded, the inflection point will shift to the right and flow limitation will occur at a lower lung volume. In contrast, NEP shifts the inflection point to the left and flow limitation will occur at a higher lung volume. However, for clinical applications, the presence or absence of flow limitation is more important than the % exhaled volume during which flow limitation occurs.

In 2 patients with other pathology, we observed a FLP only for the very last part of expiration. Both these patients were very obese. We hypothesise that these patients have already reached closing volume at the last part of expiration and that therefore no appreciable change in flow is observed. This is in agreement with findings of Pankow et al., who studied flow limitation with

NEP in obese patients. In the majority of patients, in supine position, they found flow limitation during the last part of expiration [35].

We also studied the interrupter method to establish flow limitation in mechanically ventilated patients. During an interruption of the expiratory flow, the flow limiting segment will be abolished, after re-opening of the interrupter valve flow limitation will re-appear, resulting in an overshoot in expiratory flow [3, 19, 20, 23]. In healthy subjects this method has been validated and quantified during forced expiration [23, 36]. Hage et al. studied the interrupter method for the detection of flow limitation during tidal breathing [20]. They reported in patients with flow limitation during tidal breathing a mean spike area of 27 ml, in the patients without flow limitation a mean spike area of 4 ml was found, data consistent with our findings. The small spikes left in patients without flow limitation are probably due to a slightly under damped flow transducer and a minimal contribution of gas decompression[23, 36]. In comparison with NEP and Resistance method, the interrupter method is more labour-intensive and therefore less practical for daily routine.

In conclusion, in mechanically ventilated patients flow limitation can well be detected by the three methods described in this study; the resistance, the NEP and the interrupter method. However, it should be taken into account that NEP can give an overestimation of the flow limited portion, whereas the resistance can give an under estimation of the flow limited portion. The interrupter method is found less practical for daily routine.

REFERENCES

1. Aerts JG, van den Berg B, Bogaard JM (1997) Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 10:550-6.
2. Gay PC, Rodarte JR, Hubmayr RD (1989) The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 139:621-6.
3. Gottfried SB, Rossi A, Higgs BD, Calverley PM, Zocchi L, Bozic C, Milic-Emili J (1985) Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 131:414-20.
4. Kimball WR, Leith DE, Robins AG (1982) Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am Rev Respir Dis126:991-5.
5. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chasse M, Braidy J, Milic-Emili J (1994) Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 150:1311-7.
6. Decramer M (1997) Hyperinflation and respiratory muscle interaction. Eur Respir J 10:934-41.
7. Ranieri VM, Grasso S, Fiore T, Giuliani R (1996) Auto-positive end-expiratory pressure and dynamic hyperinflation. Clin Chest Med 17:379-94.
8. Ranieri VM, Dambrosio M, Brienza N (1996) Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. Eur Respir J 9:1283-92.
9. Gottfried SB, Reissman H, Ranieri VM (1992) A simple method for the measurement of intrinsic positive end-expiratory pressure during controlled and assisted modes of mechanical ventilation. Crit Care Med 20:621-9.
10. Guerin C, Milic Emili J, Fournier G (2000) Effect of PEEP on work of breathing in mechanically ventilated COPD patients. Intensive Care Med 26:1207-1214.
11. Marini JJ (1989) Should PEEP be used in airflow obstruction? Am Rev Respir Dis 140:1-3.
12. Rossi A, Brandolese R, Milic-Emili J, Gottfried SB (1990) The role of PEEP in patients with chronic obstructive pulmonary disease during assisted ventilation. Eur Respir J 3:818-22.
13. van den Berg B, Stam H, Bogaard JM (1991) Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 4:561-7.
14. Fry D, Hyatt R (1960) Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. Am J Med 24:672-689.

15. Eltayara L, Becklake MR, Volta CA, Milic-Emili J (1996) Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154:1726-34.
16. Jones MH, Davis SD, Kisling JA, Howard JM, Castile R, Tepper RS (2000) Flow limitation in infants assessed by negative expiratory pressure. Am J Respir Crit Care Med 161:713-7.
17. Koulouris NG, Dimopoulou I, Valta P, Finkelstein R, Cosio MG, Milic-Emili J (1997) Detection of expiratory flow limitation during exercise in COPD patients. J Appl Physiol 82:723-31.
18. Koulouris NG, Valta P, Lavoie A, Corbeil C, Chasse M, Braidy J, Milic-Emili J (1995) A simple method to detect expiratory flow limitation during spontaneous breathing. Eur Respir J 8:306-13.
19. Reinoso MA, Gracey DR, Hubmayr RD (1993) Interrupter mechanics of patients admitted to a chronic ventilator dependency unit. Am Rev Respir Dis 148:127-31.
20. Hage R, Aerts JG, Verbraak AF, van den Berg B, Bogaard JM (1995) Detection of flow limitation during tidal breathing by the interruptor technique. Eur Respir J 8:1910-4.
21. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, et al. (1995) Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 8:1398-420.
22. Verbraak A, Holland W, Mulder B, Bogaard J, Versprille A (1999) A computer controlled flow resistance. Med Biol Eng Comput 37:770-775.
23. Ohya N, Huang J, Fukunaga T, Toga H (1989) Mouth pressure curve on abrupt interruption of airflow during forced expiration. J Appl Physiol 66:509-17.
24. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1:307-10.
25. Wilson T, Rodarte J, JP Butler (1986) Wave-speed and viscous flow-limitation. In: A. Fishman (ed) Handbook of Physiology, section 3: the Respiratory System. Waverly Press, Bethesda, pp 55-61.
26. Wilson T (1989) The wave speed limit on expiratory flow. In: Chang HK, Paiva M (Eds) Respiration Physiology, lung biology in health and disease series. Marcel Dekker, New York, pp139-165.
27. Hyatt R (1961) The interrelationships of pressure, flow and volume during various respiratory maneuvres in normal and emphysematous patients. Am Rev Resp Dis 83:676-683.
28. Fry D, Ebert R, Stead W, Brown C (1954) The mechanics of pulmonary ventilation in normal subjects and in subjects with emphysema. Am J Med 16:80-97.

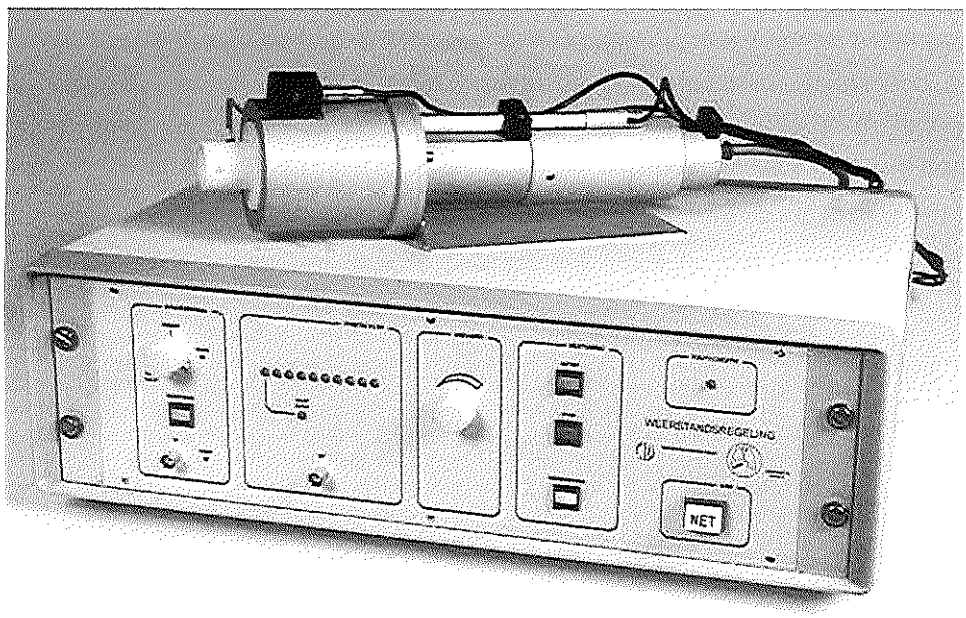
29. Tantucci C, Duguet A, Ferretti A, Mehiri S, Arnulf I, Zelter M, Similowski T, Derenne JP, Milic-Emili J (1999) Effect of negative expiratory pressure on respiratory system flow resistance in awake snorers and nonsnorers. J Appl Physiol 87:969-76.
30. Liistro G, Veriter C, Dury M, Aubert G, Stanescu D (1999) Expiratory flow limitation in awake sleep-disordered breathing subjects. Eur Respir J 14:185-90.
31. Guttmann J, Eberhard L, Fabry B, Bertschmann W, Zeravik J, Adolph M, Eckart J, Wolff G (1995) Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 8:114-20.
32. Chelucci GL, Brunet F, Dall'Ava-Santucci J, Dhainaut JF, Paccaly D, Armaganidis A, Milic-Emili J, Lockhart A (1991) A single-compartment model cannot describe passive expiration in intubated, paralysed humans. Eur Respir J 4:458-64.
33. Lourens MS, Van den Berg B, Verbraak AFM, Hoogsteden HC, Bogaard JM. Effect of series of resistance levels on flow limitation in mechanically ventilated COPD patients. Respir Physiol, in press.
34. Guerin C, Coussa ML, Eissa NT, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1993) Lung and chest wall mechanics in mechanically ventilated COPD patients. J Appl Physiol 74:1570-80.
35. Pankow W, Podszus T, Gutheil T, Penzel T, Peter J, Von Wichert P (1998) Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. J Appl Physiol 85:1236-43.
36. Knudson RJ, Mead J, Knudson DE (1974) Contribution of airway collapse to supramaximal expiratory flows. J Appl Physiol 36:653-67.

CHAPTER 8

EFFECT OF SERIES OF RESISTANCE LEVELS ON FLOW LIMITATION IN MECHANICALLY VENTILATED COPD PATIENTS

Marlies S. Lourens
Bart van den Berg
Anton F.M. Verbraak
Henk C. Hoogsteden
Jan M. Bogaard

Respiration Physiology, in press



Adjustable external resistor

ABSTRACT

In severe chronic obstructive pulmonary disease (COPD) lung emptying is disturbed by airways compression and expiratory flow limitation. Application of an external resistance has been suggested to counteract airways compression and improve lung emptying. We studied the effect of various resistance levels on lung emptying in mechanically ventilated COPD patients.

In 18 patients an adjustable resistor was applied. The effect on airways compression was assessed by iso-volume pressure-flow curves (IVPF) and by interrupter measurements. Respiratory mechanics during unimpeded expirations were correlated to the results obtained with the resistances.

The resistances caused an increase in iso-volume flow at the IVPF-curves in 6 patients, indicating that airways compression was counteracted. Interrupter measurements showed that overshoots in flow (as a measure of flow limitation) were significantly reduced by the resistor. These effects could be predicted on the basis of respiratory mechanics during unimpeded expiration.

In conclusion: mechanically ventilated COPD patients can be identified in whom application of external resistances counteracts airways compression and reduces flow limitation.

INTRODUCTION

In patients with COPD respiratory mechanics may be disturbed to such extent that dynamic airways compression and consequently expiratory flow limitation develop during relaxed breathing (Mead et al., 1967; Kimball et al., 1982; Gottfried et al., 1985; Gay et al., 1989; Valta et al., 1994; Aerts et al., 1997). Flow limitation is considered a major contributor to the development of dynamic hyperinflation and intrinsic Positive End Expiratory Pressure (iPEEP, i.e. the pressure gradient between alveoli and mouth at end-expiration). As a consequence increased work of breathing, decreased efficiency of respiratory muscles and impaired gas transport occur, resulting in respiratory failure (Kimball et al., 1982; Gottfried et al., 1985; Gay et al., 1989; Valta et al., 1994; Aerts et al., 1997). In COPD patients in whom mechanical ventilation has been instituted for respiratory failure, disturbed respiratory mechanics may also hamper discontinuation of ventilatory support (weaning). Counteracting airways compression and consequently reducing flow limitation in these patients, could have a beneficial effect on the respiratory mechanics and may avoid chronic ventilator dependency.

Flow limitation can be assessed in various ways, one of these is by computing iso-volume pressure-flow relationships. Flow limitation is defined by this method if above a certain critical driving pressure (i.e. alveolar pressure minus airway opening pressure) the flow does not increase at further increments of driving pressure (Fry and Hyatt, 1960; Mead et al.,1967; Gay et al., 1989; Valta et al., 1994; Aerts et al., 1997). During forced expiration, even a decrease in flow at an increase in driving pressure has been described (Fry and Hyatt, 1960; Mead et al., 1967). This is known as negative effort dependency (Hyatt et al., 1958; Fry and Hyatt, 1960; Mead et al., 1967; Morris and Lane, 1981). This implies that decreasing the driving pressure (e.g. by application of an external resistance) may counteract airways compression, increase expiratory flow and decrease intrinsic PEEP (Fry and Hyatt, 1960; Ingelstedt et al., 1972).

In a preliminary study, Aerts et al. (1997) have shown that in mechanically ventilated patients with COPD application of an external resistance can indeed counteract airways compression and reduce flow limitation. The latter was assessed from iso-volume pressure flow relationships, indicating an increase

in flow at a decrease in driving pressure when 2 resistance levels were compared with unimpeded expiration.
In the present study this approach is further extended. Using a controllable resistor a series of expiratory resistance levels is applied. The effect of these series of resistance levels on flow-limitation and iPEEP is studied by computation of iso-volume pressure-flow relationships and by interrupter measurements (Reinoso et al., 1993; Hage et al., 1995). The aim is to identify the patients in whom an external resistance counteracts airways compression and consequently reduces flow limitation and iPEEP. Furthermore, from patients with and without reduction in flow limitation, respiratory mechanics during unimpeded expiration are compared in order to relate the severity of pulmonary disease to the effect of the external resistance.

PATIENTS AND METHODS

PATIENTS

18 patients with COPD admitted to the medical intensive care unit were studied. The reasons for admittance were in 16 patients an acute exacerbation of COPD, in one patient gastro-intestinal bleeding and in one patient cerebral bleeding. Patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal tube with an inner diameter $\geq$ 7 mm and absence of air leaks. All patients had a history of severe COPD, according to the ERS consensus (Siafakas et al., 1995). 12 patients had undergone pulmonary function testing within a year before the period of mechanical ventilation, the mean FEV1 as percentage of predicted was 29 % (range 20 - 41%). The patients were ventilated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study, except that if present, ventilator PEEP was removed. In all patients the volume controlled mode was used. The average minute volume was 8.9 l/min, ranging from 7 to 13 l/min. The average respiratory rate was 13 breaths per minute, ranging from 10 to 20 breaths/min. The ratio between inspiratory and expiratory time was 35:65. All patients were studied in supine position. During the study the patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, Holland) and paralysed with vecuronium (Organon Teknika, Boxtel, The Netherlands).

Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

RESPIRATORY MEASUREMENTS

A heated screen pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal tube to measure flow. Volume was obtained by computerised integration of the flow signal. The pneumotachometer has proven to give a negligible phase and amplitude distortion between 0.5 and 70 Hz and a deviation in flow measurement of less than 3% up to 15 l/s, thus fulfilling the ERS requirement (Peslin et al., 1972; Duvivier et al., 1977, Quanjer et al., 1993). Airway opening pressure (Pao) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, USA). The equipment was calibrated before each measurement session. The flow was calibrated using a 1 l syringe. The pressure was calibrated using a water filled u-shaped manometer. Data were stored at a sample frequency of 100 Hz and analysed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA). In figure 1 a schematic presentation of the experimental set up is given.

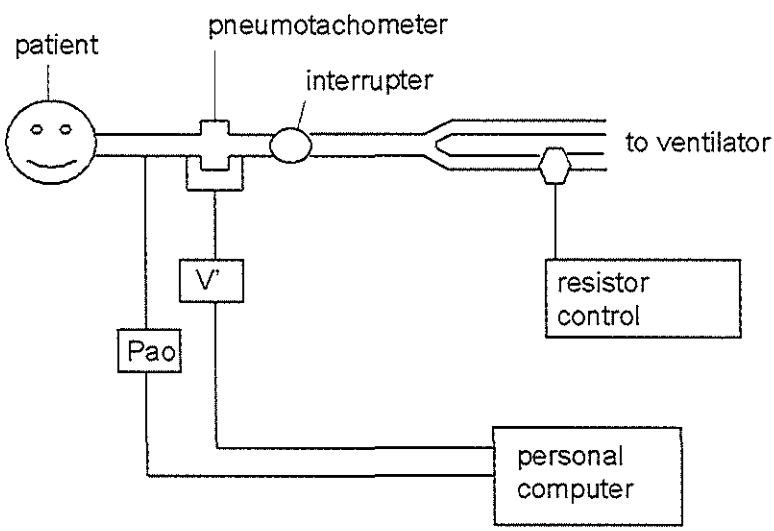


Figure 1. Schematic presentation of the experimental set up.
The ventilator tubing is divided in and inspiratory and expiratory line, controlled by the valves of the ventilator. Pao = airway opening pressure.

ISO-VOLUME PRESSURE-FLOW (IVPF) RELATIONSHIPS

An adjustable resistor was placed in the expiratory line of the ventilatory circuit. The technical details of the resistor have been described elsewhere (Verbraak et al., 1999). The pressure-flow relationships of the various resistance levels used in the study are shown in Fig. 2. In each patient increasing levels of resistance were applied, till an increase in end-expiratory plateau pressure was detected of 1 cm H20. Airway opening pressures at end-expiration and end-inspiration were obtained by application of end-expiratory and end-inspiratory occlusions respectively. The end-expiratory plateau pressure, obtained after 3-5 s, was indicated as total PEEP, being the sum of iPEEP and external PEEP. Respiratory system compliance (Crs) was calculated for each resistance level from the quotient of expiratory tidal volume and the difference between end-inspiratory pressure and total PEEP. No significant change in Crs was found at the resistance levels used. With the interrupter method, in all patients a linear relationship between plateau pressure, as static estimate of alveolar pressure and volume for the tidal volume range was established during expiration (mean r^2 = 0.98, range 0.95 - 1.00), this was consistent with the results of a previous study (Gottfried et al., 1985).

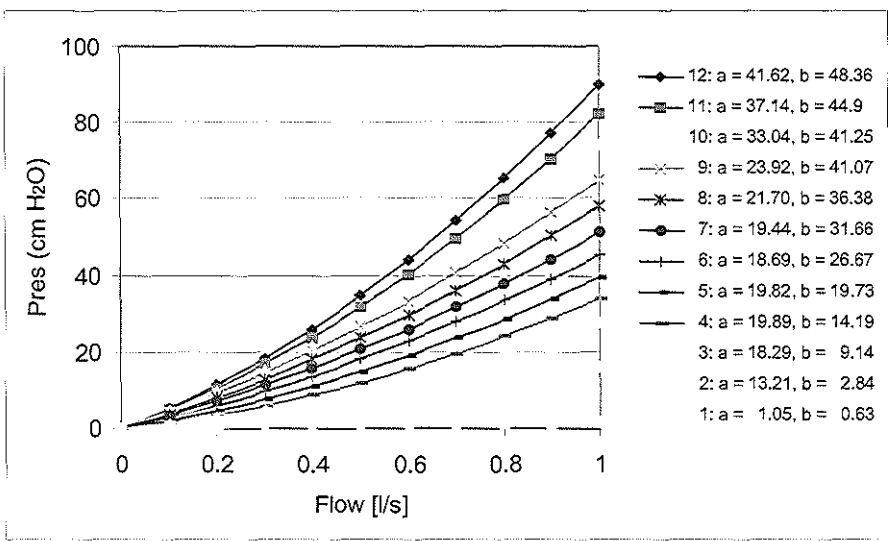


Figure 2. Pressure-flow relationships of the applied resistance levels.
P(res) is calculated as Pres= a * flow + b* flow^2

Furthermore, interrupter measurements, which will be described in more detail in the next section, showed that application of the resistances did not affect the linearity of the alveolar pressure - volume relationship for the tidal volume range. Taken into account this linear relationship, Crs was used to calculate alveolar pressure (Palv) at different levels of volume.

