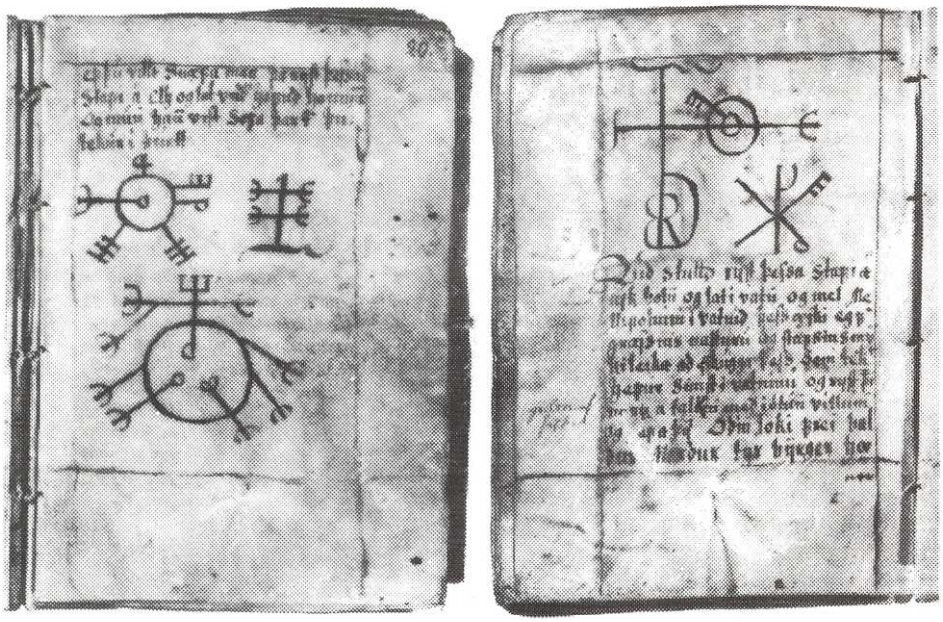
Spirodynamics

New methods for continuous monitoring of respiratory mechanics in ventilator-treated patients



by **Sigurbergur Kárason**

Göteborg 2000

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Akademisk Avhandling

Som för avläggande av medicine doktorexamen vid Göteborgs Universitet kommer att offentligen försvaras i Sahlgrenska Universitetssjukhusets aula, fredagen den 15 september 2000, kl 09.00

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Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

I Karason S, Karlsen KL, Lundin S, Stenqvist O.
A simplified method for separate measurements of lung and chest wall mechanics in ventilator-treated patients.
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II Karason S, Sondergaard S, Lundin S, Wiklund J, Stenqvist O.
Evaluation of pressure/volume loops based on intratracheal pressure measurements during dynamic conditions.
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V Karason S, Sondergaard S, Lundin S, Stenqvist O.
Manoeuvre-free, on-line, "static" respiratory system, lung and chest wall mechanics during on-going ventilatory treatment. 2000:
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Spirodynamics, new methods for continuous monitoring of respiratory mechanics in ventilator-treated patients

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Abstract of thesis defended 15th September 2000

Introduction: Ventilator treatment is often life-saving but has the inherent risk of causing damage to lung tissues. Overdistension and repetitive collapsing/opening of alveoli should be avoided. Monitoring of respiratory mechanics has a central role in accomplishing this. Methods used today to identify pressure/volume (P/V) curves are based on static/semistatic methods that necessitate a change of ventilator settings and have mainly been used as research tools. The aim of this thesis was to develop clinically applicable methods for continuous and thorough monitoring of respiratory mechanics during on-going ventilator treatment.

Methods: Studies were performed in a lung model and in patients. The use of catheters for measurement of oesophageal and tracheal pressures was evaluated. The dynostatic algorithm was created and validated for calculation of alveolar P/V-curves during dynamic conditions. The algorithm analyses pressure and flow at isovolume levels on the inspiratory and expiratory limbs of a tracheal P/V-loop, for every sample during the breath, assuming that the inspiratory and expiratory resistances are equal. Respiratory mechanics in 10 patients with acute lung injury were studied at different PEEP and tidal volume levels using this method.

Results: A double-lumen, liquid-filled stomach tube measures oesophageal pressure reliably when positioned accurately. Direct measurements of tracheal pressures are a necessity for monitoring of respiratory mechanics and can be achieved by inserting an end-hole catheter through the endotracheal tube lumen, positioning its tip within 2 cm from the tip of the tube. The dynostatic method is highly reliable when the ratio between inspiratory and expiratory resistances is between 2.3:1 and 1:2.3. Respiratory mechanics during on-going ventilator treatment showed a high individual variability but good reproducibility. Within each breath, volume-dependent compliance decreased successively through the initial, middle and final parts of the P/V-curve. This pattern became more prominent with increased PEEP and tidal volume levels, indicating increased overdistension.

Conclusions: The monitoring concept presented provides a safe, accurate and continuous method of monitoring of respiratory mechanics during on-going ventilator treatment.

Keywords: Monitoring, Respiratory mechanics, Mechanical ventilation, Compliance, Alveolar pressure, Dynostatic algorithm, ALI, ARDS, Model, Human.

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List of Papers

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Submitted for publication.

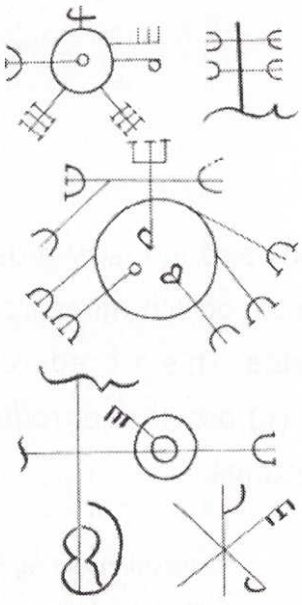
Contents

Abbreviations

ACV	Assisted/Controlled ventilation
ALFI	Automatic low flow inflation
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ECMO	Extracorporal membrane oxygenation
EI-Plat	End-inspiratory plateau pressure
ETT	Endotracheal tube
$\dot{V}_{exp}$	Expiratory flow
FiO2	Fraction of inspired oxygen
FRC	Functional residual capacity
$\dot{V}_{insp}$	Inspiratory flow
LIP	Lower inflection point
LIS	Lung injury score
MAP	Mean airway pressure
MV	Minute ventilation
ns	statistically non significant
P/V-curve	Pressure/volume curve
P/V-loop	Pressure/volume loop
$PaCO_2$	Arterial carbondioxid tension
PaO_2	Arterial oxygen tension
PC	Pressure controlled
P_{dyn}	Dynostatic pressure
PEEP	Positive end-expiratory pressure
P_{exp}	Expiratory pressure
P_{insp}	Inspiratory pressure
PIP	Peak inspiratory pressure
PSV	Pressure support ventilation
R_{exp}	Expiratory resistance
R_{insp}	Inspiratory resistance
RR	Respiratory rate
SVC	Single value compliance
TV	Tidal volume
UIP	Upper inflection point
VC	Volume controlled
VDC	Volume dependent compliance

....physiologists, clinicians and industry must develop a standardised procedure to obtain measurements of the P-V curve easily at the bedside. This procedure must be (a) simple, (b) rapid and safe, and (c) provide reproducible information on how to set ventilator settings....