The alveolar pressures used to compute IVPF curves are calculated from compliance values obtained during static conditions. This implies that "static" pressures are used for dynamic conditions. The difference between the pressure (Pinit) obtained directly after pressure equilibration at the airway opening and the plateau pressure after 0.25 s occlusion time (Pss) is caused by visco-elastic properties of the lung and chest wall and ventilation inhomogeneity in absence of flow limitation (Bates et al., 1988). In the presence of flow limitation also the dynamic behaviour of the flow-limiting segment contributes to the pressure time course during occlusion (Ohya et al., 1989, 1989). Figure 3a and b show representative time courses of flow and pressure for a patient without (a) and with flow limitation (b) during an interrupter procedure. In case of no flow limitation a rapid equilibration of airway pressure occurs after occlusion and alveolar pressure can be estimated by back extrapolation of the pressure curve to avoid influence of the oscillations during the initial part (Chowienczyk et al., 1991; Phagoo et al., 1996). As explained in the next item, flow limitation is present in case of a clear flow-overshoot (spike) after reopening of the interruptor (fig b). Within the first part of the pressure curve the pattern is then caused by the mechanisms described above but also by the disappearance of the flow-limiting segment in the absence of flow during an occlusion. The latter phenomenon causes a more gradual increase of pressure up to alveolar pressure within about 100 ms , whereafter a slight increase occurs by ventilation inhomogeneity and visco-elastic effects (Ohya et al., 1989, 1989). In all cases a minor and approximately constant difference existed between the Pss, used for the compliance estimation and the estimates of driving pressure from Pinit, of which examples are shown in fig. 3.

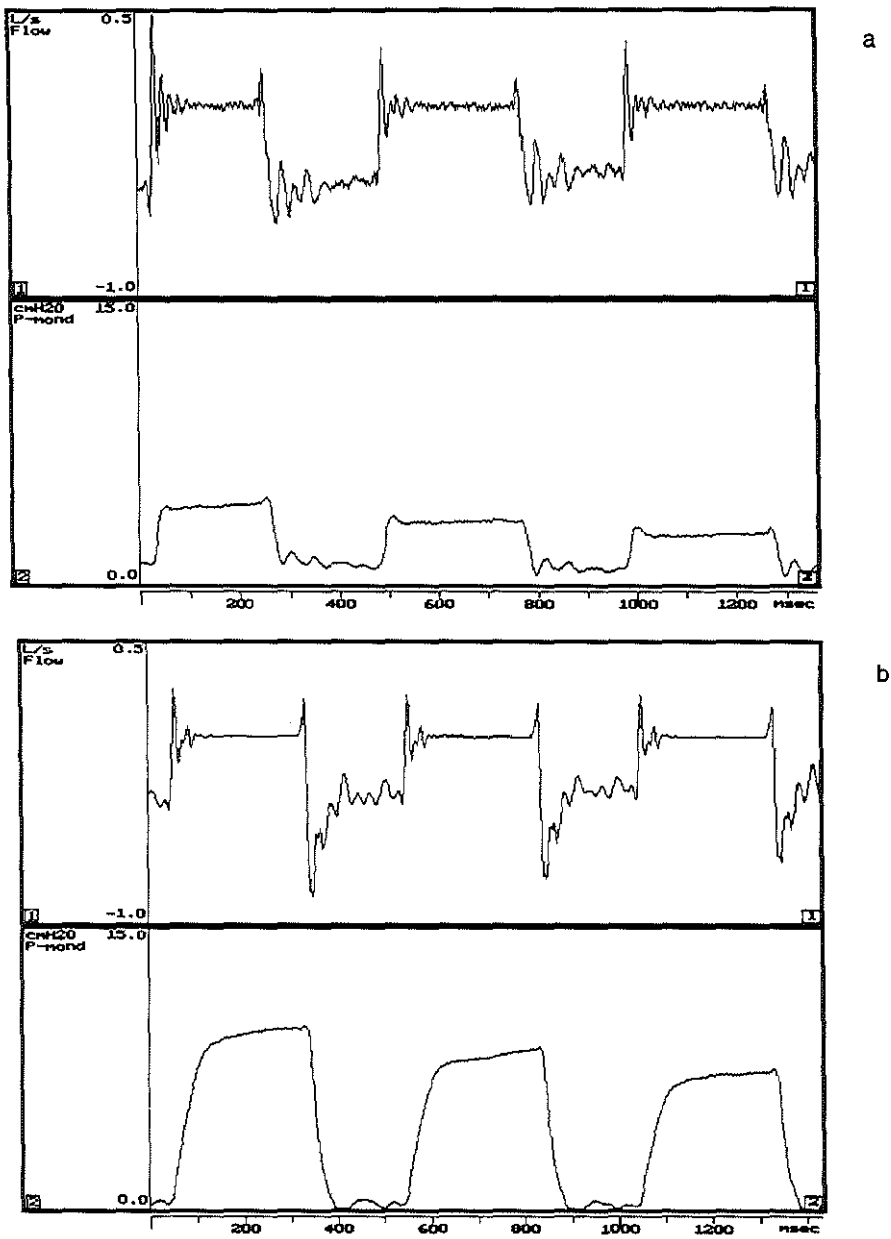


Figure 3. Representative interrupter curves during relaxed expiration in a patient without (a) and a patient with (b) flow limitation. In the upper panel the flow signal is displayed in the lower panel the pressure signal.

IVPF-curves were computed at fixed volume levels, starting with 0.125 l from the onset of expiration with increments of 0.125 l until the expiration of tidal volume was completed. For each volume level driving pressure was calculated

as the pressure difference between Palv and Pao. The driving pressure at end-expiration equals iPEEP. IVPF curves were computed by plotting expiratory flow against corresponding values of driving pressure for each volume level obtained with all consecutive resistances.

INTERRUPTER MEASUREMENT

Airways compression was established by the application of the interrupter technique. Airways collapse is assumed present when, after reopening of the interrupter, a spike flow superimposed on the ongoing mouth flow is detected (Reinoso et al., 1993; Hage et al., 1995)

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. Ohya et al. (1989) found that a closure 100 ms or more yielded equal flow spikes in patients with flow limitation, indicating that within that period the expansion of the compressed airway segment has been completed. In this study the valve was alternately open and closed for 250 ms. The dynamic properties of the interrupter device have previously been studied using a constant flow generator (Hage et al.,1995). The switching speed (complete opening to closure) was 65-110 ms. To avoid flow oscillations after opening and closing of the valve, a tubing connected to the pressure transducer of the pneumotachometer was used with the length and resistance such that the interrupter was critically damped. In the present study the system was slightly underdamped, causing small spikes of equal magnitude at opening and closure, for which we could easily correct the flow transient. Ninety percent rise time was less than 25 ms, which was considered sufficiently accurate for the purpose of the measurements. After an end-inspiratory hold procedure applied by the ventilator the interrupter valve was closed, the patient was disconnected from the ventilator tubings and the interrupter-procedure was started. After opening of the valve, flow limitation was assumed to be present when the opening transient clearly exceeded the closing transient (Reinoso et al., 1993; Hage et al., 1995).

PROTOCOL

At first, flow, pressure and volume were recorded during unimpeded expiration. End-inspiratory and end-expiratory occlusions and interrupter procedure were

performed, all in duplicate. Consecutively, the resistor was added and set at the lowest level of resistance. Flow, pressure and volume were recorded and after an equilibration period of two minutes, end-inspiratory and end-expiratory occlusions and interrupter procedure were performed. The level of resistance was increased at fixed increments and all measurements were repeated as described above. This was continued till a level of resistance was reached that caused an increase in end-expiratory plateau pressure of $\geq$ 1 cm H_2O.

DATA ANALYSIS

From flow-volume curves during unimpeded expiration respiratory time constants were obtained by calculating the quotient of exhaled volume and the corresponding change in flow for the last 75% of exhaled volume (RC75) (Aerts et al., 1999; Lourens et al.,1999, 2000). In order to analyse iso-volume driving pressure-flow relationships, all resistance levels that did not increase the end-expiratory plateau pressure with more than 1 cm H_2O, were used.

The 95% confidence interval of the iso-volume driving pressure-flow slope was used to define a positive, negative or zero slope. A positive slope represents a decrease in flow at a decrease in driving pressure, indicating positive dependency of flow on driving pressure. A zero slope represents unaltered flow at a decrease in driving pressure, indicating independency of flow on driving pressure. A negative slope represents an increase in flow at a decrease in driving pressure, indicating negative dependency of flow on driving pressure. In the latter condition, airways compression is considered to be counteracted and flow limitation to be reduced.

To quantify the analysis of the data obtained with the interrupter technique the spike area was measured (the area of the flow overshoot). The flow overshoot was determined after back extrapolation of the flow during the interval 100 - 250 ms after reopening of the interrupter (Fig. 4). For each resistance level the first 7 interruptions were analysed. To determine the effect of the resistance level on the spikes, for each patient the average spike area of the 7 spikes was calculated for each resistance level. The spikes at unimpeded expiration were compared to the spikes at the highest resistance level that did not increase end-expiratory plateau pressure.

To predict which patients would benefit from the application of an external resistance the three categories of the relationship between driving pressure and flow were related to the RC75, FEV1, spike area and iPEEP, using the

Kruskal-Wallis test. If the Kruskal-Wallis test revealed significant differences, Mann-Whitney tests were done for detection of the individual group differences. A p-value ≤ 0.05 was considered significant.

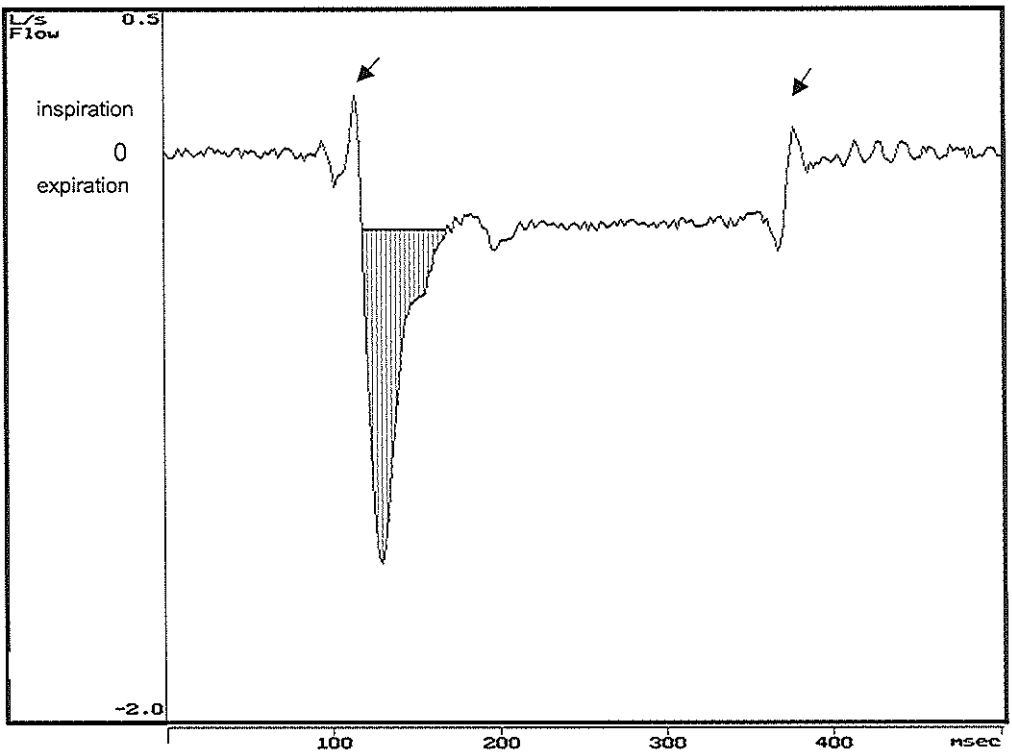


Figure 4. One interruption, the spike area (shaded) is determined after back extrapolation of the flow during the interval 100 - 250 ms after reopening of the interrupter. Inspiratory and expiratory direction are indicated, opening and closing transients are marked (↘).

RESULTS

IVPF relationships showed an increase in flow with a decrease in driving pressure (negative dependency) in 6 patients. The increase in iso-volume flow at a decrease in driving pressure was found in the later part of exhaled volume in all 6 patients. The portion of exhaled volume in which the flow increased varied from 34% to 72% of tidal volume (average 52%). In 10 patients no change in flow was found with a decrease in driving pressure (independency).

In 2 patients a decrease in flow was found with a decrease in driving pressure in 2 patients (positive dependency), indicating there was no flow limitation.
In Fig. 5 representative examples are shown of patients with negative dependency, independency and positive dependency.

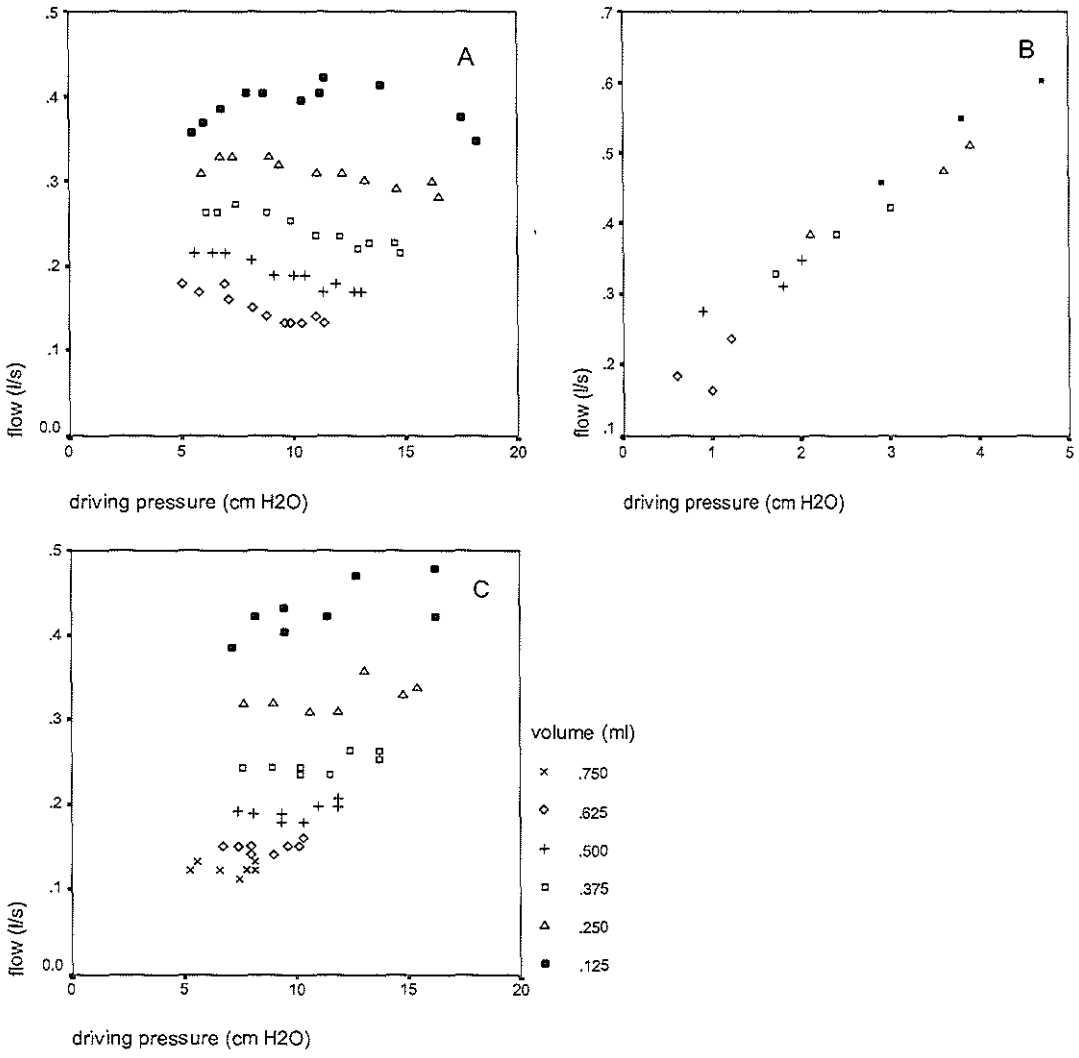


Figure 5. Iso-volume pressure flow-relationships of a patient with negative dependency (A), positive dependency (B) and independency (C) . The volume is expressed as ml from the onset of expiration. The scaling in figure B has been adapted.

During unimpeded ventilation, in the 6 patients with negative dependency and in the 10 patients with independency, interrupter measurements indicated the presence of flow limitation; the spikes after opening of the interrupter valve clearly exceeded the closing transients (Table 1). In the 2 patients with positive dependency no supra maximal spikes were detected. Application of resistance caused a decrease in spike area in the patients with negative dependency from 24 ml (sd 8) to 9 ml (sd 2) and in the patients with independency from 22 ml (sd 9) to 6 ml (sd 2). Fig. 6 shows the spike area in relation to the resistance level for all patients.

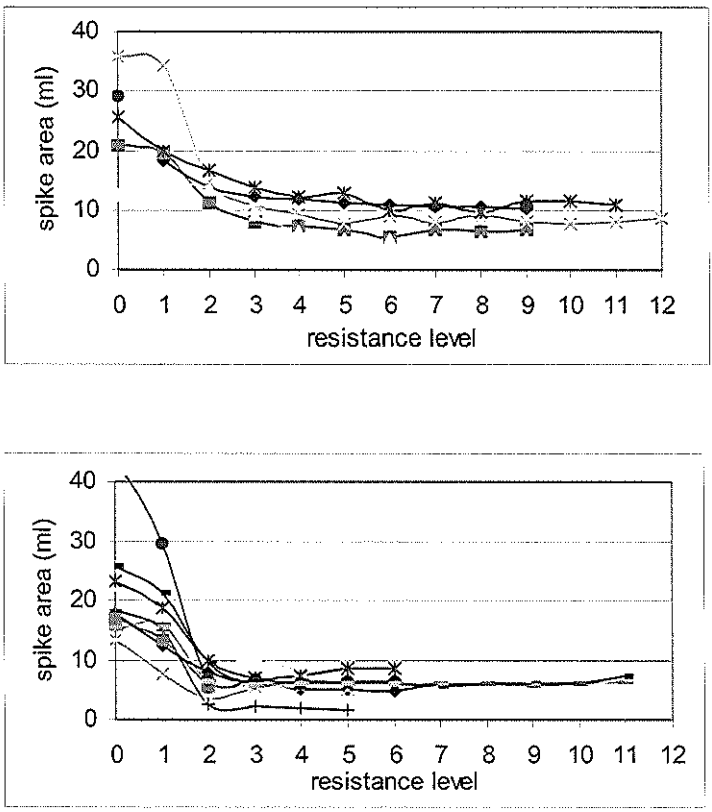


Figure 6. Spike area in relation to resistance level for each patient. In figure A the patients with negative dependency, in figure B the patients with independency.

Patient	FEV1 (l/s) (% pred)	RC75 (s)	Spike area (ml) unimpeded	Spike area (ml) highest R	ipeep (cm H2O) unimpeded	ipeep (cmH2O) highest R	Dependency	Highest level R
1	0.5 (25)	2.5	18	10	13.6	9.8	Neg	9
2		2.5	21	7	10.8	5.9	Neg	9
3	0.7 (33)	3.7	29	11	7.1	1.7	Neg	9
4		1.7	13	5	7.2	2.6	Neg	10
5	0.7 (32)	2.8	26	11	14.7	6.0	Neg	11
6	0.8 (27)	3.7	36	9	10.8	3.7	Neg	12
Mean	**0.7 (29)**	**2.8**	**24**	**9**	**10.7**	**5.0**		**10**
SD	**0.1 (4)**	**0.8**	**8**	**2**	**3.2**	**2.9**		**1**
7	1.2 (20)	1.7	17	5	6.8	5.7	In	2
8		0.6	*	*	4.6	1.6	In	4
9		2.2	18	2	3.9	1.2	In	5
10	0.8 (29)	1.5	13	5	3.7	0.8	In	5
11	1.3 (41)	1.6	23	8	11.5	5.4	In	6
12		1.9	45	6	6.4	4.1	In	6
13	0.8 (31)	2.0	18	6	7.5	4.3	In	7
14	0.9 (37)	2.2	22	8	9.3	6.1	In	10
15	0.5 (21)	5.1	26	7	6.1	3.4	In	11
16		2.2	15	6	7.4	1.0	In	11
Mean	**0.9 (30)**	**2.1**	**22**	**6**	**6.7**	**3.4**		**7**
SD	**0.3 (8)**	**1.2**	**9**	**2**	**2.4**	**2.1**		**3**
17	0.9 (29)	0.8	0	0	1.5	1.4	Pos	1
18	0.6 (20)	1.3	3	2	1.0	0.3	Pos	2

Table 1. For each patient respiratory parameters are given. FEV1 = forced expiratory volume in 1 s measured prior to mechanical ventilation; RC75 = expiratory time constant for the last 75% of expiration; spike area = area of flow overshoot determined with interrupter method; iPEEP = intrinsic positive expiratory pressure; highest level of R = highest level of resistance applied. * due to a technical problem no interrupter measurements were obtained in this patient.

During unimpeded expiration the mean iPEEP was 10.7 (sd 3.2) for the patients with negative dependency, 6.7 (sd 2.4) for the patients with independency and 1.3 (sd 0.4) for the patients with positive dependency. After application of the highest resistance level these values were 5.0 (sd 2.9), 3.4 (sd 2.1) and 0.9 (sd 0.8) respectively.
In Table 1 the highest resistance level that did not increase end-expiratory plateau pressure is shown for each patient. Spike areas and iPEEP levels before and after application of the highest resistance are also given.
In the 6 patients with negative dependency the average RC75 was 2.8 s (sd 0.8). In the 10 patients with independency the average RC75 was 2.1 (sd 1.2). In the 2 patients with positive dependency the RC75 was 1.3 s and 0.8 s (Table 1).
Comparing the spike area and the FEV1 for the patients with negative dependency and independency, no significant differences were found. The iPEEP level and the RC75 during unimpeded expiration were significantly different comparing the patients with negative dependency and independency, with p-values of respectively 0.030 and 0.044.

DISCUSSION

In this study, mechanically ventilated patients with COPD were identified, in whom application of an external resistance counteracted airways compression and reduced flow limitation as well as intrinsic PEEP. Respiratory mechanics determined during unimpeded expiration, discriminated between patients with- and without reduction of flow limitation. The intrinsic PEEP levels and expiratory time constants during unimpeded expiration were predictive for the effect of the external resistances on flow limitation.
In patients with severe COPD the rate of lung emptying is diminished due to both a low driving pressure and a high airway resistance. The low driving pressure is due to the diminished elastic recoil of the lung tissue. The high airway resistance is largely caused by dynamic airways compression during expiration. Airways compression develops when the pressure surrounding the airways exceeds the intraluminal pressure in the deformable airways (Mead et al., 1967; Hyatt et al., 1979; Kimball et al., 1982; Marini, 1989). This only occurs when the intra pleural pressure is positive. Because of the combination

of an elevated elastic equilibrium volume and dynamic hyperinflation, the thoracic wall exerts an inward force resulting in a positive intra pleural pressure throughout expiration (Mead and Agostoni, 1964; Hyatt et al., 1979; Kimball et al., 1982). Dynamic airways compression develops when both a positive intra pleural pressure and a low elastic recoil pressure of the lung tissue coincide. It has been demonstrated that airways compression can be counteracted by application of an external resistance (Aerts et al., 1997). By increasing the pressure at the airway opening, the pressure drop within the deformable airways can be diminished to such extent that compression of these airways is prevented.

The mechanism is comparable to pursed lip breathing, the generation of a positive mouth pressure during expiration. Pursed lip breathing has been reported to reduce airtrapping, decrease expiratory resistance, decrease respiratory rate and increase tidal volume, resulting in improved oxygenation (Thoman et al., 1966; Ingram and Schilder, 1967; Barach, 1968; Mueller et al., 1970; Breslin, 1992). However there are clear differences between pursed lip breathing and the controlled expiration. In this study mechanical ventilation was applied under sedation and paralysis, as a consequence respiratory rate, expiration time and tidal volume were fixed.

In the present study it was shown that the application of a series of resistance levels caused an increase in iso-volume flows at decreasing driving pressures in a subgroup of COPD patients. We have referred to this reduction in flow limitation during relaxed expiration as "negative dependency", in analogy to "negative effort dependency" during forced expiration. Negative effort dependency was first described by Hyatt and Fry (1960) and later by Mead et al. (1967). During forced expiration, when driving pressure was increased by muscle force, they observed a decrease in flow at an increase in driving pressure. In the present study, when expiration is passive and driving pressure is decreased by application of external resistances, we observe an increase in flow at a decrease in driving pressure.

Ingram and Schilder (1966) explained the negative effort dependency by compression of intra thoracic air during forced manoeuvres. However, it is unlikely that in our study compression of air accounts for the negative dependency, because driving pressures are much lower compared to those during forced expiration.

Our results might also be influenced by the use of volume data during the dynamic situation of relaxed expiration for the estimation of alveolar pressures on the basis of a static pressure volume relationship. As shown in fig. 3a and b and described in the method section, a small difference exists between the static pressure estimate, obtained after 0.25 s occlusion and the dynamic estimate directly after occlusion. Moreover, this difference was approximately equal per patient during the measurement procedure both within one breath as well as during the application of the different resistance levels. Even if the results would be influenced, this constant difference would only cause a shift along the pressure axis and would thus have no effect on our main conclusion.
During relaxed expiration the mechanism of flow limitation is different from forced expiration. During the former it can be described as viscous flow limitation, while during forced expiration local wave speed is the basic mechanism (Wilson et al., 1986; Wilson, 1989). Shapiro (1977) modelled the behaviour of a Starling resistor for laminar Poiseuille flow at a low Reynolds number, a set-up which is comparable to viscous flow limitation. In this model positive, negative- or no flow dependency on driving pressure could be demonstrated, depending on several factors such as the relationship between cross sectional area and transmural pressure (tube law), the tube diameter and the pressures upstream, downstream and surrounding the tube. Although Shapiro could elicit negative dependency in a physical model during passive expiration, until now this phenomenon could not be demonstrated in detail in patients.
In this study, by application of a series of resistance levels three groups of patients could be identified; patients with negative dependency, independency and positive dependency. Furthermore we found that these three subgroups could well be predicted on basis on respiratory mechanics obtained during unimpeded expiration. In the patients with negative dependency we found significantly higher levels of intrinsic PEEP and higher expiratory time constants during unimpeded expiration compared to patients with independency and positive dependency. These findings indicate that COPD patients with a more severe disturbance of respiratory mechanics tend to have more benefit from the application of an expiratory resistance. This may also account for the different results obtained in previous studies on expiratory pressure regulation in patients with COPD during mechanical ventilation.

One of these studies, by Gültuna et al. (1996), investigated diminished early expiratory flow (DEEF) in mechanically ventilated patients with COPD, using the DEEF feature of the Siemens Servo 900-B ventilator (Siemens Elema, Sweden). In that study no improvements in pulmonary and hemodynamic parameters could be demonstrated. They investigated post-operative patients with COPD, with an average FEV1 as percentage of predicted of 54%. In the present study we investigated patients with severe COPD (FEV1 as percentage of predicted of 29%), in whom the majority was ventilated for an acute exacerbation of COPD.

In another study by Gay et al. (1989) the effect of positive expiratory pressure on iso-volume pressure-flow relationships was investigated. For application of the expiratory pressure they used a Siemens mushroom valve. Due to the resistive properties of this valve, this device acts as an expiratory resistor. It does not only apply PEEP, but also retards the flow, whereas currently used PEEP valves allow an instant drop of pressure at the start of expiration till the set PEEP level is reached. Gay et al. demonstrated no change in iso-volume flows in flow-limited patients when PEEP was applied till a critical level. This corresponds to the independency of iso-volume flow on driving pressure in our patients with flow limitation. However, Gay did not observe negative dependency. The difference between the results of Gay et al. and ours might be related to the resistive properties of the devices used and the severity of COPD of the patients studied.

Several studies have been performed on the effects of extrinsic PEEP in mechanically ventilated patients with COPD (Marini, 1989; Tuxen, 1989; Rossi et al., 1990; van den Berg et al., 1991; Ranieri et al., 1993). In those studies threshold resistors were used, imposing various levels of extrinsic PEEP. It was shown that application of a level of extrinsic PEEP just below the intrinsic PEEP, could decrease intrinsic PEEP, but affected neither the total PEEP level nor the expiratory flow. Only when a level of extrinsic PEEP was applied that did increase hyperinflation, a change in expiratory flow was detected (van den Berg et al., 1991). In contrast, in the present study application of the external resistor did affect expiratory flow and did decrease intrinsic PEEP at unaltered end-expiratory volumes.

The increase in iso-volume flows at decreased driving pressures during late expiration, should be considered in view of changes in effective airways resistance. As a linear relationship between alveolar pressure and volume was

established for the tidal volume range, the increase in flows was found at unaltered alveolar pressures. This indicates that the total effective resistance (= the resistance of the airways and the external resistor) was decreased during late expiration.

The interrupter technique showed supra maximal flows during unimpeded expiration in 16 of the 18 patients. In those 16 patients the IVPF curve revealed flow limitation. The average spike area was 23 ml, this is in close agreement with the findings of Hage et al. (1995), who detected spikes of 27 ml in spontaneously breathing patients with flow limitation. After application of the maximal resistance level that did not increase end-expiratory pressure, the spike areas significantly reduced to an average of 7 ml. This indicates that the airways compression was counteracted. Hage et al. described spikes of 5 ml in COPD patients without flow limitation. Oscillatory transients are also caused by resonance circuits both in the respiratory system (airway and tissue compliance and inertance) and in the measuring system (pressure transducer, tubing and pneumotachometer head compliance and inertance) (Romero et al., 1990). These transients can be suppressed to a large extent by appropriate choice of tubing (Hage et al., 1995). The area of the spike was corrected for the small transients left. The maximal effect of the resistance on the spike area is already observed at resistance level 3 in all patients (Fig. 5), whereas the IVPF-curves reveal that higher resistance levels can be applied without causing an increase in end-expiratory plateau pressure. This discrepancy may be explained by the behaviour of the flow-limiting segment at different resistance levels. At a relatively small decrease in driving pressure a significant shortening of the flow limiting segment may occur, causing a decrease in spike area, whereas for complete disappearance of the flow limiting segment a higher resistance level may be needed.

We hypothesise that an optimal pattern of resistance can be predicted from the IVPF-curve obtained in the individual patient. In the IVPF-curve for each volume the point of highest flow at the lowest driving pressure can be identified. A variable pattern of resistance, applied according to these optimum points in the IVPF-curve could improve lung emptying. Although in patients on controlled mechanical ventilation the decrease in flow limitation and intrinsic PEEP is of limited value, in patients on assisted modes of ventilatory support, it could be of decisive importance for the outcome of weaning attempts.

In conclusion, in mechanically ventilated patients with COPD, a subgroup of patients can be identified, in whom application of external resistances counteracts airways compression, reduces intrinsic PEEP and increases iso-volume flows. Further studies are needed to investigate the effect of a variable resistance pattern on respiratory mechanics and gas-exchange in this group of patients.

Acknowledgements
The authors are grateful to Dr. J.G.J.V. Aerts for the helpful suggestions in revising the manuscript.

REFERENCES

Aerts, J.G., van den Berg, B., Bogaard, J.M., 1997. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur. Respir. J. 10, 550-556.

Aerts, J.G., van den Berg, B., Lourens, M.S., Bogaard, J.M., 1999. Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiologica Scandinavica 43, 322-327.

Barach, A., 1968. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br. J. Dis. Chest 62, 36-40.

Bates, J.H., Bacconier P., Milic-Emili, J., 1988. A theoretical analysis of interrupter technique for measuring respiratory mechanics. J. Appl. Physiol. 64, 2204-2214.

Breslin, E.H., 1992. The pattern of respiratory muscle recruitment during pursed-lip breathing. Chest 101, 75-78.

Chowienczyk, P.J., Lawson, C.P., Lane, S., Johnson, R., Wilson, N., Silverman, M., Cochrane, G.M.,1991. A flow interruption device for measurement of airway resistance. Eur. Repir. J. 4, 623-628.

Duvivier, C., Bohadana, A.B., Peslin, R., 1977. Technical and experimental study of two electronic spirometers. Bull. Physiopath. Resp. 13, 669-680.

Fry, D., Hyatt, R., 1960. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. American J. Med. 24, 672-689.

Gay, P.C., Rodarte, J.R, Hubmayr, R.D., 1989. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am. Rev. Respir. Dis. 139, 621-626.

Gottfried, S.B., Rossi, A., Higgs, B.D., Calverley, P.M., Zocchi, L., Bozic, C., Milic-Emili, J., 1985. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am. Rev. Respir. Dis. 131:414-420.

Gültuna, I., Huygen, P.E., Ince, C., Strijdhorst, H., Bogaard, J.M., Bruining, H.A., 1996. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Inten. Care Med. 22, 539-545.

Hage, R., Aerts, J.G.J.V., Verbraak, A.F.M., van den Berg, B., Bogaard, J.M., 1995. Detection of flow limitation during tidal breathing by the interrupter technique. Eur. Respir. J. 8, 1910-1914.

Hyatt, R., Schilder, D., Fry, D., 1958. Relationship between maximum expiratory flow and degree of lung inflation. J. Appl. Physiol. 13, 331-336.

Hyatt, R., Rodarte, J., Mead, J., Wilson, T., 1979. Changes in lung mechanics; flow-volume relations. In: Macklem, P., Permutt, S. (Eds.). The lung in transition from health to disease: Lung biology in health and disease, vol 12. Marcel Dekker, New York, 73-112.

Ingelstedt, S., Jonson, B., Nordstrom, L., Olsson, S.G., 1972. A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiologica Scandinavica 47, 7-27.

Ingram, R.H., Jr., Schilder, D.P., 1966. Effect of gas compression on pulmonary pressure, flow, and volume relationship. J. Appl. Physiol. 21, 1821-1826.

Ingram, R., Schilder, D., 1967. Effect of pursed lips expiration on the pulmonary pressure-volume relationship in obstructive lung disease. Am. J. Respir. Crit. Care Med. 96, 381-388.

Kimball, W.R., Leith, D.E., Robins, A.G., 1982. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 126, 991-995.

Lourens, M.S., van den Berg, B., Hoogsteden, H.C., Bogaard, J.M., 1999. Flow-volume curves as measurement of respiratory mechanics during ventilatory support: the effect of the exhalation valve. Inten. Care Med. 25, 799-804.

Lourens, M.S., van den Berg, B., Aerts, J.G.J.V., Vebraak, A.F.M., Hoogsteden, H.C., Bogaard, J.M., 2000. Expiratory time constants in mechanically ventilated patients with and without COPD. Inten. Care Med. 26, 1612-1618.

Marini, J.J., 1989. Should PEEP be used in airflow obstruction? Am. Rev. Respir. Dis. 140, 1-3.

Mead, J., Agostoni, E., 1964. Dynamics of breathing. In: Fenn, W.O., Rahn, H. (Eds). Handbook of physiology, vol 1, American Physiological Society, Washington DC. 411-476.

Mead, J., Turner, J.M., Macklem, P.T., Little, J.B., 1967. Significance of the relationship between lung recoil and maximum expiratory flow. J. Appl. Physiol. 22, 95-108.

Morris, M.J., Lane, D.J., 1981. Tidal expiratory flow patterns in airflow obstruction. Thorax 36, 135-142.

Mueller, R.E., Petty, T.L., Filley, G.F., 1970. Ventilation and arterial blood gas changes induced by pursed lips breathing. J. Appl. Physiol. 28, 784-789.

Ohya, N., Huang, J., Fukunaga, T., Toga, H., 1989. Mouth pressure curve on abrupt interruption of airflow during forced expiration. J. Appl. Physiol. 66, 509-517.

Ohya, N., Huang, J., Fukunaga, T., Toga, H., 1989. Airway pressure-volume curve estimated by flow interruption during forced expiration. J. Appl. Physiol. 67, 2631-2638.

Phagoo, S.B., Wilson, N.M., Silverman, M., 1996. Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3 year old children. Eur. Respir. J. 9, 1374-1380.

Peslin, R., Morinet-Lambert, J., Duvivier, C., 1972. Frequency response of tachographs. Bull. Physiopath. Resp. 8, 1363-1376.

Quanjer Ph. H., Tammeling, G.J., Cotes, J.E., Pedersen, O.F. Peslin, R., Yernault, J.C., 1993. Lung volumes and forced ventilatory flows (Report of the Working Party for Standardization of Lung Function Tests; European Community for Steel and Coal). Eur. Respir. J. 6(suppl.16), 5-40.

Ranieri, V.M., Giuliani, R., Cinnella, G., Pesce, C., Brienza, N., Ippolito, E.L., Pomo, V., Fiore, T., Gottfried, S.B., Brienza, A.B., 1993. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am. Rev. Respir. Dis. 147, 5-13.

Reinoso, M.A., Gracey, D.R., Hubmayr, R.D., 1993. Interrupter mechanics of patients admitted to a chronic ventilator dependency unit. Am. Rev. Respir. Dis. 148, 127-131.

Romero, P.V., Sato, J., Shardonofsky, F., Bates, J.H.T., 1990. High-frequency characteristics of respiratory mechanics determined by flow interruption. J. Appl. Physiol. 69, 1682-1688.

Rossi, A., Brandolese, R., Milic-Emili, J., Gottfried, S.B., 1990. The role of PEEP in patients with chronic obstructive pulmonary disease during assisted ventilation. Eur. Respir. J. 3, 818-822.

Shapiro, A., 1977. Steady flow in collapsible tubes. J. Biomech. Eng. 99, 126-147.

Siafakas, N.M., Vermeire, P., Pride, N.B., Paoletti, P., Gibson, J., Howard, P., Yernault, J.C., Decramer, M., Higenbottam, T., Postma, D.S., 1995. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur. Respir. J. 8, 1398-1420.

Thoman, R., Stoker, G., Ross, J., 1966. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 93, 100-106.

Tuxen, D.V., 1989. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am. Rev. Respir. Dis. 140, 5-9.

Valta, P., Corbeil, C., Lavoie, A., Campodonico, R., Koulouris, N., Chasse, M., Braidy, J., Milic-Emili, J., 1994. Detection of expiratory flow limitation during mechanical ventilation. Am. J. Respir. Crit. Care Med. 150, 1311-1317.

Van den Berg, B., Stam, H., Bogaard, J.M., 1991. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur. Respir. J. 4, 561-567.

Verbraak, A., Holland, W., Mulder, B., Bogaard, J., Versprille, A., 1999. A computer controlled flow resistance. Med. Biol. Eng. Comput. 37, 770-775.