VM Ranieri and AS Slutsky
Editorial in Intensive Care Medicine 1999
Vol 25, pages 1040-1043



Prologue

The cover of the book shows two pages from a 17th century Icelandic grimoire, known as the "Galdrabók", that illustrate magical symbols to produce sleep in man.

The history of the "Galdrabók" is unclear but it appears to have been smuggled out of Iceland in the mid 17th century and then bought by a Swedish scholar, JG Sparvenfeldt, in Copenhagen in 1682. Ever since then the book has been kept in Sweden and is now preserved at the Antikvariska - Topografiska Arkivet in Stockholm. The text that follows the symbols says:

Ef þú vilt svæfa mann þá rist þessa stafi á elri og lát undir höfuð honum og mun hann víst sofa þar til þú tekur í burt...

If you want to put a man to sleep, then carve these letters on birch and put it under his head and he will surely sleep until you remove it...

Most of the witchcraft in 17th century Iceland involved runes arranged according to complex rules. A "Svefnþorn" or sleep thorn, as these particular symbols are called, is an old magical element with a mythological connection to the relationship between Óðinn and the valykyrie Sigurdríía. Óðinn put Sigurdríía to sleep by pricking her with such a thorn and she did not wake up until Sigurd, the slayer of Fafner, rode over fire and cut up her armour.

The wish to rule over sleep has followed mankind for a long time. We have come quite along way in that quest but various concerns have arisen during the journey. This thesis deals with one of them.

Based on the book: Galdur á brennuöld, Reykjavík, Storð, 1996
by Docent **Matthías Viðar Sæmundsson** , and information on his home site
www.hi.is/~mattsam/index.htm, with permission.
Copies of the "Galdrabók" published with permission from
Antikvariska - Topografiska Arkivet Stockholm, Sweden.

Introduction

Mechanical ventilation is a life-saving feature in the treatment of critically ill patients. Its main purpose is to alleviate the work of breathing and gain time while waiting for resolution of the underlying disease. It has been established, however, that ventilatory treatment may harm the lung and affect mortality [1]. Monitoring of respiratory mechanics has been suggested to identify the most appropriate ventilator support and to decrease the risk of ventilator-induced lung injury [2-5]. Yet respiratory mechanics are rarely assessed thoroughly in ventilator treated patients. The reason for this is that methods for measurement of respiratory mechanics have been time consuming and cumbersome and thus of limited use in clinical practice. The need for an easy, accurate and precise method to monitor respiratory mechanics bedside has been pointed out [6].

Historical Background

Measurements of pressure, volume and flow

The modern era of measuring respiratory mechanics is considered to have begun with the work of James Carson, a Scottish physician. In 1817 he measured lung elasticity by attaching a water manometer to the trachea of recently killed animals and observed the increase in pressure on opening the thorax. Frans Cornelius Donders published a similar experiment in 1853 using a mercury manometer and human cadavers and attributed the rise in pressure to elastic retraction of lung tissue [7].

In 1844 John Hutchison introduced the spirometer, which facilitated the measurement of vital capacity and other lung volumes, and in 1925 Alfred Fleisch introduced a flowmeter for continuous measurement of inspired and expired air flow [7].

Between 1915 and 1925, Fritz Rohrer, together with his pupils, Karl Wirz and Kurt von Neergaard, carried out studies regarding resistance to flow in the airways, described the static pressure/volume (P/V) characteristics of the respiratory system and calculated work of breathing. Neergaard also described the influence of surface tension on respiratory mechanics. Rohrer's work went largely unnoticed until rediscovered by Wallace Fenn, Hermann Rahn and Arthur Otis in 1946. The work of Neergaard was also rediscovered by Edward P. Radford in 1954 [7,8].

Carl Ludwig, in 1847, was the first to report measurements of intrapleural pressures in living animals, employing a water-filled tube capped with a rubber balloon, positioned in the pleural space, connected to a mercury manometer. In 1878 Luciani, acting on a suggestion from Ceradini, put a tube down into the oesophagus and recorded pressure changes. His tube had numerous holes near the lower end and was sometimes covered with a rubber balloon. However, this method was not applied in humans until 70 years later, when Buytendijk published his thesis in 1949 using an air-filled balloon for oesophageal pressure measurements [9]. In 1952 Dorhorst and Leathart described measurement of oesophageal pressure with a water-filled narrow polyethylene catheter [10].

Endotracheal tubes, tracheostomy and intubation

After general anaesthesia was introduced in 1846, methods to safeguard the airway during operation, especially head and neck operations, became necessary. Gags and tongue depressors of different kinds were produced but were not protective for the larynx. In 1871 Trendelenburg introduced a new technique with a tracheostomy and insertion of a tube which was surrounded by an inflatable cuff. As time passed, this cuff was forgotten but reinvented in 1893 by Eisenmenger, who added a pilot balloon to the cuff inflation line in order to see if the cuff was inflated. The inflatable cuff still went unrecognised and was rediscovered again by Dorrance in 1910 and yet again by Guedel and Waters in 1928 [11,12].

Blind, oral, tactile intubation is an old method, although it was very seldom used before the development of anaesthesia and probably mostly for resuscitation purposes. The first man to intubate the larynx for anaesthetic purposes is thought to have been Sir William Macewen,

who did this in 1878, but he did not make any attempts to spread the method. The man who established intubation and made it widely known was Joseph O'Dwyer, who started to use the method in patients with diphtheria in 1882. His tubes were short and straight and various types of straight tubes were soon on the market. They needed a curved introducer, which was then detached, leaving the tube in place [11].

In the early 1920s Magill and Rowbotham introduced a method for blind nasal intubation. A curved tube was necessary to obtain entry into the larynx and this was found in a shop selling rubber tubing. The tubing was delivered in coils and when pieces of suitable length were cut they remained curved [11].

In 1913 Chevalier Jackson developed a laryngoscope similar to those used today, allowing direct visualisation of the larynx and thereby making it much easier to insert an endotracheal tube. The Macintosh laryngoscope, which is used world wide, was presented in 1943 [11].

Ventilators

Positive pressure ventilation came into use surprisingly late in both anaesthesia and the treatment of critically ill patients. Rhythmic ventilation of the lungs of a pig had been done by Vesalius in 1543, Robert Hook did the same in a dog in 1667, physiologists during the 19th century used both bellows and pumps for rhythmic artificial ventilation in animals and in 1892 O'Dwyer described the use of positive pressure ventilation. In 1899 Rudolph Matas found it curious that the profession had failed to apply this simple method earlier and in 1902 he described an air-pump combined with a modified O'Dwyer tube for this purpose [13].

In the beginning of the 20th century, Sauerbruch described the use of negative pressure chambers to perform operations in, thereby keeping the lungs of the patient inflated. Such chambers were established at many medical centres in Europe and the USA. In the 1920s Philip Drinker developed the total-body or tank type respirator, which became known as the "iron lung", based on negative pressure ventilation. The "cuirass respirator" using negative pressure was also presented. For decades afterwards, negative pressure was the method of

choice for long-term artificial respiration. However, in the operating theatre first constant airflow and then rhythmic inflation gradually replaced the negative pressure chambers [13].

This was the situation in 1952 when the polio epidemic broke out in Copenhagen. Because of the large number of patients and failure of established treatment with mortality rates of 90%, an anaesthesiologist, Bjørn Ibsen, was consulted at the Blegdamhospital. He recognised the symptoms of the patients as CO_2 accumulation and respiratory acidosis, indicating that the negative pressure ventilators were insufficient. Ibsen had previously been working experimentally with an apparatus, the Brinkman Carbovisor, to measure carbon dioxide continuously in expired air. He proposed treatment with manual intermittent positive pressure ventilation through a tracheostomy tube with an inflatable cuff. He demonstrated the use of the method on a patient by monitoring the CO_2 content continuously with the Carbovisor and the oxygen saturation using a Millikan Oximeter. Blood samples taken by one of the doctors at the hospital, Paul Astrup, showed normalisation of "total CO_2 in plasma" after institution of positive pressure ventilation. Astrup then contacted Radiometer A/S in Copenhagen, a firm that had recently developed a pH electrode, and the next day he was able to measure pH in blood directly using this new electrode. This new treatment reduced the mortality to 25% but needed much personnel for the manual ventilation 24 hours a day. This led to a rapid increase in the development and use of ventilators. In the autumn of 1952 the volume-regulated ventilator developed by the Swedish physician Carl-Gunnar Engström was successfully tested in Blegdamshospital. The polio epidemic in Copenhagen led to acceleration of developments that had already started and created new lines of research [14].

The development of clinical laboratory medicine became of central importance in the prolonged care of patients during artificial ventilation. Paul Astrup, together with Radiometer A/S, designed an apparatus for blood gas analysis and developed new parameters like "base excess" and "standard bicarbonate" to increase insight into the acid-base equilibrium in blood [14].

It was soon realised that the new volume-regulated ventilators could be used for patients with varying causes of acute or chronic respiratory insufficiency, including barbiturate intoxication, postoperative pulmonary insufficiency, skull trauma and brain tumours. This encouraged the development of intensive care units in Scandinavia in close collaboration with

anaesthesiologists. The development in other countries was also rapid and as early as 1953 there were a number of different types of ventilators on the market [14].

Since then more and more sophisticated ventilators and ventilatory modes have become available on the market. However, it is still difficult for physicians to select the most appropriate way of providing ventilatory support to patients and which parameters should be used as guidance for that purpose, especially since it is now widely accepted that the lung tissue can be injured by mechanical ventilation and cause deterioration of critically ill patients [15].

Ventilator-Induced Lung Injury

Various complications of ventilator therapy were soon recognised, air-leaks being one of them, indicating direct injury to the lung tissue [16-19]. However, only very recently was it recognised that more subtle physiological and morphological changes can occur in lung tissues during mechanical ventilation and that these may lead to multiorgan failure via inflammatory mediators and translocation of bacteria [20-24] and even affect mortality [1,25]. The alveoli are the main victim of ventilator-induced lung injury (VILI), with increased endothelial and epithelial permeability and ultrastructural damage [15,26]. The causes of this iatrogenic lung injury are considered to be a high inspired oxygen fraction, high pressures and volumes, tidal collapse and reinflation of alveoli and increased capillary permeability and induction of local and systemic inflammatory processes.

Oxygen toxicity

Normobaric oxygen toxicity is well described in all animal species. The susceptibility varies with age and strains, however, and primates appear to have higher resistance. Oxygen free radicals play a key role in the pathophysiology of oxygen toxicity and the pulmonary capillary endothelium seems to be their primary target. The threshold for pulmonary oxygen toxicity in humans is unknown. Prolonged high oxygen exposure in normal humans is reported to induce cough, shortness of breath, decreased vital capacity and increased alveolar-capillary permeability. In patients with previous lung injury, this threshold is even more difficult to

define, as pathological pulmonary lesions might result from hyperoxia or the primary lung insult. Lung injury and previous exposure to high oxygen concentrations might also prime the specific defence systems against oxygen free radicals. Situations with decreased diffusion capacity of the blood-gas barrier might also be protective for the capillary endothelium as they produce low oxygen pressure in the vascular compartment [27,28]. There are several reports of a favourable outcome in patients after prolonged oxygen exposure [27] and it has even been stated that there is no evidence that a high fraction of inspired oxygen is dangerous in patients with acute respiratory distress syndrome (ARDS) [29].

Baro/Volutrauma

Traditional ventilatory strategies have evolved from anaesthetic practice, where the lungs are usually healthy and have normal elasticity. These have included supranormal tidal volumes of 10 – 15 mL/kg body weight to prevent microatelectases (the resting tidal volume is 6 - 7 mL/kg), respiratory rate adjusted to normalise pH and/or $PaCO_2$ and sufficient positive end-expiratory pressure (PEEP) to achieve acceptable oxygen delivery at nontoxic concentrations of inspired oxygen. This high tidal volume, normoxic and normocapnic approach became a standard to support the critically ill patients, even those with lung injury [30]. This has led to ventilatory treatment with high peak airway pressures, which is now recognised as leading to excessive distension of aerated alveoli. It has been shown in animals that large tidal volumes can cause disruption of the pulmonary epithelium and endothelium, inducing oedema, atelectasis, hypoxemia and release of inflammatory mediators [31-39]. It is, however, not the pressure value itself which is the likely causative factor but the amount of alveolar stretch, which led to the concept of volutrauma [34]. After all, trumpet players can tolerate positive airway pressures above 150 cmH_2O, created by activation of expiratory muscles [40], without developing air-leaks as the muscles limit the expansion of the chest and thereby the alveoli.