Wilson, T.A., Rodarte, J.R., Butler, J.P., 1986. Wave speed and viscous flow limitation. In: Macklem, P.T., Mead, J. (Eds.). Handbook of Physiology, the respiratory system, American Physiological Society, Bethesda. 55-61.

Wilson, T.A., 1989. The wave speed limit on expiratory flow. In: Chang, H.K., Paiva, M. (Eds.), Respiration Physiology; Lung biology in health and disease, vol 40. Marcel Dekker, New York, 139-165.

CHAPTER 9

EFFECT OF EXPIRATORY RESISTANCE ON GAS EXCHANGE IN MECHANICALLY VENTILATED PATIENTS WITH COPD

M.S. Lourens
B. van den Berg
J.M. Bogaard.

In 2000 "3-zuid" temporarily moved to "10-zuid", the Surgical Intensive Care.

ABSTRACT

Background: In mechanically ventilated patients with severe COPD dynamic airways compression and flow limitation are a common finding, even during relaxed exhalation.

As a consequence dynamic hyperinflation and intrinsic PEEP occur, which have deleterious side effects. In a previous study a subgroup of COPD patients was identified in whom application of an external resistance counteracted airways compression, reduced iPEEP and increased iso-volume flow. In this study we investigate whether in this subgroup of patients, application of an external resistance might have a beneficial effect on gas exchange as well.

Methods: 8 mechanically ventilated patients with COPD were studied. The patients all had an iPEEP > 7 cm H2O, an expiratory time constant >1.7 s and flow limitation. Increasing levels of external resistance were applied and for each patient IVPF-curves were computed. From the IVPF-curves the optimal level of resistance was estimated, i.e. the resistance level that caused the highest flow at the lowest driving pressure. This resistance level was applied for 1 hour. Blood gases were obtained after one hour of standard mechanical ventilation and after 1 hour with the optimal resistance level.

Results: IVPF-curves showed an increase (3 patients) or unaltered flow at a decrease in driving pressure. The mean blood gas values during standard mechanical ventilation were: pH 7.46 (SD 0.04), PCO2 6.0 (SD 0.7), PO2 12.8 (SD 4.5) and O2 saturation 97 (SD 2). After one hour of application of the external resistance these values were: pH 7.47 (SD 0.05), PCO2 5.8 (SD 0.7), PO2 13.5 (SD 5.0) and O2 saturation 98 (SD 2). None of these changes were significant.

Conclusion: In patients with COPD on controlled mechanical ventilation application of an individually adapted expiratory resistance level did not improve gas exchange.

INTRODUCTION

In mechanically ventilated patients with severe COPD dynamic airways compression and flow limitation are a common finding, even during relaxed exhalation. As a consequence dynamic hyperinflation and intrinsic positive end expiratory pressure (iPEEP) occur. A high level of iPEEP is associated with increased work of breathing, decreased efficiency of respiratory muscles, hampered hemodynamics and impaired gas transport[1-6]. Various methods have been proposed to improve respiratory mechanics and gas-exchange in mechanically ventilated patients with COPD. The basic principle in these studies is to counteract airways compression and consequently reduce flow limitation, hyperinflation and iPEEP. Application of external PEEP has been advocated, however, only when a level of ePEEP was applied greater than iPEEP, an effect on lung emptying was observed[7]. Several authors have studied the effects of external PEEP on gas-exchange, however, the results of these studies were conflicting[7-11]. Aerts et al. showed that application of an external resistance can counteract airways compression and reduce iPEEP. However, no effect on gas-exchange could be established in the 4 patients studied[1]. In an more recent study, we were able to identify a subgroup of COPD patients, in whom application of an external resistance counteracts airways compression, reduces iPEEP and increases iso-volume flows[12]. We hypothesize that in this subgroup of patients application of an external resistance might have a beneficial effect on gas-exchange as well. In the present study, in this group of mechanically ventilated COPD patients, the effect of the individual adapted level of external resistance on gas exchange is studied. The level of resistance was titrated for each patient on basis of iso-volume pressure-flow curves.

PATIENTS AND METHODS

PATIENTS

Eight mechanically ventilated patients (4 male) with COPD were studied. The reasons for mechanical ventilation were in four patients acute exacerbations of COPD, in two patients post-operative complications, in one patient pneumonia and in one patient pulmonary bleeding. All patients had a diagnosis of severe COPD[13]. In 6 patients pulmonary function tests were performed with in a year before mechanical ventilation, the mean FEV1 as percentage of predicted was 35% (range 21 - 47%). The presence of flow limitation was established in all patients using negative expiratory pressure (NEP)[5]. In a previous study we have shown that the intrinsic PEEP level and the expiratory time constant during unimpeded expiration were predictive for the effect of application of an external resistance on flow limitation[12]. Therefore, in the present study patients were included if they fulfilled the following criteria: an iPEEP level > 7 cm H2O, an expiratory time constant > 1.7 s, presence of flow limitation established with NEP and absence of airleaks. All patients were mechanically ventilated via an endotracheal tube with an inner diameter ≥ 7 mm using a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study. If present, ventilator PEEP was removed. In all patients the volume controlled mode was used. The average minute volume was 8.3 l/min, ranging from 7 tot 12.5 l/min. The average respiratory rate was 12 breaths per minute, ranging from 10 to 16 breaths/min. The ratio between inspiratory and expiratory time was 35:65. The average FiO2 was 0.33, ranging from 0.21 to 0.45. All patients were studied in supine position. During the study the patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, Holland). Informed consent was obtained from the patient or their next of kin. The study was approved by the local ethics committee.

RESPIRATORY MEASUREMENTS

A heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal tube to measure flow. 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 at a sample frequency of 100 Hz and analyzed using a personal computer (Commodore 486 SX33, Commodore Business Machines Inc., West Chester, USA).

iPEEP

By application of an end-expiratory occlusion of 3-5 s airway opening pressure at end-expiration was obtained. The end-expiratory plateau pressure was indicated as total PEEP, being the sum of iPEEP and external PEEP. The airway opening pressure measured just prior to the end-expiratory occlusion was assumed to equal external PEEP. Although no ventilator PEEP was applied, low levels of external PEEP were detected at airway opening in all patients. These pressures represent the pressure gradient over the ventilator circuit and the expiratory valve of the ventilator.

Expiratory time constant

From flow-volume curves during unimpeded expiration expiratory time constants were obtained by calculating the quotient of exhaled volume and the corresponding change in flow for the last 75% of exhaled volume[14]. The average of three time constants was calculated.

Flow limitation

To establish the presence of flow limitation the negative expiratory pressure method (NEP) was used in all patients[5]. The patient was rapidly subjected to a negative pressure of -5 cm H2O at end-inspiration. The flow-volume curve recorded during NEP was superimposed upon the immediately preceding normal breath. Flow limitation was considered present if no increase in flow was found compared to the preceding breath. Flow limitation was expressed as percentage of expiratory tidal volume during which no increase in flow was found. All measurements were performed in triplicate, the average was calculated.

Expiratory resistor

An adjustable resistor was placed in the expiratory line of the ventilatory circuit, enabling application of various levels of resistance. The technical details of the resistor have been described elsewhere[15]. In each patient iso-volume

pressure- flow characteristics (IVPF) were obtained by application of increasing levels of resistance[12]. The level of resistance was increased till an increase in end-expiratory plateau pressure was detected of 1 cm H2O. IVPF-curves were computed by plotting expiratory flow against corresponding values of driving pressure (alveolar pressure minus airway opening pressure) for each volume level obtained with all consecutive resistance levels[12]. From the IVPF-curves the optimal level of resistance was estimated (Ro), i.e. the resistance level that caused the highest flow at the lowest driving pressure (figure 1).

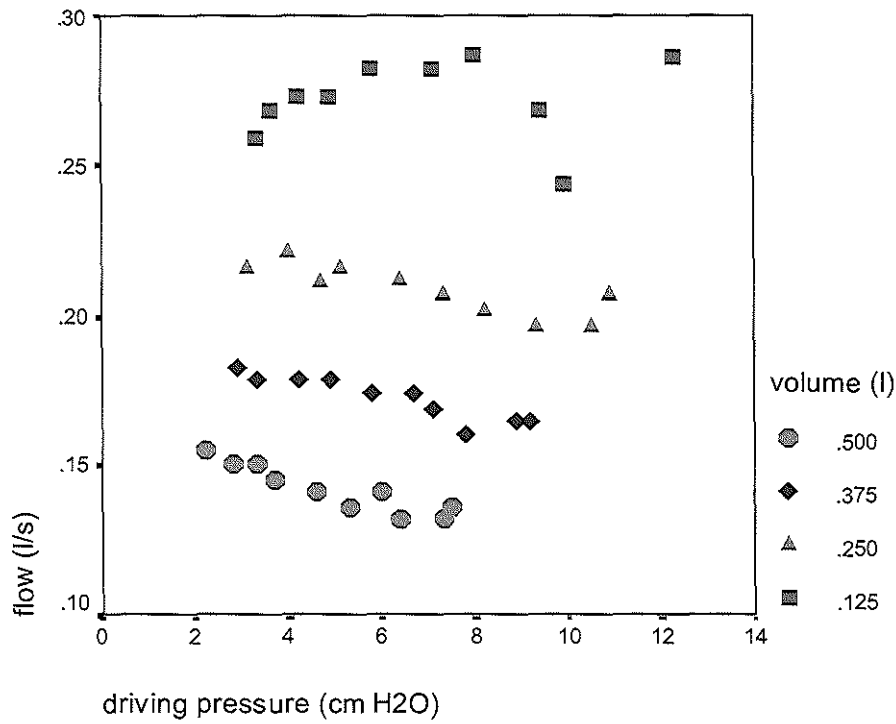


Figure 1. Iso-volume pressure-flow curve (IVPF-curve). From this curve the optimal level of resistance was estimated (Ro), i.e. the resistance level that caused the highest flow at the lowest driving pressure.

BLOOD GASSES

Blood samples were obtained from an indwelling catheter in the radial artery. PaCO2, PaO2, pH and O2 saturation were determined (ABL 725, 700 series, Radiometer, Copenhagen, Denmark).

PROTOCOL

After one hour of mechanical ventilation as set by the primary physician, arterial blood gas values were obtained in duplicate. Subsequently the optimal level of resistance was added in the expiratory circuit of the ventilator. No adjustments were made to the settings of ventilator. After 1 hour of mechanical ventilation with the optimal resistance, arterial blood gas values were determined in duplicate. The average of the blood gases during conventional mechanical ventilation was calculated and compared to the average of the blood gases obtained after one hour of ventilation with the external resistance.

DATA ANALYSIS

The arterial blood gas values before and after application of the resistance were compared using a Wilcoxon signed rank test.

RESULTS

Respiratory mechanics during conventional mechanical ventilation are shown in table 1. The average time constant was 3.3 s (sd 0.9 s), the average iPEEP 9.5 cm H2O (sd 2.3 s). With application of NEP a mean flow limited portion of expiratory tidal volume of 92% (range 82 - 97%) was found.

In all patients IVPF- curves revealed an increase or unchanged flow at a decrease in driving pressure. In all patients the optimal resistance level was defined as the resistance that caused the highest flow at the lowest driving pressure (figure 1). In 3 patients an increase in iso-volume flow was found during application of the optimal resistance, in the other patients the iso-volume flow remained unchanged.

The mean blood gas values for the individual patients before and after application of the optimal resistance are shown in table 2.

No significant differences could be found before and after application for any of the blood gas values.

Patient	RC75 (s)	iPEEP (cm H2O)	NEP (flp in % of Vt)
1	2.7	8.9	96
2	3.7	7.1	94
3	2.7	11.6	97
4	5.1	7.4	97
5	2.2	8.1	94
6	2.7	9.0	82
7	4.3	13.9	95
8	2.9	9.8	84
Mean (sd)	3.3 (0.9)	9.5 (2.3)	93 (6)

Table 1. Respiratory mechanics during conventional mechanical ventilation. RCfv75 = expiratory time constant determined from the last 75% of expiration. PEEPi = positive end-expiratory pressure. NEP = negative expiratory pressure.

Patient	PH before	pH after	PCO2 before	PCO2 after	PO2 before	PO2 after	O2sat before	O2sat after
1	7.40	7.36	6.5	6.6	11.3	10.0	97	96
2	7.50	7.48	6.3	6.2	12.6	13.2	98	99
3	7.46	7.47	6.8	6.5	23.0	23.3	99	99
4	7.41	7.45	6.6	6.1	12.1	18.0	98	100
5	7.53	7.50	4.8	5.4	11.4	13.4	98	99
6	7.47	7.49	5.8	5.6	13.5	12.9	99	98
7	7.45	7.46	5.6	5.3	7.5	8.0	92	93
8	7.45	7.51	5.2	4.4	10.9	9.4	97	96
Mean	7.46	7.47	6.0	5.8	12.8	13.5	97	98
sd	0.04	0.05	0.7	0.7	4.5	5.0	2	2
p-value		0.674		0.161		0.674		0.529

Table 2. The mean blood gas values for the individual patients before and after application of the optimal resistance are shown.

DISCUSSION

In this study, in mechanically ventilated patients with COPD, the effect of an individually titrated level of expiratory resistance on gas-exchange was studied. No significant beneficial effect on gas-exchange could be established. The majority of patients ventilated for acute exacerbations of COPD experience dynamic airways compression and flow limitation during tidal exhalation. Airways compression occurs when the pressure surrounding the airways (pleural pressure) exceeds the intraluminal pressure in the deformable airways. This only occurs if the intrapleural pressure is positive as during forced expiration or in case of marked hyperinflation during passive expiration[16,17]. Airways compression can be explained on the basis of the equal pressure point (EPP) concept[18-20]. Alveolar pressure (Palv) is the sum of elastic recoil pressure (Pell) and pleural pressure (Ppl)[18,20]. During expiration a pressure gradient exists within the airways; in the bronchioles pressures are almost equal to alveolar pressure and decrease to atmospheric pressure at the mouth. At some point along the airway the intraluminal pressure equals pleural pressure, i.e. the equal pressure point. The intraluminal pressure downstream from the EPP is less than pleural pressure, as a result the airways have a tendency to collapse. In healthy individuals the EPP is located in the larger airways which have less tendency to collapse because of their cartilaginous support. In COPD patients with loss of elastic recoil the EPP may move more peripherally to the collapsible small airways.
It has been demonstrated that in this situation, increasing the airway opening pressure by application of a resistance, will move the EPP more downstream to the non collapsible airways[1,12]. A decrease in airways compression will diminish the expiratory resistance and improve the distribution of ventilation, which may result in improved respiratory mechanics and gas exchange[1,12].
Various studies about expiration in mechanically ventilated COPD patients have been performed, the majority of these studies deals with the application of PEEP[2,7-9,11,21,22]. In these studies, during the whole expiration a constant pressure-level is applied at the airway opening mostly at a level just below the iPEEP. Theoretically such a constant pressure-level does not affect total PEEP nor expiratory flow. This can be explained by the waterfall analogy as proposed by Tobin and Lodato[23]. In this model the critical closing point of

the airways causing expiratory airflow limitation is compared to the crest of a waterfall. The pressure at the airway opening is represented by the water level downstream from the waterfall. As long as the water level downstream does not exceed the crest of the waterfall the flow is independent of that level. This implies that a ePEEP level below the iPEEP does not affect lung emptying and EEV and would have no effect on gas-exchange. Higher levels of external PEEP will have an effect on lung emptying but will also cause an increase in end-expiratory lung volume.

The results of a study of Rossi et al. are in contradiction with the "waterfall" theory. In that study, in 8 patients with COPD, application of a ventilator PEEP equal to 50% of iPEEP resulted in a significant decrease in PaCO2 and increase in PaO2[8]. The effect on hyperinflation was not reported. In contrast, other studies on the effect of various levels of ventilator PEEP, fail to report any beneficial effect on gas-exchange without increasing hyperinflation[9,11]. Ranieri et al. studied a patient population similar to ours and found that even at an increase in delta EEV no decrease in PaCO2 was found[9]. An increase in PaO2 was found, but cardiac output was significantly reduced by the high level of PEEP applied. In our study, we did not determine cardiac output. However, it is unlikely that a hemodynamic deterioration occurred since total PEEP remained unchanged.

In the present study a controllable resistor was used, which enabled the application of series of resistance levels. This resistance differs from ventilator PEEP in that it gradually decreases the pressure at the airway opening and retards the flow.

The mechanism is comparable to pursed lip breathing; the generation of a positive mouth pressure during expiration. Already in 1934 Barach described the clinical beneficial effect of pursed lip breathing[24]. Further studies on pursed lip breathing have shown that it reduces air trapping, decreases expiratory resistance, decreases respiratory rate and increases tidal volume, resulting in improved oxygenation[25-29].

In 1972, in analogy to pursed lip breathing, a resistance mechanism was incorporated in the Siemens Servo 900-B ventilator, based on the hypothesis that reduction of the early expiratory flow would improve lung emptying[30] . The clinical application of this feature, the diminished expiratory flow (DEEF) was studied in mechanically ventilated post-operative patients with COPD[31]. In

that study no improvement in arterial blood gas values with application of DEEF was shown. However, the outcome might be explained by the population studied. They studied post-operative COPD patients with less severe lung impairments than the patients in the present study. The average FEV1 as percentage of predicted and the blood gas values during standard mechanical ventilation were respectively; FEV1 54% vs 31%, PCO2 of 4.8 kPa vs 6.0 kPa and PO2 14.1 kPa vs 12.8 kPa. Furthermore, the presence of flow limitation was not assessed. In a situation of optimal blood gas values it might be hard to establish an effect of the application of DEEF.

The same reason might account for the lack of improvement in blood gas values in the present study. In the latter, patients with more severe COPD were studied; flow limitation was established and respiratory mechanics were seriously hampered. However, since all patients were on controlled mechanical ventilation as set by the attending physician, the blood gas values in the standard situation were almost optimal already. Although we observe a trend that application of the resistance has a positive effect on blood gas values, this fails to reach significance.

Another reason for the minor effect on gas exchange in this study might be that all patients were sedated and on controlled mechanical ventilation. As a consequence respiratory rate, expiration time and tidal volume were fixed. There is an important difference between the application of a resistance during controlled expiration and pursed lip breathing. During the latter, the beneficial effect is mediated by the decrease in respiratory rate and the increase in tidal volume, which result in improved oxygenation. We hypothesize that in patients on assisted modes of ventilation the application of an external resistance might be closer to the physiological situation of pursed lip breathing. In that situation, the effect of an external resistance might be twofold; improving both respiratory mechanics and gas exchange.

In conclusion, in patients with COPD on controlled mechanical ventilation application of an expiratory resistance did not significantly improve gas-exchange. On theoretical basis a more positive effect is expected during assisted modes of mechanical ventilation, this needs to be addressed in future studies.

REFERENCES

1. Aerts JG, van den Berg B, Bogaard JM. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10:550-6.
2. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989; 139:621-6.
3. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 1985; 131:414-20.
4. Kimball WR, Leith DE, Robins AG. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am Rev Respir Dis 1982; 126:991-5.
5. Valta P, Corbeil C, Lavoie A, et al. Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 1994; 150:1311-7.
6. Yang KL, Wang C. An intrinsic positive end-expiratory pressure lung model, with and without flow limitation. Crit Care Med 1996; 24:1261-5.
7. van den Berg B, Stam H, Bogaard JM. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 1991; 4:561-7.
8. Rossi A, Santos C, Roca J, Torres A, Felez MA, Rodriguez-Roisin R. Effects of PEEP on VA/Q mismatching in ventilated patients with chronic airflow obstruction. Am J Respir Crit Care Med 1994; 149:1077-84.
9. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 1993; 147:5-13.
10. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989; 140:5-9.
11. Georgopoulos D, Giannouli E, Patakas D. Effects of extrinsic positive end-expiratory pressure on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation. Intensive Care Med 1993; 19:197-203.
12. Lourens MS, Van den Berg B, Verbraak AFM, Hoogsteden HC, Bogaard JM. Effect of series of resistance levels on flow limitation in mechanically ventilated COPD patients. Respir Physiol, in press.

13. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir Jl 1995; 8:1398-420.
14. Lourens M, van den Berg B, Aerts J, Verbraak A, Hoogsteden H, Bogaard J. Expiratory time constants in mechanically ventilated patients with and without COPD. Intensive Care Med 2000;26:1612-1618.
15. Verbraak A, Holland W, Mulder B, Bogaard J, Versprille A. A computer controlled flow resistance. Med Biol Eng Comput 1999; 37:770-775.
16. Marini JJ. Should PEEP be used in airflow obstruction?. Am Rev Respir Dis 1989; 140:1-3.
17. Mead J, Agostoni E. Dynamics of breathing. Handbook of physiology. Vol. 1. Washington DC: American Physiological Society, 1964:411-476.
18. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol1967; 22:95-108.
19. Pride NB, Permutt S, Riley RL, Bromberger-Barnea B. Determinants of maximal expiratory flow from the lungs. J Appl Physiol 1967; 23:646-62.
20. Weng JT, Smith DE, Graybar GB, Kirby RR. Hypotension secondary to air trapping treated with expiratory flow retard. Anesthesiology 1984; 60:350-3.
21. Guerin C, Milic Emili J, Fournier G. Effect of PEEP on work of breathing in mechanically ventilated COPD patients. Intensive Care Med 2000; 26:1207-1214.
22. Rossi A, Brandolese R, Milic-Emili J, Gottfried SB. The role of PEEP in patients with chronic obstructive pulmonary disease during assisted ventilation. Eur Respir J 1990; 3:818-22.
23. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. Chest 1989; 96:449-51.
24. Barach A, Bickerman H, Petty T. Perspective in pressure breathing. Respir Care 1975; 20:627-642.
25. Thomam R, Stoker G, Ross J. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966; 93:100-106.
26. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970; 28:784-9.
27. Ingram R, Schilder D. Effect of pursed lips expiration on the pulmonary pressure-volume reslationship in obstructive lung disease. Am J Respir Crit Care Med 1967; 96:381-388.
28. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. Chest 1992; 101:75-8.

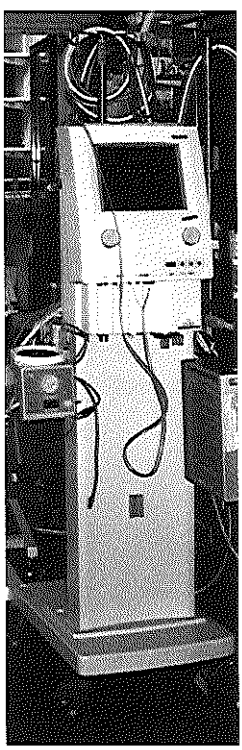
29. Barach A. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br J Dis Chest 1968; 62:36-40.
30. Ingelstedt S, Jonson B, Nordstrom L, Olsson SG. A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiol Scand.1972; 47:7-27.
31. Gultuna I, Huygen PE, Ince C, Strijdhorst H, Bogaard JM, Bruining HA. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Intensive Care Med 1996; 22:539-45.

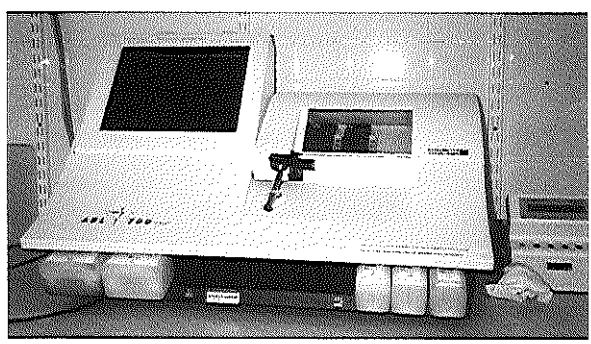
CHAPTER 10

EFFECT OF EXPIRATORY RESISTANCE ON GAS-EXCHANGE AND BREATHING PATTERN IN COPD PATIENTS WEANING FROM THE VENTILATOR.

M.S. Lourens
B. van den Berg
H.C. Hoogsteden
J.M. Bogaard.

Acta Anaesthesiologica Scandinavica, in press





Analysing a bloodgas sample.

Galileo Mechanical Ventilator, equipped with a controllable expiration valve.

ABSTRACT

Background: The majority of patients with severe COPD have flow limitation, which has deleterious side effects. If these patients are mechanically ventilated, this often results in difficult weaning. Spontaneously breathing COPD patients experience a beneficial effect of pursed lip breathing. We investigated if in intubated COPD patients application of an external resistance could produce the same beneficial effects on breathing pattern and gas-exchange as pursed lip breathing.

Methods: 10 COPD patients with flow limitation, were studied during pressure support mechanical ventilation. Two types of expiratory resistances were applied; one fixed level of resistance and one decelerating resistance. Each resistance was applied in 5 patients and the highest level was chosen that did not cause hyperinflation. Blood gas values and breathing pattern with and without resistance were compared.

Results: With resistance 1, gas-exchange and breathing pattern did not change significantly; average PCO2 changed from 8.0 to 8.1 kPa, PO2 from 10.2 to 10.3 kPa, tidal volume from 0.380 to 0.420 l, respiratory rate from 25 to 23 bpm and inspiratory : expiratory ratio from 1:1.9 to 1:2.0. With resistance 2, gas-exchange and breathing pattern did not change significantly; average PCO2 changed from 5.8 to 6.0 kPa, PO2 from 11.1 to 12.1 kPa, tidal volume from 0.733 to 0.695 l, respiratory rate from 16 to 18 bpm and inspiratory : expiratory ratio from 1:2.3 to 1:2.9.

Conclusion: In intubated COPD patients weaning from the ventilator, application of an external resistance did not have the same beneficial effects as pursed breathing.

INTRODUCTION

In patients with COPD mechanical ventilation is hampered by the dynamic airways compression and flow limitation, which develop even during relaxed exhalation (1-4). As a consequence dynamic hyperinflation and intrinsic positive end expiratory pressure (iPEEP) occur. iPEEP is associated with increased work of breathing, while at the same time respiratory muscle efficiency and hemodynamics are impaired (1-5). This discrepancy between workload and capacity often results in difficult weaning from the ventilator.
Various methods have been proposed to improve respiratory mechanics and gas-exchange in mechanically ventilated patients with COPD (3,6-12). The final goal in most of these studies is to diminish iPEEP and consequently the inspiratory work load. Previously, application of an external resistance has been shown to counteract airways compression and to reduce iPEEP in patients on controlled mechanical ventilation (3,10). The concept of adding an expiratory resistance is based on the mechanism of pursed lip breathing. It is well known that spontaneously breathing patients with COPD relief dyspnea by pursing their lips during expiration. Several studies have suggested that pursed lip breathing decreases airways compression (13-17). Patients were also found to decrease respiratory rate and to increase tidal volume during pursed lip breathing (13-17). The finding that pursed lip breathing results in improved oxygenation, can therefore be attributed to various mechanisms. This indicates that application of an external resistance during controlled mechanical ventilation resistance can only partially simulate the effects of pursed lip breathing, as in that condition respiratory rate and tidal volumes are fixed. The purpose of the present study was to evaluate if the application of an external resistance can produce the same beneficial effects as pursed lip breathing in intubated patients who are weaning from the ventilator. In contrast to controlled modes of ventilation, during weaning modes the patient can, to a certain degree, determine the breathing pattern. We studied the effect of an external resistance on breathing pattern and gas-exchange in COPD patients in whom pressure support ventilation was applied.

PATIENTS AND METHODS

PATIENTS

10 mechanically ventilated patients (8 male) with COPD were studied. The conditions leading to mechanical ventilation are shown in table 1. All patients had a diagnosis of severe COPD (18). In 8 patients pulmonary function tests were performed within the year before mechanical ventilation, the mean FEV1 as percentage of predicted was 33% (range 21 - 43%).

Patient	Age (years)	Sex	Diagnosis	FEV1 (% pred.)
1	61	M	Exacerbation COPD	26
2	74	M	Exacerbation COPD	33
3	74	M	Exacerbation COPD	33
4	60	F	Exacerbation COPD	21
5	80	F	Pneumococcal pneumonia, COPD	*
6	75	M	Gastro-intestinal bleeding, COPD	*
7	67	M	Pneumonia, COPD	31
8	76	M	Pulmonary bleeding, COPD	43
9	70	M	Exacerbation COPD	37
10	74	M	Commotio cerebri, COPD	36

Table 1. Patient characteristics.
FEV1 = forced expiratory volume in 1 s, expressed as percentage of predicted.
* no pulmonary function data were available of these patients.

Patients were included if they fulfilled the following criteria: an expiratory time constant > 1.7 s and presence of flow limitation. The presence of flow limitation was established using negative expiratory pressure (NEP) (4). The expiratory time constant (RC75) was assessed from the last 75% of expiratory tidal volume (19). In a previous study we have shown that in patients with an expiratory time constant > 1.7 s application of an external resistance could abolish flow limitation (10).

Nine patients were mechanically ventilated via an oro-tracheal tube with an inner diameter ≥ 7.5 mm, one patient was ventilated via a naso-tracheal tube (inner diameter 7 mm). Five patients (1-5) were ventilated with a Galileo ventilator (Hamilton Medical, Rhäzüns, Switzerland), in the other five patients

(6-10) a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden) was used. Ventilator settings were set by the primary physician and remained unchanged during the study. In all patients the pressure support mode was used. The average inspiratory pressure level was 14 cm H2O, ranging from 10 to 20 cm H2O. The average positive end expiratory pressure (PEEP) level was 5, ranging from 5 to 8 cm H2O. The average FiO2 was 0.35, ranging from 0.21 to 0.49. Informed consent was obtained from the patient or their next of kin. The local ethics committee approved the study.

RESPIRATORY MEASUREMENTS

Flow was measured with a disposable fixed orifice differential flow sensor (Novametrix Medical Systems Inc., Wallingford CT, USA), connected to the endotracheal tube. Volume was obtained by computerised integration of the flow signal. Pressure is measured by a differential pressure transducer referenced to atmosphere (Novametrix Medical Systems Inc., Wallingford CT). Data were stored at a sample frequency of 100 Hz (Novametrix, Cosmo Plus, Medical Systems inc., Wallingford, USA) and analysed using a personal computer.

EXPIRATORY TIME CONSTANT

From flow-volume curves expiratory time constants were obtained by calculating the quotient of exhaled volume and the corresponding change in flow for the last 75% of exhaled volume (19). The average of three time constants was calculated.

FLOW LIMITATION

To establish the presence of flow limitation the negative expiratory pressure method (NEP) was used (4). The patient was rapidly subjected to a negative pressure of -5 cm H2O at end-inspiration. The flow-volume curve recorded during NEP was superimposed upon the immediately preceding normal breath. Flow limitation was considered present if no increase in flow was found compared to the preceding breath during any part of expiration. Flow limitation was expressed as percentage of expiratory tidal volume during which no increase in flow was found. All measurements were performed in triplicate, the average was calculated.

EXPIRATORY RESISTOR GALILEO VENTILATOR

For research purposes the Galileo ventilator (Hamilton Medical, Rhäzüns, Switzerland) was equipped with a device which allowed regulation of the expiratory pressure decay by manipulating the PEEP valve. Both the time of decay of PEEP to the nominal value and the pressure-drop from end-inspiratory pressure to initial PEEP level could be adjusted. The pressure decay curve followed and exponential curve (exp (-t/tau)) with tau equal to the expiratory time constant determined from the last 75% of expiration (see above). The rationale of this procedure is to create a resistance behaviour with maximal added resistance at the start of expiration. The level of resistance was increased till an elevation in end-expiratory plateau pressure was detected of 1 cm H2O and subsequently set at this fixed level.

EXPIRATORY RESISTOR USED WITH SERVO VENTILATOR

An adjustable resistor was placed in the expiratory line of the ventilatory circuit, enabling application of various levels of resistance. In this set-up, fixed resistance levels were applied during the entire expiration. The technical details of the resistor have been described elsewhere (20). The level of resistance was increased till an elevation in end-expiratory plateau pressure was detected of 1 cm H2O and subsequently set at this fixed level.

BLOOD GASES

Blood samples were obtained from an indwelling catheter in the radial artery. PaCO2, PaO2, pH and O2 saturation were determined (ABL 725, 700 series, Radiometer, Copenhagen, Denmark).

BREATHING PATTERN

The average tidal volume, respiratory rate and ratio between inspiratory and expiratory time were calculated during conventional ventilatory support and during application of the resistance. Average values of 60 s. were calculated every 5 minutes for one hour.

PROTOCOL

The patient was connected to the measurement device and flow, volume and pressure were monitored continuously. After one hour of pressure support ventilation as set by the primary physician, arterial blood gas values were

obtained. Subsequently the resistance was added in the expiratory circuit of the ventilator. No adjustments were made to the settings of ventilator. After 1 hour of pressure support ventilation with the resistance, arterial blood gas values were determined. Blood gas values and breathing pattern parameters during pressure support ventilation with the external resistance were compared to those obtained during conventional pressure support ventilation.

DATA ANALYSIS

Arterial blood gas values and breathing pattern parameters before and after application of the resistance were compared using Wilcoxon signed rank test.

RESULTS

Respiratory mechanics during standard mechanical ventilation are shown in table 2. The average time constant was 3.1 s (range 1.7 - 5.1 s). With application of NEP a mean flow limited portion of expiratory tidal volume of 89 % (range 77 - 97%) was found.

Patient	FLP NEP (% tidal volume)	RC75 (s)
1	*	1.9
2	94	3.7
3	94	3.3
4	97	5.1
5	94	2.2
6	77	1.7
7	82	2.7
8	85	4.3
9	84	2.9
10	82	2.7

Table 2. Respiratory mechanics during mechanical ventilation.
FLP NEP = flow limited portion assessed with negative expiratory pressure, expressed as percentage of expiratory tidal volume. RC75 = expiratory time constant determined from the last 75% of expiratory tidal volume, expressed in s. * due to a technical problem NEP measurements were not performed in this patient.

The blood gas values for the individual patients before and after application of the resistances are shown in table 3. During conventional ventilatory support with the Galileo (patients 1-5), the average PCO2, PO2 and O2 saturation were respectively 8.0 kPa (range 6.5 to 10.1), 10.2 kPa (range 8.5 to 12.8) and 94 % (range 90 to 98). During application of the external resistance these values were respectively 8.1 kPa (range 6.9 to 9.2), 10.3 kPa (range 8.3 to 14.3) and 94 % (range 91 to 98). No significant differences could be established before and after application of the resistance for any of the blood gas values. During conventional ventilatory support with the Servo ventilator (patients 6-10), the average PCO2, PO2 and O2 saturation were respectively 5.8 kPa (range 4.8 to 6.8), 11.1 kPa (range 8.8 to 13.0) and 97 % (range 95 to 98). During application of the external resistance these values were respectively 6.0 kPa (range 5.2 to 6.6), 12.1 kPa (range 10.5 to 14.3) and 98 % (range 96 to 99). The differences were not significant for any of the blood gas values.

Patient	PCO2 (kPa) standard	PCO2 (kPa) resistance	PO2 (kPa) standard	PO2 (kPa) resistance	O2-sat. (%) standard	O2-sat (%) resistance
1	8.5	8.2	8.5	10.1	90	94
2	6.8	6.9	12.1	10.1	98	96
3	8.3	8.8	8.5	8.8	91	91
4	10.1	9.2	12.8	14.3	97	98
5	6.5	7.2	9.0	8.3	94	92
6	6.8	6.6	8.8	10.6	95	97
7	5.7	6.4	10	10.5	96	96
8	5.7	5.6	12.7	12.3	98	98
9	5.9	6.0	13	14.3	98	99
10	4.8	5.2	10.9	13	97	98

Table 3. Blood gas values during standard pressure support ventilation and during pressure support ventilation with the external resistance. Patients 1-5 were ventilated with Galileo ventilator and a decelerating resistance was applied, whereas patients 6-10 were ventilated with the Servo ventilator and a fixed resistance level was applied. O2-sat = O2 saturation.

Average tidal volume, respiratory rate and I:E ratio before and after application of the resistances are shown for the individual patients in table 4. During

conventional ventilatory support with the Galileo ventilator, the average tidal volume, respiratory rate and I:E ratio were respectively 0.380 l (range 0.257 to 0.528) , 25 min^{-1} (range 15 to 35) and 1: 1.9 (range 1:1.5 to 1: 2.3), during application of the external resistance these values were respectively 0.420 l (range 0.250 to 0.630), 23 min^{-1} (range 13 to 34) and 1:2.0 (range 1;1.6 to 1: 2.6). No significant differences could be found before and after application of the resistance for any of the parameters. During conventional ventilatory support with the Servo ventilator, the average tidal volume, respiratory rate and I:E ratio were respectively 0.733 l (range 0.446 to 0.935), 16 min^{-1} (range 9 to 26) and 1: 2.3 (range 1:1.3 to 1: 2.8), during application of the external resistance these values were respectively 0.695 l (range 0.450 to 1.380), 18 min^{-1} (range 7 to 29) and 1:2.9 (range 1:1.5 to 1: 4.0). The differences were not significant for any of the parameters.

Patient	Vte (l) standard	Vte (l) resistance	RR (min^{-1}) standard	RR (min^{-1}) resistance	I:E standard	I:E resistance
1	0.440	0.545	26	21	1:1.8	1:2.0
2	0.528	0.631	15	12	1:2.3	1:2.6
3	0.257	0.254	35	34	1:1.5	1:1.6
4	0.288	0.317	28	24	1:1.9	1:1.8
5	0.386	0.352	21	25	1:1.9	1:1.8
6	0.446	0.459	26	22	1:2.3	1:2.4
7	0.903	0.446	9	21	1:2.4	1:2.6
8	0.935	1.384	10	7	1:2.8	1:3.8
9	0.468	0451	26	29	1:1.3	1:1.5
10	0.912	0.734	9	10	1:2.6	1:4.0

Table 4. Breathing pattern parameters during standard pressure support ventilation and during pressure support ventilation with the external resistance. Vte = expiratory tidal volume (l); RR = respiratory rate (breaths per minute); I:E = ratio of inspiration and expiration. Patients 1-5 were ventilated with Galileo ventilator and a decelerating resistance was applied, whereas patients 6-10 were ventilated with the Servo ventilator and a fixed resistance level was applied.

DISCUSSION

We evaluated in COPD patients weaning from the ventilator whether application of an external expiratory resistance could produce the same beneficial effects as pursed lip breathing and thereby have a positive effect on lung emptying. We found that application of an external resistance did not act as pursed lip breathing; no beneficial effect on breathing pattern and gas-exchange could be established.