It has recently been shown that lower tidal volumes (6 mL/kg) as compared to traditional tidal volumes (12 mL/kg) decreased mortality rates in patients with acute lung injury (ALI) and ARDS from 40% to 31%, a reduction of 22% [1]. Three previous studies on tidal volume reduction have failed to show any improvement in mortality [41-43], possibly because of less difference between traditional and reduced tidal volumes in the study groups [44].

Atelectrauma

Atelectrauma, or shearing injury, refers to damage caused by cyclic closing and opening of alveoli and terminal airways within each breath. This phenomenon was first described by Bengt Robertson during studies on surfactant in premature lungs [45]. It has been predicted that the stress forces applied to re-expand collapsed zones could exceed 100 cmH_2O, even though the transpulmonary pressure may only be 30 cmH_2O, and thereby produce further damage [46]. It has been shown that repetitive opening and closing of alveoli causes lung injury independently of alveolar overdistension and that it can be avoided by using PEEP [31,38,47-49].

A recent study [5] using a ventilator strategy to minimise atelectrauma and overdistension showed improved survival in patients with ARDS at 28 days (38% versus 71%) but not at hospital discharge. This study has been criticised for an unusual high mortality rate in the control group and the fact that this ventilator strategy is difficult to apply because of technical complexity in measuring respiratory mechanics [50].

Biotrauma

Alveolar overdistension coupled with atelectrauma may cause an increase in capillary permeability and initiate a cascade of proinflammatory cytokines. This has been shown in animal models by increased translocation of bacteria from the lung into the bloodstream [23,24], increased granulocyte infiltration [51], increased cytokine levels in lung lavage [39] and increased cytokine levels in the systemic circulation [52,53].

The presence of inflammatory mediators has been shown to play a critical role in the pathophysiology of multiple system organ failure and shock [54]. The spillover of inflammatory mediators from the lung into the circulation could contribute to the initiation or propagation of a systemic inflammatory response leading to multiple organ dysfunction [20,21,55].

A recent study showed a higher cytokine response both in the lungs and in the systemic circulation in patients with ARDS that had received traditional ventilator treatment compared to patients treated with a ventilator strategy to minimise overdistension and atelectrauma [22,25]. The authors suggested that these results could explain the development of multiple organ failure in many patients with ARDS [56] and the high mortality rate of the syndrome (40 – 60% [44]).

Lung-protective ventilator strategy

Concerns about atelectrauma and gas exchange disturbances caused by atelectasis led to trials of various ventilator treatments [57-59] and the creation of the "open lung concept" by Lachmann in 1992 [60]. It emphasises the need of high end-inspiratory pressures to open up atelectasis, i.e. recruit alveoli, and adequate PEEP to prevent their collapsing again [61]. How to recruit and which pressures should be used has been debated [62]. Which PEEP level is ideal and how to identify this level has also been a subject of controversy through the years [3,60,63,64,65,]. However, recent studies suggest that ventilator settings for optimal oxygen delivery and lung-protective ventilation do not coincide [66,67], making it even more important to monitor respiratory mechanics and also take into consideration their effect on hemodynamics [68,69].

Concerns about lung injury caused by overdistension of alveoli led to the recommendation of the American College of Chest Physicians (ACCP) consensus conference 1993 [70] to keep end-inspiratory plateau pressure below 35 cmH_2O. This was based on animal studies and reports of increased survival in patients with a pressure-limited approach [71,72].

This lung-protective approach, aiming to minimise atelectrauma and overdistension, has been used in two of the studies mentioned above [5,22] and has been considered to give positive results in comparison with traditional ventilator treatment.

All the aspects of ventilator-induced injury become highly relevant in the treatment of patients with ALI and ARDS, where a compromise has to be made between oxygenation and the possible complications of ventilator treatment.

Acute Lung Injury and Acute Respiratory Distress Syndrome

Definition

The acute respiratory distress syndrome is relatively newly recognised as it emerged with the development of mechanical ventilation and intensive care units. It was first described by Ashbaugh et al in 1967 [73]. The clinical hallmarks are acute respiratory distress, hypoxemia refractory to oxygen, reduced lung compliance, diffuse bilateral pulmonary infiltrates on chest radiography and the need for mechanical ventilation [74].

The initial definition lacked criteria to identify patients systematically and in 1988 an expanded definition was proposed by Murray [75], the "lung injury score" system (LIS), which is based on four items: PEEP level, PaO_2/FiO_2 ratio, static lung compliance and degree of infiltration on the chest radiographs. The primary cause and the presence of non-pulmonary organ dysfunctions were also noted. The LIS system has, however, been unable to predict the outcome during the first 24-72 hours after onset of acute respiratory distress syndrome [76] but when used after 4 -7 days scores of 2.5 or higher may predict a complicated course and need for prolonged mechanical ventilation [77].

In 1994 the American-European Consensus Conference Committee recommended a new definition [78] where acute lung injury (ALI) preceding ARDS is defined by acute onset, a PaO_2/FiO_2 ratio of 300 mmHg (40 kPa) or less (regardless of PEEP level) and presence of bilateral infiltrates on chest radiographs with no clinical evidence of left heart failure (or pulmonary capillary wedge pressure 18 cmH_2O or less if a pulmonary artery catheter is in place). ARDS is defined in the same manner except that the PaO_2/FiO_2 must be less than 200 mmHg (27 kPa). This scoring system is simple and is widely accepted in clinical research [44]. The most serious flaw is the lack of data regarding ventilator settings and respiratory mechanics. The use of PEEP could easily move patients between the definition limits of ALI and ARDS or even out of them and certainly affect respiratory compliance simultaneously. The absence of these factors might reflect the lack of reliable bedside monitoring methods for respiratory mechanics.

Epidemiology

The incidence of ALI/ARDS has been difficult to estimate because of ambiguous definitions and has varied between 1.5 (1989) [79] and 75 (1972) cases per 100.000 population [80]. The first epidemiological study to use the 1994 consensus definition was recently performed in Sweden, Denmark and Iceland by Luhr [81] and showed an incidence of 17.9 per 100.000 for ALI and 13.5 per 100.000 for ARDS. Most studies have reported mortality following ARDS between 40 and 60% [44]. There have been indications that the mortality might be decreasing [82,83]. The study by Luhr showed a mortality of 42% for ALI patients and 41% for ARDS patients. Further, patients with acute respiratory failure, defined as intubation and mechanical ventilation for more than 24 h (including ALI and ARDS patients), had a mortality rate of 41% [81]. The majority of deaths in ARDS patients are not caused by respiratory failure but by sepsis or multiorgan dysfunction [44,56,80]. In a recent study comparing the use of lower tidal volumes (6 mL/kg) than traditional ones (12 mL/kg), a 22% reduction in mortality was reached or 31 % versus 40 % respectively [1].