The majority of mechanically ventilated patients with COPD encounter serious weaning problems. Several studies have addressed the various reasons for weaning difficulties in these patients (21-23). In the majority of patients, expiratory flow limitation hampers complete expiration till the relaxed state (FRC). As a consequence iPEEP occurs, resulting in increased inspiratory workload and decreased respiratory muscle capacity. Furthermore, hemodynamics and gas-exchange are disturbed, which may also reduce muscle capacity. Finally, the respiratory system tends to resort to rapid shallow and chaotic breathing (6,24,25). It is still unclear why this breathing pattern develops. By rapid shallow breathing, the work of breathing per breath is decreased, but in time the work load is increased and CO2 elimination is hampered (6). Especially in patients with COPD, rapid shallow breathing is considered deleterious. A way to decrease iPEEP and to improve gas-exchange should be to counteract flow limitation in patients with COPD. To achieve this, some spontaneously breathing COPD patients purse their lips, which has been reported to decrease airways compression. Moreover, a decreased respiratory rate, an increased tidal volume and improved oxygenation are observed (13-17). Already in 1934 Barach described a patient with COPD who clearly relieved dyspnoea by exhaling against partially closed lips (26). This inspired him to develop a continuous positive pressure breathing (CPPB) technique for patients with COPD. He showed roentgenographically that this technique increased the width of the branches of the bronchial tree in these patients (27). The CPPB technique used by Barach is comparable to continuous positive airway pressure (CPAP) devices used nowadays. In the setting of mechanical ventilation this positive expiratory airway pressure is known as PEEP. In clinical practice external PEEP is frequently used in mechanically ventilated patients with COPD. However, both CPAP and PEEP differ from pursed lip breathing in that they act as threshold

resistors; only one set-pressure level is applied during expiration. In contrast, pursed lip breathing gradually decreases the airway opening pressure and retards the flow. To our knowledge, no information exists about the exact pattern of resistance exerted by pursed lip breathing. In the present study we used resistances that decreased airway opening pressure and retarded flow.

Numerous studies have been performed on the effects of ePEEP in mechanically ventilated patients with COPD. In most studies a level of ePEEP is chosen just below the level of iPEEP, in order to avoid hyperinflation. Although the inspiratory workload is diminished, such an approach affects neither lung emptying nor gas-exchange in case of flow limitation (28,29). This is consistent with the results of several studies (7,11,30,31). Only one study reported a positive effect on gas-exchange when a level of ePEEP was applied smaller than the iPEEP (32).

Recently, Reissmann et al. showed that application of CPAP had a positive effect on breathing pattern and gas exchange in COPD patients during a weaning trial (6). In 9 patients with COPD spontaneous 30 minute breathing trials with and without CPAP were compared. They found that CPAP had a beneficial effect on completion of the trial, it decreased respiratory rate and increased tidal volume. They found an increase in Vt of 40 ml and a decrease in respiratory rate of 3 breaths / minute after 30 minutes of CPAP.

In the present study, instead of CPAP, two types of resistances are used. Both these resistances differ from CPAP in that they decelerate flow instead of applying a threshold pressure. In 5 patients fixed levels of resistance were used, in the others a decelerating resistance was used, which had the facility to retard flow more at the start of expiration and less later in expiration. Considering the results of the separate groups we observe that, although the individual results are variable, in the group of decelerating resistance (patients 1-5) an average increase in Vt of 40 ml, a decrease in RR with 2 min^{-1} and a minor decrease in I:E (from 1:1.9 to 1:2.0), results comparable to those of Reissman et al. In the patients with a fixed resistance level (patients 6-10) only a decrease in I:E (from 1:2.3 to 1: 2.9) was found. Application of the fixed resistance also resulted in a slight increase in PO2, although not significant.

In the present study PEEP was applied in series with the resistance. We choose to maintain PEEP since application of external PEEP is standard practise in patients with COPD on assisted ventilatory support in view of the omnipresent iPEEP. Comparing application of resistance with normal pressure

support mechanical ventilation would be unacceptable in view of the standard practise. Furthermore, removal of PEEP caused an increase in missed inspiratory efforts complicating objective interpretation of the breathing pattern. In three patients, in whom we also obtained measurements without PEEP, no significant changes in blood gas values were observed.

Only few studies have been published about expiratory pressure regulation (not using threshold resistors). In 1968 Abboud et al. showed that expiratory retard increased efficiency of breathing (33). In 1972, the mechanism of flow retard was adapted for mechanically ventilated patients; a resistance mechanism was incorporated in the Siemens Servo 900-B ventilator (8). This mechanism, the diminished expiratory flow (DEEF) was studied in mechanically ventilated patients with COPD (9). In that study no beneficial effect of application of DEEF was shown. However, in that study only patients with moderate COPD (average FEV1 as percentage of predicted 54%) were included and the presence of flow limitation was not assessed. It was shown that the majority of patients who benefit from pursed lip breathing have airway collapse (15). In the present study, no reliable information is available whether the patients benefited from pursed lip breathing in the non intubated situation. However, in all patients airways collapse was established, which suggest that they are likely to benefit.

The question remains how to explain the discrepancy between the positive effect of pursed lip breathing in non intubated patients and the absence of effects of various expiratory resistances in intubated patients? We hypothesise that spontaneously breathing patients are able to regulate the expiratory resistance by their pursed lips such that at each volume level the optimal resistance is applied. An improved oxygen transport and decreased work of breathing probably result in a feeling of improved well being for the patient, thereby creating a closed-loop feed back system. Until now, we are unable to design an external resistance system which can compete with pursed lip breathing.

In conclusion, in intubated patients with COPD weaning from the ventilator the application of external expiratory resistances did not have the same beneficial effects as pursed lip breathing. No positive effect on respiratory pattern or gas exchange could be established.

Acknowledgements We would like to thank Hamilton Medical (Rhäzüns, Switzerland) for the technical adaptations of the Galileo ventilator.

REFERENCES

1. Gottfried SB, Rossi A, Higgs BD, Calverley PM, Zocchi L, Bozic C, Milic-Emili J. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. Am Rev Respir Dis 1985: 131:414-420.
2. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989: 139:621-626.
3. Aerts JG, van den Berg B, Bogaard JM. Controlled expiration in mechanically-ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997: 10:550-556.
4. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chasse M, Braidy J, Milic-Emili J. Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 1994: 150:1311-1317.
5. Kimball WR, Leith DE, Robins AG. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. Am Rev Respir Dis 1982: 126:991-995.
6. Reissman H, Ranieri V, Goldberg P, Gottfried S. Continuous positive airway pressure facilitates spontaneous breathing in weaning chronic obstructive pulmonary disease patients by improving breathing pattern and gas exchange. Intensive Care Med 2001:(online first)
7. Ranieri VM, Giuliani R, Cinnella G, Pesce C, Brienza N, Ippolito EL, Pomo V, Fiore T, Gottfried SB, Brienza A. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 1993: 147:5-13.
8. Ingelstedt S, Jonson B, Nordstrom L, Olsson SG. A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiol Scand. 1972: 47:7-27.
9. Gultuna I, Huygen PE, Ince C, Strijdhorst H, Bogaard JM, Bruining HA. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Intensive Care Med 1996: 22:539-545.
10. Lourens M, Van den Berg B, Verbraak A, Hoogsteden H, Bogaard J. Effect of series of resistance levels on flow limitation in mechanically ventilated COPD patients. Respir Physiol, in press.

11. van den Berg B, Stam H, Bogaard JM. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 1991: 4:561-567.
12. van den Berg B, Aerts JG, Bogaard JM. Effect of continuous positive airway pressure (CPAP) in patients with chronic obstructive pulmonary disease (COPD) depending on intrinsic PEEP levels. Acta Anaesthesiol Scand 1995: 39:1097-1102.
13. Barach A. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br J Dis Chest 1968: 62:36-40.
14. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. Chest 1992: 101:75-78.
15. Ingram R, Schilder D. Effect of pursed lips expiration on the pulmonary pressure-volume relationship in obstructive lung disease. Am J Respir Crit Care Med 1967: 96:381-388.
16. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970: 28:784-789.
17. Thomam R, Stoker G, Ross J. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966: 93:100-106.
18. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995: 8:1398-1420.
19. Lourens M, van den Berg B, Aerts J, Verbraak A, Hoogsteden H, Bogaard J. Expiratory time constants in mechanically ventilated patients with and without COPD. Intensive Care Med 2000: 26:1612-1618.
20. Verbraak A, Holland W, Mulder B, Bogaard J, Versprille A. A computer controlled flow resistance. Med Biol Eng Comput 1999: 37:770-775.
21. Vassilakopoulos T, Zakynthinos S, Roussos C. The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 1998: 158:378-385.
22. Zakynthinos SG, Vassilakopoulos T, Zakynthinos E, Mavrommatis A, Roussos C. Contribution of expiratory muscle pressure to dynamic intrinsic positive end-expiratory pressure. Am J Respir Crit Care Med 2000: 162:1633-1640.
23. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 1997: 155:906-915.
24. El-Katib M, Jameleddine G, Soubra R, Muallem M. Pattern of spontaneous breathing: potential marker for weaning outcome. Intensive Care Med 2001 (online first)

25. Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR. The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 1986: 134:1111-1118.
26. Barach A, Bickerman H, Petty T. Perspective in pressure breathing. Respir Care 1975: 20:627-642.
27. Barach A, Swenson P. Effects of breathing gases under positive pressure onlumens of small and medium sized bronchi. Archiv Int Med 1939: 63:946-948.
28. Guerin C, Milic Emili J, Fournier G. Effect of PEEP on work of breathing in mechanically ventilated COPD patients. Intensive Care Med 2000: 26:1207-1214.
29. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. Chest 1989: 96:449-451.
30. Marini JJ. Should PEEP be used in airflow obstruction? Am Rev Respir Dis 1989: 140:1-3.
31. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989: 140:5-9.
32. Rossi A, Santos C, Roca J, Torres A, Felez MA, Rodriguez-Roisin R. Effects of PEEP on VA/Q mismatching in ventilated patients with chronic airflow obstruction. Am J Respir Crit Care Med 1994: 149:1077-1084.
33. Abboud R, Beidas-Jubran N, Feisal K, Fuleihan F. The effect of added expiratory obstruction on gas exchange in chronic airways obstruction. Br J Dis Chest 1968: 62:36-40.

CHAPTER 11

SUMMARY AND GENERAL CONSIDERATIONS

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SUMMARY

In chronic obstructive pulmonary disease (COPD), acute respiratory failure is a common and, in many cases, life threatening complication, requiring ventilatory support as rescue therapy. Mechanical ventilation in these patients is often complicated by disturbed respiratory mechanics. Even during tidal breathing, airways compression and consequently flow limitation are encountered, which have deleterious side effects. As a result these patients are at risk of cumbersome mechanical ventilation, difficult weaning and chronic ventilator dependency. The studies described in this thesis are aimed at the detection and improvement of the disturbed respiratory mechanics in patients with COPD on ventilatory support.

In CHAPTER 1 a general introduction is given to the thesis and the aims of the studies are described. The two main questions of this thesis are:

1) How can we measure respiratory mechanics with simple tools at the bedside in mechanically ventilated patients with COPD ?
2) Can we improve disturbed respiratory mechanics in patients with COPD on ventilatory support ?

In CHAPTER 2 mechanisms, detection and influencing of the disturbed respiratory mechanics in patients with COPD on ventilatory support are reviewed. The key issue is the airways compression which even occurs during tidal breathing in these patients. A consequence is flow limitation, which results in dynamic hyperinflation and iPEEP. Dynamic hyperinflation and iPEEP have deleterious side effects, which often hamper mechanical ventilation and weaning. The various methods for the detection of flow limitation, iPEEP, hyperinflation and for the description of lung emptying are discussed. The last part of this chapter deals with the possibilities to improve respiratory mechanics in patients with COPD on ventilatory support. The basic principle of these methods is to counteract airways compression and consequently reduce flow limitation.

In CHAPTER 3 the feasibility of the flow volume curve as measurement of respiratory mechanics is described. When the expiratory flow-volume curve is used to estimate patient's respiratory mechanics, it is important to establish to

what extent external elements affect the shape of the flow-volume curve. In this study, the effect of the exhalation valve of the ventilator on the shape of the flow-volume curve is evaluated. Flow-volume curves are obtained both with and without the exhalation valve in place. It was shown that the exhalation valve of the ventilator caused a significant reduction in peakflow but did not affect the slope of the flow-volume curve during the last 50% of expired volume. This suggests that the second part of the expiratory flow-volume curve can be used to estimate patients' respiratory mechanics during ventilatory support.

In CHAPTER 4 we investigated the feasibility and clinical value of a time constant determined from the expiratory flow-volume curve in patients with and without COPD during mechanical ventilation under sedation and paralysis. The expiratory time constant can provide information on the mechanical properties of the respiratory system, lung emptying and minimal time needed for exhalation. Time constants were determined at different percentages of exhaled volume and were compared to reference time constants calculated from compliance and resistance obtained with the interrupter method (a conventional more complicated method, not suitable for bedside use). The study showed that the time constant was best calculated from expiratory flow-volume curve for the last 75% of exhaled volume. This time constant was in good agreement with the time constant obtained with the conventional method. Furthermore, this time constant was found to be a good prognosticator of the actual time needed for complete exhalation and to be an indicator for the severity of COPD. From these results it is concluded that a time constant determined from the last 75% of the expiratory flow-volume curve is a simple method to assess respiratory mechanics at the bedside in artificially ventilated patients. This information can be used to adjust ventilator settings and medical treatment to the patient's respiratory mechanics.

In CHAPTER 5 is studied if the applicability of the expiratory time constant, as described in chapter 4 during sedation and paralysis, can be extrapolated to the daily situation of ventilatory support without muscle relaxants. During mechanical ventilation under sedation and paralysis, expiration is determined by the elastic recoil of the respiratory system (the driving force) and the resistance of the respiratory system and tube (the opposing force). During

mechanical ventilation without muscle relaxants, muscle activity may interfere during expiration. In patients with COPD time constants were obtained during controlled mechanical ventilation with and without muscle relaxants and during pressure support ventilation. Close agreement was established between time constants determined during controlled ventilation with and without muscle relaxants. Time constants determined during pressure support ventilation showed greater variability if compared to time constants determined during controlled mechanical ventilation. It is concluded that the determination of expiratory time constants is feasible in patients with COPD who are ventilated without muscle relaxants. Thus, expiratory time constants may be used for estimating respiratory mechanics at the bedside and adjusting ventilator settings in patients with COPD on ventilatory support without paralysis.

In CHAPTER 6 a new method, fuzzy clustering, is proposed to determine expiratory time constants. By fuzzy clustering time constant behaviour can be assessed, instead of a single time constant. Furthermore, fuzzy clustering differs from other methods since it neither interferes with expiration nor presumes any functional relationship between the variables analysed. Fuzzy clustering is based on the recognition of multiple local linear models. In patients with and without COPD, fuzzy clustering was applied and for each expiration four time constants were calculated. Fuzzy clustering revealed two patterns of expiratory time constant behaviour. In the patients with COPD, an initial low time constant was found, followed by higher time constants. In the other patients only minor changes in time constants were found. Both the pattern as well as the individual time constants differed significantly between the patients with and without COPD. Time constants obtained with fuzzy clustering from the later part of expiration correlated well with time constants determined from flow-volume curves as described in chapter 4 and 5. These findings indicate that fuzzy clustering can be a valuable addition in the determination of the expiratory time constant; it not only makes a clear distinction between patients with and without COPD, it also give a time constant behaviour over the complete expiration.

In CHAPTER 7 three methods are compared for the detection of flow limitation in mechanically ventilated patients: the resistance method, the negative expiratory pressure method (NEP) and the interrupter method. The first two

methods are based on the principle of alteration of driving pressure for the detection of flow limitation; in the presence of flow limitation, flow will remain unaltered when driving pressure is changed to a certain extent. For the resistance method flow limitation is expressed as percentage of expiratory tidal volume in which flow does not decrease (FLP-R) when driving pressure is decreased by application of a resistance. For the NEP method flow limitation is expressed as percentage of expiratory tidal volume in which flow does not increase (FLP-NEP) when driving pressure was increased by application of negative pressure. With the third method, the interrupter method, flow limitation is assumed present when after a brief occlusion of the airway, a spike flow superimposed on the ongoing mouth flow is detected. The area of the spike flow was used as a measure of flow limitation. This study showed that flow limitation could well be detected by all three methods described. However, it should be taken into account that NEP can give an overestimation of the flow limited portion, whereas the resistance can give an underestimation of the flow limited portion. The interrupter method was found less practical for daily routine.

In CHAPTER 8 the effect of various resistance levels on lung emptying in patients with COPD during mechanically ventilation under sedation and paralysis, was studied. Using a controllable resistor, increasing levels of resistance were applied, until an increase in end-expiratory plateau pressure was detected. Respiratory mechanics were obtained during mechanical ventilation with and without the resistance. The effect of the resistances on airways compression was assessed by iso-volume pressure-flow curves (IVPF) and by interrupter measurements. During unimpeded expiration, airways compression was established in the vast majority of patients. During application of the resistance, it was shown by both the interrupter method as well as the IVPF curves that airways compression was counteracted in these patients. In a subgroup of patients an increase in iso-volume flow was shown at a decrease in driving pressure by application of the resistances. We have referred to this reduction in flow limitation during relaxed expiration as "negative dependency" of flow on driving pressure. In the other flow limited patients, application of the resistances resulted in unaltered iso-volume flow, which we have called "independency" of flow on driving pressure. In the non flow limited patients application of a resistance led to a decrease in flow, which

we called "positive dependency" of flow on driving pressure. In the patients with "negative" and "independency" also a significant reduction in iPEEP was observed. Respiratory mechanics determined during unimpeded expiration, discriminated between patients with- and without reduction of flow limitation. The iPEEP levels and expiratory time constants during unimpeded expiration were predictive for the effect of the external resistances on flow limitation. It is concluded that in mechanically ventilated patients with COPD, a subgroup of patients can be identified, in whom application of external resistances counteracts airways compression, reduces iPEEP and increases iso-volume flows, without increments in end-expiratory lung volume.

In CHAPTER 9 is investigated whether in the subgroup of mechanically ventilated patients with COPD, as identified in chapter 8, application of an external resistance might have a beneficial effect on gas exchange as well. In all patients during controlled mechanical ventilation, increasing levels of resistance were applied and IVPF-curves were computed. From the IVPF-curve the optimal level of resistance was estimated for each patient, i.e. the resistance level that caused the highest flow at the lowest driving pressure. This resistance level was applied for 1 hour. Although in all patients IVPF-curves showed an increase or unaltered flow at a decrease in driving pressure, no effect on blood gas values was established. It was concluded that in patients with COPD on controlled mechanical ventilation application of an individually adapted resistance level did not improve gas exchange. On theoretical basis a more positive effect was predicted during assisted modes of mechanical ventilation.

In CHAPTER 10 we investigated if in intubated patients with COPD during weaning from the ventilator, application of an external resistance could produce the same beneficial effects as pursed lip breathing. Pursed lip breathing has been reported to improve airways compression and oxygenation, this beneficial effect was associated with a decrease in respiratory rate and increase in tidal volume. During controlled modes of mechanical ventilation, respiratory rate and tidal volume are fixed, in contrast, during pressure support ventilation the patient can determine the breathing pattern. In this study, during pressure support ventilation, in half of the patients a fixed level of resistance was applied, in the other patients a decelerating

resistance was applied. Compared to standard pressure support ventilation only minimal changes in tidal volume, respiratory rate and ratio of inspiratory and expiratory time could be found for during application of both resistances. Also for the blood gas values no significant changes were established. It was concluded that in intubated patients weaning from the ventilator, application of an external resistance did not have the same beneficial effects as pursed lip breathing.

GENERAL CONSIDERATIONS

Mechanical ventilation in patients with severe COPD is complicated by the underlying disturbances in respiratory mechanics. The importance of monitoring respiratory mechanics in this condition is generally accepted, but simple bedside techniques for this purpose are lacking. In studies described in this thesis we have tried to fill this gap. Subsequently, monitoring of respiratory mechanics should prompt to action. Methods of improving respiratory mechanics have had only limited success. The studies described in this thesis were aimed at detection and influencing of disturbed respiratory mechanics in patients with COPD on ventilatory support.