Pathology

The pathology of ALI/ARDS comprises a nonspecific pattern of lung injury, i.e. diffuse damage of the alveolar endothelium and epithelium, caused by inflammation and increased capillary alveolar permeability, which can evolve from acute to chronic stages. It is usually separated into three histological phases. The acute or exudative stage can be seen up to 6 days after the initial event and is characterised by influx of protein-rich oedema fluid into the alveoli as a consequence of increased alveolar–endothelial permeability. The second or proliferative phase develops between days 4 and 10 and is characterised by marked proliferation of fibroblasts in the alveoli. This may evolve into the third phase, the chronic fibrotic phase, with extensive fibrosis, after a period of 8 to 10 days. The recovery phase is characterised by gradual resolution of hypoxemia and radiographic abnormalities and improvement of respiratory compliance. In most patients who survive, pulmonary function returns to normal within 6 to 12 months [44,84]. The initiation of ALI/ARDS can be caused

by *direct lung injury* (pneumonia, aspiration, pulmonary contusion, fat emboli, near-drowning, inhalational injury, reperfusion pulmonary oedema) or *indirect lung injury* (sepsis, severe trauma, cardiopulmonary bypass, drug overdose, acute pancreatitis, transfusion of blood products) [44]. Studies have shown a difference in respiratory mechanics between these two entities which might be of importance in the ventilator treatment of patients [85,86]. Puybasset recently used computed tomography images to classify patients with ARDS into subgroups with different patterns of lung injury. He also noted a different response in respiratory mechanics to ventilator therapy and mortality differences between the groups [87].

Treatment

The inability to reduce the mortality of ARDS has over the years led to extensive research and trials of new modes of therapy. The most appropriate way to ventilate these patients has been vigorously debated, as has which levels of PaO_2 and $PaCO_2$ to aim at, especially after a report from Hickling in 1990 [72], where a low mortality rate in patients with ARDS was achieved by using low tidal volumes, to reduce end-inspiratory pressure, disregarding the inevitable hypercapnea, thus, abandoning the traditional normocapnic ventilator treatment.

Ventilatory strategies that have been tried in the treatment of ARDS include [44]:

• High peak airway pressures/large tidal volumes (traditional treatment) [1,5,22]	Considered negative
• Supranormal PEEP levels (44 cmH_2O) [88]	Considered negative
• Prophylactic PEEP levels (8 cmH_2O) [89]	No benefit
• High frequency jet ventilation [90]	No benefit
• Inverse ratio ventilation [91]	Inconclusive data
• High frequency oscillatory ventlation [92]	Pilot study in adults
• Prone position during ventilation [93,94]	Inconclusive data
• The open lung approach [5]	Considered positive
• Low tidal volumes	3 studies showed no benefit [41-43] 1 study positive [1]

Adjuncts to ventilator therapy that have been used include:

• Extracorporeal membrane oxygenation [95]	No benefit
• Liquid ventilation [96]	Observational study
• Inhalation of vasodilators, NO [97] and Prostacyclin [98]	No benefit, although oxygenation could be improved
• Surfactant therapy [99]	No benefit, although considered not fully studied

Different *measures to decrease the arterial CO_2 level* have been tried as this will become more important with a low tidal volume approach:

• Extracorporeal removal of carbon dioxide [100]	No benefit
• Tracheal gas insufflation [101,102]	Not studied
• Double-lumen coaxial tube [103]	Not studied

During the last decade the trend has been towards a gentler form of mechanical ventilation of patients with ARDS, with a consensus report in 1993, concerning ventilator therapy, emphasising the importance of avoiding overdistension by limiting upper pressures [70]. Recently, five studies comparing the use of low tidal volumes with the traditional approach have been published [1,5,41-43] (Table 1). Two of them showed increased survival but also had the largest difference in mean end-inspiratory plateau pressure between the treatment and control patient groups, 6.7 [5] and 8.0 cmH_2O [1] as compared to 4.5 [43], 6.0 [42] and 5.7 cmH2O [41], indicating a larger difference in distension of alveoli [104]. The traditionally treated control patient group in the two positive studies had end-inspiratory plateau pressures above 32 cmH_2O [1,5] and the three negative studies [41-43] at or below 32 cmH_2O during the study period, indicating that higher pressures were used in the control groups of the two positive studies [104]. Differences in the treatment of respiratory acidosis, accompanying low tidal volumes, might also be a source of disparity between the studies [104].

But what should be used as guidelines to set the ventilator? All the above studies have used empirical ventilator settings to limit the upper pressures. Only in one, the open lung approach

study [5], static methods,to measrue respiratory mechanics, were used to identify the lower inflection point on the pressure/volume curve (P/V-curve) to set PEEP. One might consider the two positive studies [1,5] as only showing that it is truly possible to use the ventilator in a harmful way because of the high end-inspiratory pressure used in the traditionally treated patient group [104]. How the ventilator therapy should be adjusted for each individual in terms of ventilator modes, end-inspiratory pressures, PEEP and adjunct therapies has not been demonstrated yet. This is probably because of the lack of continuous, accurate, bedside monitoring methods for measuring respiratory mechanics.