DETECTION OF DISTURBED RESPIRATORY MECHANICS

The maximal flow-volume curve is one of the basic tools to determine pulmonary function. The configuration of the curve, combined with the forced vital capacity (FVC) and the forced expiratory volume in 1 s (FEV1) derived from it, provides in a simple way a large amount of information on respiratory mechanics. Although this maximal forced manoeuvre has become standard in the assessment of pulmonary functioning, it is questionable whether these forced manoeuvres represent physiologic patterns during quiet breathing. In nonintubated patients, assessment of respiratory mechanics from tidal breathing has been proposed, although this is not widely used currently[1,2].
In the respiratory intensive care unit, the flow-volume curve never became very popular, even though it is available on most modern ventilators and the patient is in an ideal condition to determine respiratory mechanics. As in the ventilator-dependent patient, forced expiration is hardly feasible, only the flow-volume curve of passive expiration can be analysed. Although this may be of

more physiological interest, until now no clinically applicable measures are known from these curves.

Interpretation of the flow volume curve has mostly been qualitative until now. In this thesis we tried to derive quantitative data from the expiratory flow volume curve. Few other studies have tried to determine a quantitative index, from the relaxed expiratory flow volume curves[3-6]. This index, the expiratory time constant could reflect compliance and resistance and provide information about lung emptying and could be used to set the ventilator. However, several factors complicate the determination of the expiratory time constant from the flow-volume curve in mechanically ventilated patients[7].

When flow-volume curves are used to estimate the patient's respiratory mechanics, the influence of external elements should be taken into account[8, 9]. In this thesis it was shown that the initial part of the flow-volume curve was affected by the exhalation valve of the ventilator, but that the later part of expiration was not altered by external elements. This is in agreement with other studies in patients with COPD, which show that in the presence of airways compression, a resistance added downstream the flow limiting segment will not alter the flow[10,11].

In patients with COPD, determination of an expiratory time constant is also complicated by the presence of airways compression and flow limitation. It is well known that in these patients the expiratory flow volume curve has a distinct shape with a downward concavity. The early rapid component of expiration mainly reflects the resistive behaviour of the extrathoracic resistive elements, whereas the consecutive slower component reflects elastic and viscous properties of the lung and chest wall[12]. In the expiratory flow-volume curve, the transition between the two components has been referred to as the inflection point[4]. In patients with COPD the contribution of the first component is minimal due to the rapid development of airways compression early in expiration. Therefore, the rate of lung emptying is determined by the second component. This underlines that the later part of the expiratory flow-volume curve should be analysed, instead of the complete expiration, as proposed previously[5].

Furthermore, in patients with COPD lung emptying is often prolonged. During controlled mechanical ventilation, expiration is usually terminated before the

end-expiratory flow reaches zero l/s. Assuming an end-expiratory flow of 0 l/s, as suggested previously, will result in underestimation of the time constant[3].
We studied the expiratory time constant determined from different percentages of exhaled volume and found that a time constant determined from the last 75% of expiration yielded a good estimation of respiratory mechanics, lung emptying and severity of COPD. However, this time constant is a rough measure of the last 75% of expired volume. It assumes a linear relationship in the latter part of expiration and thus, although clinically it seems feasible, better measures should be tested, which take into account the exact shape of the flow-volume curve.
In a pilotstudy, time constant behaviour during expiration was analysed with fuzzy clustering, a method based on the automatic detection of multiple local linear models[13]. Although this method is not yet suitable for bedside use, it provides a promising extension to the determination of a single time constant. Until now, however, the expiratory time constant determined from the last 75% of the expiratory flow-volume curve has proved to be a robust method to monitor patients' respiratory mechanics.

Flow limitation is one of the cornerstones in the problems of mechanical ventilation in patients with COPD. Although the presence of flow limitation can be suspected from the concave shape of the flow volume curve, we evaluated more direct methods to assess flow limitation. Two of these methods were based on the principle of altering the driving pressure for the detection of flow limitation; in presence of flow limitation, flow will remain unaltered when driving pressure is changed within certain limits[14,15]. Negative expiratory pressure (NEP) increases driving pressure and application of resistances decreases driving pressure[10,16]. Although NEP is becoming increasingly popular, it never has been truly validated[16]. We showed that as a bedside technique to detect flow limitation, both methods proved to be feasible. However, it was found that both methods influence the development of airways compression. By application of NEP, flow limitation occurred at a higher lung volume (a leftward shift of the inflection point in the flow-volume curve). We hypothesise that by application of NEP the equal pressure point (EPP) is shifted more to the peripheral airways. The opposite effect is caused by application of the resistance, the initial flow is retarded, the inflection point is shifted to the right

and flow limitation occurs at a lower lung volume. This is in agreement with the hypothesis that by application of a resistance the EPP will move downstream to the more central parts of the lung[17-19].

INFLUENCING OF DISTURBED RESPIRATORY MECHANICS

The hypothesis that application of a resistance will move the EPP downstream to the less compressible airways is the basic mechanism for the methods used in the studies of this thesis to improve respiratory mechanics. The idea of application of an expiratory resistance to improve respiratory mechanics originates from a physiological mechanism "invented" by the COPD patient self: pursed lip breathing[14,20]. It is well known that a group of COPD patients get relief from dyspnea by breathing with pursed lips, thereby applying an expiratory resistance[18,21].

During mechanical ventilation, various types of resistors were applied at the airway opening to improve respiratory mechanics. Most of these resistors were threshold resistors, which impose a fixed positive pressure during the entire expiration. The mostly applied threshold resistor is positive end expiratory pressure (PEEP). Application of external PEEP has been shown to reduce the work of breathing during mechanical ventilation when patients trigger their own breaths[22,23]. However, no effects on lung emptying or gas exchange have been convincingly established[23,24]. Previously it has been shown that in mechanically ventilated patients with COPD application of an external resistance could counteract airways compression[11]. However no effects on gas exchange could be established. It was suggested that this contradictory result could be ascribed to the limited adaptation possibilities of the resistor used. In this thesis this approach was further extended.

In the studies in this thesis, resistances were used which gradually decreased the airway opening pressure and retarded the flow. This mechanism was considered more close to pursed lip breathing. A subgroup of mechanical ventilated patients was identified, in whom application of external resistances counteracted airways compression, reduced flow limitation and reduced intrinsic PEEP. In these patients, at a decrease in driving pressure by application of the resistances an increase in iso-volume flow was found. Although this phenomenon has been described in a physical model during passive expiration, until now this could not be demonstrated in detail in

patients[25]. In the iso-volume pressure-flow curves of these patients a resistance pattern could be identified, which combined the lowest driving pressures with the highest iso-volume flows. We hypothesise that ideally the level of resistance should follow that pattern. However, this implies a closed loop system computing iso-volume pressure-flow relationships while applying resistances, which was technically not feasible in our department until now.

In patients on controlled mechanical ventilation the clinical effect on flow limitation and iPEEP was of limited value: we were unable to show an effect of application of the resistances on gas-exchange. An explanation for this might be that the effect on airways compression could have been too limited to cause an improvement in determinants of gas exchange. Apart from this, the limited effect might also be related to the fact that the patients were sedated and on controlled mechanical ventilation, as a consequence respiratory rate, expiration time and tidal volume were fixed. During pursed lips breathing the beneficial effect has been associated with a decrease in respiratory rate and an increase in tidal volume[18,26]. Although theories about the underlying mechanism of the beneficial effect of pursed lip breathing are still based on speculations, the improvement in gas-exchange might also be mediated by the alteration in breathing pattern[18,21,26,27]. Therefore, we investigated the effect of a resistance in patients on assisted modes of ventilation. Patients on assisted modes of ventilator support can adapt respiratory rate and tidal volume to a certain extent. In patients on pressure support ventilation, we applied two different resistances, one fixed level derived from the iso-volume pressure-flow curve and one declining resistance level. However, neither of these resistances was found to increase tidal volume, decrease respiratory rate or have a beneficial effect on gas-exchange.

The question remains how to explain the discrepancy between the positive effect of pursed lip breathing in non intubated patients and the absence of effects of various expiratory resistances in intubated patients?

We hypothesise that spontaneously breathing patients are able to regulate the expiratory resistance by their pursed lips to such extent that at each volume level the optimal resistance is applied, which results in a feeling of improved well being for the patient, thereby creating a closed-loop feed back system. Until now, we are unable to design an external resistance system which can compete with nature.

References

1. Morris MJ, Madgwick RG, Collyer I, Denby F, Lane DJ. Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. Eur Respir Jl 1998; 12:1113-1117.
2. Williams EM, Madgwick RG, Morris MJ. Tidal expired airflow patterns in adults with airway obstruction. Eur Respir J 1998; 12:1118-1123.
3. Galbusera C, Cortis G, Olivei M, et al. Breath-by-breath evaluation of the expiratory time constant during mechanical ventilation. Am Rev Respir Crit Care Med 1999; 159:A366.
4. Guttmann J, Eberhard L, Fabry B, et al. Time constant/volume relationship of passive expiration in mechanically ventilated ARDS patients. Eur Respir J 1995; 8:114-120.
5. Brunner JX, Laubscher TP, Banner MJ, Iotti G, Braschi A. Simple method to measure total expiratory time constant based on the passive expiratory flow-volume curve. Crit Care Med 1995; 23:1117-1122.
6. Aerts JG, van den Berg B, Lourens MS, Bogaard JM. Expiratory flow-volume curves in mechanically ventilated patients with chronic obstructive pulmonary disease. Acta Anaesthesiol Scand 1999; 43:322-327.
7. Rossi A, Polese G. As simple as possible, but not simpler. Intensive Care Med 2000; 26:1591-1594.
8. Kayaleh RA, Wilson AF. Mechanisms of expiratory valves resistance. Am Rev Respir Dis 1988; 137:1390-1394.
9. Fabry B, Haberthur C, Zappe D, Guttmann J, Kuhlen R, Stocker R. Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilatory demands during inspiratory pressure support and automatic tube compensation. Intensive Care Med 1997; 23:545-552.
10. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis 1989; 139:621-626.
11. Aerts JG, van den Berg B, Bogaard JM. Controlled expiration in mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10:550-556.
12. Chelucci GL, Brunet F, Dall'Ava-Santucci J, et al. A single-compartment model cannot describe passive expiration in intubated, paralysed humans. Eur Respir J 1991; 4:458-464.
13. Babuska R, Alic L, Lourens MS, Verbraak AF, Bogaard J. Estimation of respiratory parameters via fuzzy clustering. Artif Intell Med 2001; 21:91-105.

14. Fry D, Hyatt R. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. Am J Med 1960; 24:672-689.
15. Hyatt R. The interrelationships of pressure, flow and volume during various respiratory maneuvres in normal and emphysematous patients. Am Rev Resp Dis 1961; 83:676-683.
16. Valta P, Corbeil C, Lavoie A, et al. Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 1994; 150:1311-1317.
17. Gultuna I, Huygen PE, Ince C, Strijdhorst H, Bogaard JM, Bruining HA. Clinical evaluation of diminished early expiratory flow (DEEF) ventilation in mechanically ventilated COPD patients. Intensive Care Med 1996; 22:539-454
18. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. J Appl Physiol 1970; 28:784-789.
19. Weng JT, Smith DE, Graybar GB, Kirby RR. Hypotension secondary to air trapping treated with expiratory flow retard. Anesthesiology 1984; 60:350-353.
20. Barach A. Physiological advantages of grunting, groaning and pursed-lips breathing: adaptive symptoms related to the development of continuous positive pressure breathing. Br J Dis Chest 1968; 62:36-40.
21. Ingram R, Schilder D. Effect of pursed lips expiration on the pulmonary pressure-volume relationship in obstructive lung disease. Am J Respir Crit Care Med 1967; 96:381-388.
22. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 1988; 65:1488-1499.
23. van den Berg B, Stam H, Bogaard JM. Effects of PEEP on respiratory mechanics in patients with COPD on mechanical ventilation. Eur Respir J 1991; 4:561-567.
24. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 1993; 147:5-13.
25. Shapiro A. Steady flow in collapsible tubes. J. Biomech. Eng. 1977; 99:126-147.
26. Thoman R, Stoker G, Ross J. The efficacy of pursed lips breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1966; 93:100-106.
27. Schmidt R, Wasserman K, Lillington G. The effect of air flow and oral pressure on the mechanics of breathing in patients with asthma and emphysema. Am Rev Respir Dis 1964; 90:564-571.

HOOFDSTUK 12

SAMENVATTING

DANKWOORD

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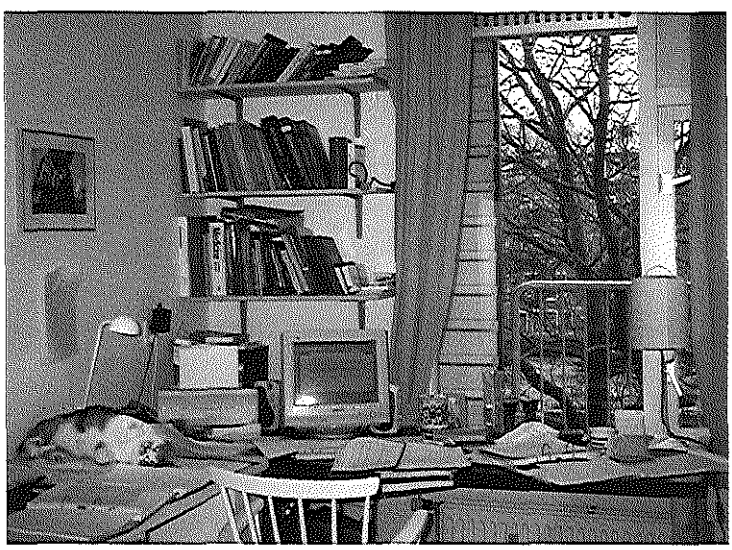

SAMENVATTING

Bij patiënten met chronisch obstructief longlijden (COPD) is acute ademnood een veel voorkomende, vaak levensbedreigende complicatie die alleen met kunstmatige beademing behandeld kan worden. Omdat bij patiënten met COPD de ademmechanica vaak ernstig gestoord is, verloopt de beademing vaak moeizaam. Het grootste probleem hierbij is het optreden van luchtweg compressie tijdens de uitademing, met als gevolg flow limitering. Hierdoor zijn patiënten met COPD vaak moeilijk te beademen en te ontwennen van de beademing en lopen zij het risico chronisch afhankelijk te worden van kunstmatige ademhalingsondersteuning. De onderzoeken beschreven in dit proefschrift zijn gericht op de detectie en verbetering van de gestoorde ademmechanica bij patiënten met COPD tijdens kunstmatige beademing.

In HOOFDSTUK 1 wordt een algemene introductie tot het proefschrift gegeven. De twee centrale vragen van het onderzoek beschreven in dit proefschrift zijn:
1) Hoe kunnen we in de kliniek op eenvoudige wijze ademmechanica bepalen bij beademde patiënten met COPD?
2) Is het mogelijk om de verstoorde ademmechanica te verbeteren bij patiënten met COPD tijdens beademing en ontwennen van de beademing?

In HOOFDSTUK 2 wordt een overzicht gegeven van de mechanismen, detectie en beïnvloeding van de verstoorde ademmechanica bij beademde patiënten met COPD. Het centrale probleem bij deze patiënten is de luchtweg compressie met als gevolg flow limitering. Hierdoor ontstaan dynamische hyperinflatie en intrinsieke positieve eind expiratoire druk (iPEEP), welke nadelige bijwerkingen hebben voor zowel de circulatie, als de longen, als de ademhalingsspieren. Verschillende methoden worden besproken voor de detectie van flow limitering, iPEEP en hyperinflatie en de beschrijving van de longlediging. Het laatste deel van dit hoofdstuk gaat over de mogelijkheden om de ademmechanica te verbeteren in patiënten met COPD aan de beademing. Het basale principe van al deze methoden is het tegen gaan van de luchtweg compressie waardoor ook de flow limitering zal verminderen.

In HOOFDSTUK 3 wordt de toepasbaarheid onderzocht van de flow-volume curve als manier om de ademmechanica te bestuderen. Wanneer de flow-volume curve wordt gebruikt om de ademmechanica te beschrijven is het van belang om de invloed van externe elementen op de vorm van de curve vast te stellen. In dit hoofdstuk wordt het effect van de uitademingsklep van het

beademingsapparaat op de vorm van de flow-volume curve onderzocht. Hiertoe worden flow-volume curven geregistreerd met en zonder deze klep. Wij toonden aan dat de uitademingsklep een significante daling van de piekflow gaf, maar dat de helling van de curve over de laatste helft van de uitademing niet beïnvloed werd. Dit suggereert dat de tweede helft van de expiratoire flow-volume curve goed gebruikt kan worden om ademmechanica te bestuderen tijdens beademing.

In HOOFDSTUK 4 hebben we de toepasbaarheid en klinische waarde onderzocht van de tijdsconstante afgeleid van de expiratoire flow-volume curve. De expiratoire tijdsconstante bevat informatie over de respiratoire mechanica, is een maat voor de longlediging en de tijd die nodig is om uit te ademen tot rust volume.
De studie werd gedaan bij zowel patiënten met als zonder COPD met sedatie en spierverslapping tijdens gecontroleerde beademing. Tijdsconstanten werden bepaald over verschillende percentages van de uitademing en werden vergeleken met tijdsconstanten bepaald uit compliantie en weerstand verkregen met de interruptie methode (een algemeen geaccepteerde, maar gecompliceerde methode die niet geschikt is voor dagelijks gebruik in de kliniek). De resultaten lieten zien dat de tijdsconstante het best bepaald kon worden over de laatste 75% van de uitademing. Deze tijdsconstante kwam goed overeen met de tijdsconstante bepaald met de interruptie methode. Verder bleek deze tijdsconstante een goede maat te zijn voor de uitademingstijd en de ernst van COPD. De conclusie luidde dat een tijdsconstante bepaald over de laatste 75% van de expiratoire flow-volume curve een eenvoudige methode is om informatie over de respiratoire mechanica te verkrijgen bij beademde patiënten. Deze informatie kan gebruikt worden om de medische behandeling en de instellingen van het beademingsapparaat aan te passen aan de respiratoire toestand van de patiënt.

In HOOFDSTUK 5 werd onderzocht of de tijdsconstante als beschreven in hoofdstuk 4 tijdens sedatie en verslapping, ook gebruikt kan worden tijdens beademing zonder spierverslapping. Immers, in de dagelijkse praktijk worden de meeste patiënten zonder spierverslapping beademd. Tijdens beademing met verslapping wordt de uitademing bepaald door elasticiteit van het respiratoire systeem (de drijvende kracht) en de weerstand van luchtwegen en beademingsbuis (de tegenwerkende kracht). Als de patiënt zonder spierverslapping beademd wordt, kan de spieractiviteit de uitademing

beïnvloeden. Bij patiënten met COPD werden tijdsconstanten bepaald tijdens gecontroleerde beademing met en zonder spierverslapping en tijdens druk ondersteunende beademing. De tijdsconstanten met en zonder spierverslapping bepaald tijdens gecontroleerde beademing kwamen goed overeen. De tijdsconstanten bepaald tijdens ondersteunende beademing vertoonden een grotere variabiliteit vergeleken met de tijdsconstanten tijdens gecontroleerde beademing. Geconcludeerd wordt dat ook bij patiënten met COPD tijdens beademing zonder spierverslapping, de expiratoire tijdsconstante goed gebruikt kan worden om informatie te krijgen over de respiratoire mechanica.