	ARDS network [1] Day 1		**Brower [41] Day 1**		**Brochard [42] Day 1**		**Stewart [43] Day 1**		**Amato [5] first 36 hours**	
	Low TV	**Trad TV**	**Low TV**	**Trad TV**	**Low TV**	**Trad TV**	**Low TV**	**Trad TV**	**Prot-ective**	**Trad**
TV	6.2	11.8	7.5	10.2	7.1	10.3	7.0	10.7	6(aim)	12(aim)
PIP	32	39	-	-	-	-	24.2	32.1	30.5	46.0
EI-Plat	25	33	26	32	25.7	31.7	22.3	26.8	30.1	36.8
PEEP	9.4	8.6	8.2	9.5	10.7	10.7	8.6	7.2	16.4	8.7
MAP	17	17	-	-	-	-	-	-	23.5	17.9
RR	29	16	-	-	-	-	22.1	15.6	-	-
MV	12.9	12.6	-	-	-	-	11.1	11.7	6.8	13.1
Out-come	**↓ Mortality at discharge by 22%**		**No benefit**		**No benefit**		**No benefit**		**↓ 28-day mortality but not in-hospital**	

Table 1. *The mean values of respiratory mechanical parameters at the first day in 5 recent interventional, prospective studies on patients with ARDS. The values were similar throughout the study periods. (*Trad *traditional,* TV *tidal volume,* PIP *peak inspiratory pressure,* EI-Plat *end-inspiratory plateau pressure,* PEEP *positive end-expiratory pressure,* MAP *mean airway pressure,* RR *respiratory rate,* MV *minute ventilation).*

Monitoring Pressure/Volume Relationships in the Respiratory System

In 1929 von Neergaard applied Laplace´s law to demonstrate that the pressures required to expand an air-filled lung were almost 3 times higher than those needed to distend a lung filled with fluid if the surface tension effect at the air-liquid boundary was eliminated [105,106]. His work was rediscovered by Radford in 1954 and became clinically relevant when Avery and Mead published direct evidence linking absence of pulmonary surfactant to the appearance of stiff lungs in premature babies [8].

However, it was Rahn (1946) and Fenn (1951) who laid the foundations of modern monitoring of respiratory mechanics by analysing the pressure/volume diagram of the respiratory system. They described a sigmoidal static P/V-curve of the total respiratory system in individuals with normal lung function. The initial compliance, below functional residual capacity, is considered to be lowest while at FRC the compliance becomes highest and then decreases successively with increasing volumes. The total respiratory system P/V-curve is the sum of chest wall compliance and lung compliance. With increasing tidal volumes the static chest wall P/V-curve will show increasing compliance while the static lung P/V-curve will show lower compliance. The decrease in lung compliance is larger, however, as the total respiratory system compliance also decreases with higher tidal volumes [107] (fig. 1).

In 1972 Falke [2] traced dynamic P/V-loops in patients with ARDS at different PEEP levels and showed increased compliance with recruitment. In 1975 Suter [3] identified an optimal PEEP level in the treatment of ARDS patients where maximum oxygen transport coincided with highest FRC and static compliance of the total respiratory system. This was assumed to be caused by movement of the tidal volume on a hypothetical curvilinear P/V-curve with an inflection at low tidal volume similar to that identified in normal subjects but lying at other volume and pressure levels in ARDS patients. In 1981 Lemaire evaluated static respiratory system mechanics in patients with ARDS and noted a sigmoidal static P/V-curve with a prominent lower inflection (above FRC) [108]. In 1984 Matamis [4] proposed

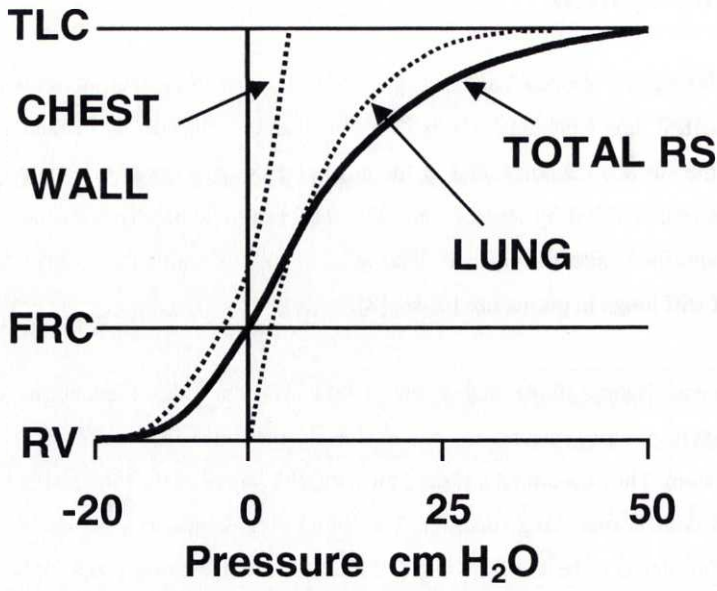


Fig. 1. *Schematic illustration of static P/V-curves of the total respiratory system, chest wall and lung traced from residual volume (RV) to total lung capacity (TLC). Notice that the chest wall compliance increases with increasing volume as the lung compliance decreases. The curve for the total respiratory system, a sum of the other two curves, crosses the zero pressure line at functional residual capacity (FRC).*

the use of the *lower inflection point* (LIP) to titrate PEEP and suggested that the initial portion of the static P/V-curve was a sign of progressive alveolar recruitment that would be completed once the curve became linear. An *upper inflection point* (UIP) indicating overdistension of alveoli had also been described but it seems not to have been used to identify an upper pressure limit during ventilator treatment and empirical pressure limits used instead [1,5,41-43]. In the ACCP consensus report about mechanical ventilation in 1993, it was stated that there were no data indicating that any ventilatory support mode was superior to others for patients with ARDS [70]. However, results from animal models and trials using a limited upper pressure approach in ARDS patients [71,72] led to the recommendation to keep the end-inspiratory plateau pressure below 35 cmH_2O. An appropriate PEEP level was recognised as useful to support oxygenation and possibly helpful in preventing lung damage.

It was recommended that the PEEP level should be identified by an empirical trial but should be minimised as it could also have deleterious effects.

Numerous mechanisms have been proposed to explain the behaviour of lung mechanics in patients with lung injury. These include increased surface tension because of surfactant inactivation, airway block caused by air-liquid interfaces and bubble formation in small airways, reflex bronchoconstriction and peribronchial oedema [108].

The segment between the LIP and the UIP represents a zone of optimal compliance within which ventilation should preferably occur within [109,110]. However, this interpretation of the static P/V-curve has been questioned and studies suggest that alveolar recruitment is an on-going process throughout inflation, beyond the lower inflection point [111-114]. This puts in question the concept of the open lung approach in ventilator treatment, according to which the lower inflection point reflects the critical opening pressure for the majority of alveoli [109], especially a peak airway pressures of 45 – 60 cm H_2O during 10 to 30 seconds are recommended to recruit collapsed alveoli [61].

Static and semistatic methods

Since Asbaugh [73] described the syndrome of ARDS in 1967, the pressure volume relationship in the respiratory system in ARDS patients has been analysed to assess respiratory mechanics and used as a tool for diagnose [115], prognosis [116] and treatment [2,3,5]. During the last 30 years there has been a steady flow of articles in the scientific literature concerning various methods of tracing P/V-curves.

It has been assumed that the true values of the P/V relationship in the alveoli could only be obtained during static/semistatic conditions, i.e. no flow/low flow conditions, because of artefacts during measurements under dynamic conditions caused by [117]:

- friction along the endotracheal tube, airways and lung and chest wall tissues effecting flow (viscous forces),
- elastic forces within the lung and chest wall (elastic forces),

- stress adaptation units within lung and chest wall tissues (viscoelastic forces),
- inertial forces (at the start of inspiration and expiration),
- compressibility of thoracic gas,
- inhomogeneity within the respiratory system and
- distortion of the respiratory system from the configuration during muscle relaxation (e.g. high intra-abdominal pressure).

The first three factors are supposed to be those that provide the most important opposing forces against inspiratory flow. These factors are also considered to be flow, volume and frequency dependent [118-123]. Static/semistatic monitoring methods may be divided into step-by-step or occlusion methods and continuous flow methods. They all rely on the ventilator-treated patient being sedated and muscle relaxed.

Step-by-step and occlusion methods

The super syringe method

The super syringe method has generally been considered the reference technique for measuring static P/V-curves [124]. It consists of a 1.5-2 L syringe which is used to inflate and deflate the lungs stepwise with 100 ml aliquots with a 2-3 sec pause at each step [107]. The method has several drawbacks. The volume history of the lungs must be standardised before with several large breaths from the ventilator, the patient must be disconnected from the ventilator, the manoeuvre takes between 30 and 90 seconds and gas exchange during the manoeuvre, gas decompression and temperature and humidity changes of the inspired gas will cause artefacts [107,125,126]. The method is time consuming, potentially dangerous to the patient and has serious flaws.

Flow interruption during a single breath

The flow interrupter technique during constant flow inflation, from zero end expiratory pressure, is a combination of the interrupter and elastic subtraction methods proposed by von Neergaard and Wirtz to measure airway resistance [127]. It was further developed by Gottfried [128] to measure respiratory mechanics using a pneumatically operated valve to produce a series of rapid occlusions (0.2 s) either during passive deflation following end-

inspiratory occlusion or during both inspiration and expiration [128,129]. Most patients studied with this method have shown a linear P/V relationship and it has never been used clinically, probably because of its additional equipment requirements [107].

Multiple occlusions at different tidal volumes

These methods are based on a large number of interrupted breaths at different tidal volumes during constant inspiratory flow from zero end expiratory pressure, and usually during both inspiration and expiration, each interruption yielding a point on the static P/V-curve. The first method was described by Levy et al in 1989 [130] but has been refined over the years [131-133]. In its later version, it uses an external device to override the frequency set by the ventilator to keep constant inspiratory flow at different volumes and predefines the volume history and distribution of points on the pressure/volume curve. About 20 study breaths are sampled with at least 3 normal breaths between each (to stabilise the lung volume history) and occlusions are performed during both inspiration and expiration. Servillo [134] recently published a study using this method and concluded that it was safe, easy and rapidly performed.

A similar method has been described by Sydow et al [135] where a pneumatic valve, automatically controlled by a computer, was used to achieve repeated inspiratory and expiratory occlusions lasting 6 seconds. Two normal breaths were interspersed between each study breath. The authors used the super syringe technique as a reference and found substantial differences in the static P/V-curves produced by the two methods. The occlusion method showed no hysteresis and very few inflections points were identified even in patients with severe ALI. The super syringe method showed hysteresis even if corrected for gas exchange, temperature and humidity. The authors suggested that the correction factors were insufficient and the volume cumulative super syringe method altered the lung volume history at each step while the occlusion method gave measurement points independent of each other. In interpreting their results, they questioned the occurrence of alveolar recruitment during the respiratory cycle [136].

The PEEP-wave technique

The PEEP-wave technique was proposed by Putensen [137] and is based on calculation of static compliance after tracing the difference in expiratory tidal volumes before and after a PEEP change to follow gain and loss in lung volume. A similar method was used by Valta

[138], who calculated static compliance at different PEEP levels and followed changes in lung volume by respiratory inductive plethysmography.

These methods or similar ones have been used by many authors in studies [109,139-141] and as reference methods [124,142,143]. However, they are seldom used clinically though they avoid the problem of disconnection and gas exchange inherent in the super syringe method. This is probably because they are time consuming with respect to both data recording and analysis, they are technically complex, and they require substantial additional equipment to perform the procedure. They also require standardisation of the volume history of the lung between study breaths. The number of normal breaths between study breaths has varied largely between studies, or from 2 to 20 [124,128,130,131,139,141-143], and sometimes the number is not reported.

Constant flow inflation

To avoid the need of intermittent airway occlusions and increase the speed of analysis, constant flow inflation methods have been proposed. They use constant inspiratory flow either in the normal flow range or at a very low velocity.

Normal flow range

The pulse method was proposed by Surratt [144]. This method is based on the assumption that when inspiratory flow is constant during passive inflation of the relaxed respiratory system the rate of change of airway pressure is related to the compliance of the respiratory system. An upward displacement of the curve would therefore be a sign of increase in compliance and indicate recruitment while a downward deflection would be a sign of decreased compliance and indicate overdistension. This method was used by Ranieri [141], who sampled about 20 breaths at each setting to obtain data. A group led by Barnas has developed a system depending on an external computer to drive a ventilator to produce a *quasi-sinusoidal flow pattern* and collect data at eight combinations of frequency and tidal volume using a simplified Fourier transformation for analysis [145].

These dynamic measurements will be influenced to some extent by both viscous and elastic properties of the respiratory system and are time consuming as they require several study breaths at each level to obtain data.

Low flow inflation

To minimise the effect of viscous resistance, Mankikian [146] used the very *low constant inspiratory flow* of 1.7 L/min and allowed deflation to occur passively at a controlled constant flow. They compared this method with the super syringe method and concluded that they produced identical P/V-curves. As the super syringe method was not corrected for gas exchange, the flow velocity used has probably been so low that continuous gas exchange caused similar artefacts in both methods [113].