In HOOFDSTUK 6 wordt een nieuwe methode, fuzzy clustering, beschreven om expiratoire tijdsconstanten te bepalen. Met behulp van fuzzy clustering kan het verloop van de tijdsconstante tijdens de uitademing worden bepaald, in plaats van één enkele tijdsconstante. Daarnaast verschilt fuzzy clustering van andere methoden doordat de methode niet interfereert met de uitademing en geen functionele relatie (b.v. lineaire relatie) veronderstelt tussen de te analyseren variabelen. Fuzzy clustering is gebaseerd op automatische detectie van lokale lineaire modellen. Bij zowel patiënten met als zonder COPD werden voor iedere expiratie vier tijdsconstanten berekend met behulp van fuzzy clustering. Dit resulteerde in twee patronen van beloop in tijdsconstanten. Bij de patiënten met COPD, werd er eerst een lage tijdsconstante gedetecteerd, die gevolgd werd door hogere tijdsconstanten. Bij de patiënten zonder COPD werden er slechts kleine veranderingen in tijdsconstanten gezien. Zowel het patroon als de individuele tijdsconstanten waren significant verschillend voor de patiënten met en zonder COPD. De tijdsconstanten bepaald met fuzzy clustering voor het laatste deel van de expiratie kwamen goed overeen met tijdsconstanten bepaald volgens de methode beschreven in hoofdstuk 4 en 5. Deze bevindingen wijzen er op dat fuzzy clustering een waardevolle aanvulling is op de bestaande methoden voor het bepalen van de expiratoire tijdsconstante. De methode is in staat een duidelijk onderscheid te maken tussen patiënten met en zonder COPD. Daarnaast kan met fuzzy clustering het verloop van de tijdsconstanten over de gehele expiratie worden beschreven.

In HOOFDSTUK 7 worden drie methoden vergeleken om flow limitering te meten bij beademde patiënten: de weerstandsmethode, de negatieve expiratoire druk methode (NEP) en de interruptie methode. De eerste twee methoden zijn gebaseerd op het principe van het veranderen van de drijvende druk voor het

detecteren van flow limitering. Wanneer er flow limitering bestaat zal bij een verandering van de drijvende druk (binnen zekere grenzen) de flow onveranderd blijven. Voor de weerstandsmethode wordt flow limitering uitgedrukt als het percentage van het expiratoire teugvolume waarover de flow niet afneemt wanneer de drijvende druk wordt verlaagd door het opleggen van een weerstand. Bij de NEP methode wordt flow limitering uitgedrukt als het percentage van het expiratoire teugvolume waarover de flow niet toeneemt wanneer de drijvende druk wordt verhoogd door het opleggen van negatieve druk. Bij de derde methode, de interruptie methode wordt er flow limitering verondersteld wanneer er na een korte afsluiting van de luchtweg tijdens uitademing een piekje in het flow signaal optreedt. De oppervlakte van dit piekje wordt genomen als maat voor de flow limitering. Het onderzoek liet zien dat flow limitering goed gedetecteerd kon worden door de drie bovengenoemde methoden. Echter, men moet er op bedacht zijn dat de NEP methode een overschatting van het uitademingsdeel met flow limitering kan geven, terwijl de weerstandsmethode een onderschatting kan geven. Voor dagelijks gebruik in de kliniek is de interruptie methode het minst geschikt.

In HOOFDSTUK 8 werd het effect van verschillende weerstandsniveaus op de longlediging onderzocht bij patiënten met COPD tijdens beademing onder sedatie en verslapping. Met behulp van een regelbare weerstand werden toenemende weerstanden opgelegd tot er een toename van de eind expiratoire plateau druk werd gevonden. Ademmechanica werd gemeten tijdens beademing met en zonder de weerstanden. Het effect van de weerstanden op de flow limitering werd geëvalueerd met behulp van iso-volume druk-flow (IVPF) curven en door interruptie metingen. Tijdens beademing zonder weerstand had de meerderheid van de patiënten flow limitering. Tijdens beademing met de weerstanden, lieten zowel de IVPF curven als de interruptie methode een afname in luchtweg compressie zien. In een subgroep werd een toename van de iso-volume flow gezien bij een afname van de drijvende druk door het opleggen van de weerstanden. Deze afname in luchtweg compressie hebben we "negatieve afhankelijkheid" van de flow van drijvende druk. Bij de andere patiënten met flow limitering bleef de iso-volume flow onveranderd tijdens het opleggen van de weerstanden, dit hebben we "onafhankelijkheid" van de flow van de drijvende druk genoemd. Bij de patiënten zonder flow limitering leidde het op leggen van de weerstanden tot een vermindering van de flow, wat "positieve afhankelijkheid" werd genoemd. Tevens werd er bij de patiënten met "negatieve" en "onafhankelijkheid" een significante afname van de iPEEP gevonden door

opleggen van de weerstanden. De respiratoire mechanica gemeten tijdens normale beademing was voorspellend voor het effect van de weerstand op de luchtweg compressie. Patiënten met een positief effect van de weerstand op de luchtweg compressie vertoonden een significant hogere tijdsconstante en iPEEP. De conclusie luidt dat bij beademde patiënten met COPD een subgroep patiënten kan worden geïdentificeerd, bij wie het opleggen van externe weerstanden luchtweg compressie tegen gaat, iPEEP verlaagt en iso-volume flow doet toenemen.

In HOOFDSTUK 9 wordt gekeken of in de subgroep patiënten, als beschreven in hoofdstuk 8, het opleggen van externe weerstanden ook een positief effect heeft op de bloedgaswaarden. Tijdens gecontroleerde beademing werden toenemende weerstanden opgelegd en werden IVPF-curven geconstrueerd. Met behulp van deze IVPF curven werd het optimale weerstandsniveau voor de individuele patiënt geschat, d.w.z. het weerstandsniveau dat gepaard ging met de hoogste flow bij de laagste drijvende druk. Deze weerstand werd 1 uur opgelegd. Ondanks dat bij alle patiënten de IVPF curven een toename of onveranderde flow lieten zien bij afname van de drijvende druk, werd er geen effect op de bloedgaswaarden gevonden. Geconcludeerd werd dat tijdens gecontroleerde expiratie bij patiënten met COPD het opleggen van een individueel getitreerd weerstandniveau geen effect had op gaswisseling.

In HOOFDSTUK 10 hebben we onderzocht of bij geïntubeerde patiënten met COPD door het opleggen van een weerstand pursed lip breathing nagebootst kan worden en er daardoor een positief effect op het ademhalingspatroon en de gaswisseling bewerkstelligd wordt. Van pursed lip breathing is beschreven dat het een positief effect heeft op de luchtweg compressie en de gaswisseling. Dit gunstige effect gaat gepaard met een afname van de ademhalingsfrequentie en een toename van het teugvolume. Tijdens gecontroleerde vormen van beademing worden de ademhalingsfrequentie en het teugvolume door het beademingsapparaat opgelegd. Daarentegen, worden tijdens ondersteunende vormen van beademing de ademhalingsfrequentie en het teugvolume in grote mate door de patiënt zelf bepaald. In de studie beschreven in dit hoofdstuk, worden tijdens drukondersteunende beademing twee soorten weerstanden opgelegd. In één patiënten groep werd een vaste weerstand opgelegd, bij een andere groep werd een tijdens de uitademing afnemend weerstandspatroon opgelegd. Voor beide weerstanden werden, vergeleken met standaard beademing, slechts minimale veranderingen gevonden in ademfrequentie, teugvolume en expiratie

tijd. Ook de bloedgaswaarden vertoonden geen significante verbetering. De conclusie luidde dat bij geïntubeerde patiënten tijdens het ontwennen van de beademing met het opleggen van een externe weerstand het niet mogelijk was pursed lip breathing na te bootsen; zowel ademhalingpatroon als bloedgaswaarden bleven onveranderd.

HOOFDSTUK 11 geeft een samenvatting en algemene beschouwing van het proefschrift. In het onderzoek beschreven in dit proefschrift stonden de detectie en beïnvloeding van de verstoorde ademmechanica centraal.
Bij het meten van longfunctie van niet geïntubeerde patiënten speelt de maximale geforceerde flow-volume curve een belangrijke rol. Bij beademde patiënten wordt de flow-volume curve nauwelijks gebruikt, hoewel deze makkelijk te verkrijgen is en veel informatie bevat over de ademmechanica. Er zijn echter verschillende factoren die de evaluatie van de flow-volume curve bij beademde patiënten met COPD bemoeilijken. Tot nu toe is men er niet in geslaagd de flow-volume curve op een kwantitatieve en klinisch toepasbare manier te beschrijven bij deze patiënten.
Wij hebben geprobeerd om in de vorm van de expiratoire tijdsconstante de flow-volume curve tijdens beademing te beschrijven. Factoren die dit bemoeilijken, zoals het gebrek aan coöperatie van de patiënt, de aanwezigheid van externe elementen als beademingsslangen en apparaat, de vorm van beademing en het optreden van luchtweg compressie en flow limitering zijn systematisch onderzocht. Wij vonden dat een tijdsconstante goed bepaald kon worden uit de laatste 75% van de passieve expiratoire flow-volume curve. In tegenstelling tot tijdsconstanten beschreven in andere studies, is bij de bepaling van deze expiratoire tijdsconstante rekening gehouden met de bovengenoemde complicerende factoren. Hoewel de tijdsconstante informatie bevat over de respiratoire mechanica en een maat is voor de longlediging, beschrijft het toch een gemiddelde waarde voor de laatste 75% van de expiratie. In een vooronderzoek is gekeken naar een methode, "fuzzy clustering", om een tijdsconstante verloop tijdens de uitademing te bepalen. Alhoewel deze methode nog niet klinisch toepasbaar is, lijken de resultaten veelbelovend.
Daarnaast hebben we methoden om flow limitering aan te tonen met elkaar vergeleken. Flow limitering is één van de basale problemen bij beademde patiënten met COPD. Alhoewel de vorm van de flow-volume curve de

aanwezigheid van flow limitering vaak al doet vermoeden hebben wij meer directe methoden onderzocht om flow limitering aan te tonen. Twee van deze methoden zijn gebaseerd op het veranderen van de drijvende druk; de negatieve expiratoire druk methode (NEP) vergroot de drijvende druk, terwijl de weerstandsmethode deze verlaagt. Met beide methoden kon flow limitering goed en eenvoudig aangetoond worden. Echter, het optreden van luchtweg compressie (met als gevolg flow limitering) werd ook beïnvloed door de beide methoden.

Bij de beïnvloeding van de flow limitering hebben we gebruik gemaakt van dit mechanisme. De hypothese is dat door het opleggen van een externe weerstand de luchtweg compressie wordt tegen gegaan. Dit idee is afgeleid van een natuurlijk fenomeen, het door getuite lippen uitademen ("pursed lip breathing"), wat bij patiënten met COPD vaak wordt gezien.

Er zijn veel onderzoeken geweest die met behulp van weerstanden een gunstig effect op de ademhaling probeerden te bewerkstelligen. De meeste onderzoeken gebruikten hiervoor positieve eind-expiratoire druk (PEEP). Hiervan is aangetoond dat het de ademarbeid vermindert, echter een positief effect op de longlediging of de gaswisseling is nooit overtuigend bewezen. In een eerdere studie vond men dat door het opleggen van een weerstand tijdens de uitademing luchtweg compressie kon worden tegengegaan. Deze benadering hebben we verder uitgewerkt. Wij toonden aan dat bij een groep patiënten door het opleggen van een weerstand de luchtweg compressie werd tegengegaan en er een toename in iso-volume flow was. Bij deze patiënten kon een weerstandspatroon worden geïndentificeerd dat theoretisch tot optimale longlediging zou moeten leiden. Praktisch waren wij echter niet instaat om dit te testen aangezien het technisch niet haalbaar was. Het opleggen van een weerstand tijdens gecontroleerde beademing ging niet gepaard met een verbetering in de gaswisseling. De oorzaak hiervoor zou kunnen zijn dat het effect op de luchtweg compressie te gering was om een verbetering in gaswisseling te bewerkstelligen. Daarnaast zou het gebrek aan effect ook te maken kunnen hebben met het feit dat de patiënten gecontroleerd beademd werden, met als gevolg een vast teugvolume, ademhalingsfrequentie en uitademingstijd. Volgens sommige onderzoeken is het gunstige effect van het "pursed lip breathing" gerelateerd aan een verandering in ademhalingspatroon. Dit zijn echter speculaties, over het onderliggende mechanisme van het gunstig effect van "pursed lip breathing"

bestaat nog geen consensus. Ook bij patiënten met ondersteunende beademing, die tot zekere mate hun frequentie en teugvolume konden regelen, vonden wij geen effect van een externe weerstand op het ademhalingspatroon en de gaswisseling.

De vraag blijft hoe verklaren we de discrepantie tussen het gunstige effect van "pursed lip breathing" bij niet geïntubeerde patiënten en het gebrek aan effect van het opleggen van verschillende weerstanden bij geïntubeerde patiënten? We veronderstellen dat spontaan ademende patiënten in staat zijn om een optimaal weerstandspatroon op te leggen met hun getuite lippen dat resulteert in een gevoel van verbetering. Hierdoor onstaat er waarschijnlijk een soort "closed-loop" systeem waarbij een gevoel van verbetering in welbevinden de hoeveelheid op te leggen weerstand continu bijstuurt. Tot nu toe zijn wij niet instaat om een extern weerstandssysteem te ontwikkelen dat dit natuurlijk mechanisme kan benaderen.

DANKWOORD

Velen hebben direct of indirect een bijdrage geleverd aan dit proefschrift, ik ben iedereen daar erg dankbaar voor, in het bijzonder de volgende personen:

Dr. B. van den Berg, Bart, zonder jouw enthousiasme en inzet voor "de wetenschap" was dit proefschrift er nooit gekomen. Ik vind het een groot voorrecht met jou drie jaar onderzoek te hebben mogen doen. Nog vaak zal ik met genoegen terug denken aan "onze" metingen en discussies over artikelen.

Prof.dr. J.M. Bogaard, uw eeuwige optimisme, enthousiasme en kritische kijk op de zaken waren van onschatbare waarde. Altijd stond uw deur open, tot op het strand toe las u artikelen en altijd was u geïnteresseerd in zowel het onderzoek als de onderzoeker, u zult niet alleen door mij gemist worden.

Prof.dr. H.C. Hoogsteden, Henk, je bood me de gelegenheid om in Rotterdam onderzoek te doen en de opleiding tot longarts te volgen, waarbij je me altijd alle mogelijkheden en vrijheden gaf. Ik ben je hiervoor erg dankbaar. Daarnaast zal ik je vaderlijke bruinbroodadviezen niet snel vergeten.

Dr. (bijna) G.J. Braunstahl, Gert-Jan, zonder jou zou dit proefschrift er ook wel zijn geweest, maar met jou was het schrijven ervan een groot plezier.
Jouw belangstelling, steun, kritiek en gezelligheid waren van onuitsprekelijke waarde. Drie jaar lang rug aan rug werken aan de wetenschap met een dierbare vriend en dat dan samen afronden door op dezelfde dag te promoveren, ik denk dat weinig mensen zo bevoorrecht zijn.

Hier hoort ook een woord van dank aan alle patiënten en natuurlijk hun familie, die toestemming gaven om aan het onderzoek deel te nemen. Zonder hen was dit onderzoek niet mogelijk geweest.

Dank ook aan Prof.dr. J.C. de Jongste, dr. A. Klein en Prof.dr. Ph.H. Quanjer en Prof.dr. A.J. van Vught voor het beoordelen van het proefschrift.

De verpleging van 3-zuid beademing ben ik zeer erkentelijk voor hun flexibele inzet, hulp én gezelligheid. Ik kijk er naar uit om weer op 3-zuid te werken.
Ina Daniels, dank dat ik je mooie foto's mocht gebruiken voor dit proefschrift.

Het Trustfonds Erasmus Universiteit bedank ik voor alle congressponsoring.

De mensen van de technische -en computerondersteuning ben ik als niet-techneut zeer erkentelijk. Allereerst dr.ir. Ton Verbraak, je ontwikkelde de weerstand die ik in dit proefschrift heb gebruikt en leverde nog vele andere bijdragen. Ing. Julius de Vries en Ing. Ed Hoorn, geen computer probleem was jullie te gek. Jan van der Kolk stond altijd klaar op de beademing. Ema Tahitu leverde geestelijke bijstand bij vastgelopen computers. Dr. Henk Stam had altijd handige tips. En natuurlijk ook alle stagiaires van de HTS en TU, jullie hulp bij computerproblemen en metingen werd bijzonder op prijs gesteld.

Ir. L. Alić en dr. R. Babuška, Leila en Robert, zonder jullie was hoofdstuk 6 er niet geweest. Dank voor al het werk dat jullie hebben verzet.

Dr. J.G.J.V. Aerts, Joachim, het onderzoek is een vervolg op jouw eerdere werk. Vanaf het begin stond je klaar om te helpen en mee te denken, dit heb ik ontzettend gewaardeerd.

De longfunctieassistentes wil ik hartelijk bedanken voor de belangstelling, gezelligheid én taart die ik deze drie jaar bij jullie op de afdeling heb mogen genieten. Dit geldt zeker ook voor Miranda Frijters en Ruud van Engelen.

De stafleden en arts-assistenten van de afdeling Longziekten en Intensive Care dank ik voor de interesse in het onderzoek. Speciaal Christine Groeninx van Zoelen die altijd bereid was gelegenheid tot meten te scheppen op de IC en dr. O. die met drop en belangstelling voor de nodige afleiding zorgde.

Aline Sprikkelman en Wim van Aalderen, door te laten zien dat onderzoek en longziekten erg leuk zijn hebben jullie in grote mate mijn keuze in deze richting bepaald. Voor deze indirecte bijdrage ben ik jullie nog steeds dankbaar.

Ook buiten het ziekenhuis is er erg meegeleefd, gekookt en genoten; Ingeborg, Loes, Frederieke, Michiel, Ron en Boeing, jullie vriendschap is bijzonder waardevol voor mij. Alaa, by being a little ahead in writing your thesis you always prepared me for the next pitfall, thanks for your constant support and loyal friendship. En Marjolein, Koen wat zal ik onze "hotline" missen als jij straks in Zambia zit, dank voor al je lieve support op alle fronten.

Tot slot wil ik mijn ouders, broer en grootouders danken die aan de basis van dit alles stonden.

CURRICULUM VITAE

Marlies Lourens werd geboren op 9 mei 1973 te Haan. In 1991 behaalde zij het eindexamen VWO aan het Rhedens Lyceum in Rozendaal. Datzelfde jaar begon zij met de studie Geneeskunde aan de Rijksuniversiteit te Groningen. Tijdens haar studie deed zij op de afdeling kinderlongziekten van het Academisch Ziekenhuis Groningen onderzoek naar het gebruik van trachea auscultatie en diafragma- en intercostaalspier-EMG's voor het vaststellen van bronchiale hyperreactiviteit bij kinderen met astma (begeleiders: dr. W.M.C. van Aalderen en dr. A.B. Sprikkelman). In 1995 ontving zij de Penn-prijs, een onderzoeksbeurs van de medische faculteit Groningen. Deze beurs stelde haar instaat om onderzoek te doen op de afdeling kinderlongziekten van het Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine in de Verenigde Staten. Daarnaast deed zij tijdens haar studie stages in ziekenhuizen in Italië, Spanje en Engeland. De co-schappen werden doorlopen in de Deventer Ziekenhuizen te Deventer. In februari 1998 behaalde zij haar artsexamen en startte zij met het in dit proefschrift beschreven onderzoek op de afdeling Longziekten en Intensive Care van het Academisch Ziekenhuis Rotterdam Dijkzigt. In mei 2001 is zij begonnen aan de Interne vooropleiding in het Havenziekenhuis in Rotterdam (opleider: dr. A.G.C. Bauer), in het kader van de opleiding tot arts voor Longziekten en Tuberculose in het Academisch Ziekenhuis Rotterdam (opleider: Prof.dr. H.C. Hoogsteden).