During the last few years several articles concerning low flow inflation using different flow velocities have been published. They all try to identify a clinically applicable "single breath" method that can be used to analyse respiratory mechanics instead of the time-consuming static occlusion methods. For this purpose, they have used commercially available ventilators with varying amounts of sophisticated extra equipment. In 1997 Servillo [142] introduced the *automatic low flow inflation* (ALFI) method using an external computer to control the ventilator to give a flow velocity of 15 L/min. The in vitro determined endotracheal tube resistance was subtracted, as was the airway resistance, determined previously from a normal breath (calculated as the ratio between the area of the pressure volume loop and the area of the flow volume loop). The authors used the static occlusion method as reference and found good agreement except at high volumes, where the ALFI curve showed less compliance. In 1999 Lu [124] presented P/V-curves obtained with flows of 3 and 9 L/min and used the inflation limb of the super syringe and the static occlusion method as reference. Because of technical limitations from the ventilator, the tidal volumes were 500 mL with 3 L/min and 1500 mL with 9 L/min. The authors concluded that the reference methods and 3 L/min flow P/V-curves were identical while the 9 L/min flow curves were affected by resistance and shifted to the right but to a degree that was not clinically relevant. No correction factors were used. Rodriguez [143] also published a study in 1999 using a flow velocity of 7 L/min and a tidal volume of 1100 mL and used the static occlusion method as a reference. They concluded that the curves obtained with the two methods were of similar value.

The correct flow rate for low flow inflation is difficult to determine. If the flow is too low the P/V-curve will be affected by continuous gas exchange and if the flow rate is too high it will be affected by the resistive components of the endotracheal tube and conducting airways, creating a need for correction factors, which will have an inherent uncertainty. If the ventilator is not able to provide constant flow from the very beginning of inspiration, it will affect the initial part of the P/V-curve, showing a lower compliance.

The normal flow range methods are not considered reliable, because of the effect of resistance. None of the static or semistatic methods have come into routine clinical use, even though the basic techniques have been known for over two decades. This has primarily been blamed on the slowness and inconvenience of the methods, but also that they require much additional technical equipment both for data sampling and for analysis. In recent papers, an effort has been made to simplify the technological part and/or make the analysis faster. The quickest analysis with the low flow inflation technique is reported to be about 2 minutes [124], and with the static occlusion method about 10 minutes [134].

None of the static/semistatic methods can be used to perform continuous monitoring of respiratory mechanics. They are all intermittent and require interruption of the on-going ventilator treatment and replacing it with a special state of flow, i.e. no flow, low flow or sinusoidal flow, that is never encountered during normal breathing or during normal ventilator treatment. These static or semistatic measurements are then used to try to predict the behaviour of the respiratory system during dynamic conditions.

When collecting data with the static occlusion method, a standardised lung volume history is necessary so that the results will not be affected, as has been shown with changes in low flow P/V-curves after recruitment manoeuvres [147]. These methods therefore do not reflect the "only true" P/V-relationship in the respiratory system as it will vary with different ventilator settings and recruitment. Neither is it clear what information static/semistatic methods provide for the description of a dynamic system, where compliance and resistance are considered to depend on volume, flow velocity and respiratory rate [118-123]. It seems in a way inappropriate to evaluate a dynamic system only with static/semistatic methods and dynamic parameters might be more relevant when deciding the most appropriate ventilator settings. It would also be of major value to be able to follow on-line, at the bedside, what happens with respiratory mechanics when ventilator settings are changed.

Airway resistance

The resistive components of the breathing circuit, the endotracheal tube and respiratory system cause a variable distortion of dynamic airway pressure measurements, depending on the measurement site, concealing the alveolar pressure.

When the pressure is measured at the Y-piece or ventilator, the endotracheal tube is the element causing the largest distortion in airway pressure measurements [148]. The errors of measuring airway pressure at the Y-piece or ventilator can be avoided by direct measurements of tracheal airway pressures. This can be accomplished by inserting a pressure line through the lumen of the endotracheal tube [149,150]. In that way, pressure measurements are obtained much closer to the alveoli.

However, it is not possible to measure pressure directly in the alveoli and there is no consensus about how to measure the pressure drop between the tip of the endotracheal tube and alveoli during inspiration and expiration. Many approaches, both technical and mathematical have been used to measure airway resistance (providing a variety in nomenclature and results) but a clinically applicable method providing "accurate" measurements of inspiratory and expiratory resistances does not exist.

Classically, airway resistance has mainly been considered to be caused by a frictional component, in phase with flow, and an elastic component, in phase with volume. The frictional component is considered to occur between the tip of the endotracheal tube and alveoli due to opposition to motion, and the elastic component between the alveoli and the pleural surface due to tissue elastance. However, the bronchial tree does not behave as a rigid tube system and the pressure losses along the airway are therefore dependent on lung volume and flow. They are also strongly influenced by the respiratory rate. This makes comparisons of resistance values meaningless unless the volume and flow are standardised [118-123,151]. Airway resistance is a highly complicated component to describe and using only a single value to describe the resistance behaviour of a whole breath or the inspiration and expiration separately is probably an oversimplification. Different values of resistance and different approaches to obtain them have been used in the literature.

Effective resistance

This is a single value of resistance representing the whole respiratory cycle and is calculated as the ratio between the area of the P/V-loop and the area between the flow/volume loop. It includes both the frictional and the elastic fraction of resistance [152].

Inspiratory resistance

The flow interrupter technique is the most common method and is used during constant flow inflation. It is the same method as used during static occlusion described previously. After a rapid occlusion, the airway pressure shows a rapid drop followed by a slower decay. The rapid pressure drop is considered mainly to represent airway resistance and the slower decay the tissue viscoelasticity (it is, however, not pure resistance as the flow has already stopped). By dividing the pressure differences by the preceding constant flow at the time of occlusion, the airway and additional resistance can be calculated separately. If oesophageal pressure is measured simultaneously, as a substitute for pleural pressure, the lung and chest wall resistances may be partitioned. The closing time of the ventilator valve has to be sufficiently rapid so that flow will cease immediately [127].

Expiratory resistance:

Flow interruption is also used during expiration. The flow is passive, however, and therefore decelerating and the resistance calculated only represents the resistance at the point of occlusion [151]. The *passive exhalation time constant method* assumes the respiratory system to behave as a single compartment. The exhalation time course of lung volume above resting volume is fitted by a first degree exponential equation. Its time constant, i.e. the product of resistance and compliance, represents the time needed to exhale 63% of lung volume above resting volume [127].

The methods usually used to calculate resistance clinically depend on an inspiratory square wave flow curve and an end-inspiratory pause. Some of them calculate inspiratory resistance, some expiratory resistance and some calculate a combination of inspiratory and expiratory resistance. Hess [153] compared six methods of calculating respiratory resistance on the same breath and found a significant difference between them, the range of values being between 12 and 27 cmH_2Os/L.

A group led by Björn Jonson has recently measured inspiratory and expiratory resistances in ventilator-treated patients with normal lung function, ARDS and chronic obstructive pulmonary disease. For this purpose, they have used the interruption technique and measured the resistance as a single value at the mid-inspiratory and mid-expiratory volumes. In individuals with normal lung function the average values for inspiratory and expiratory resistances at mid-inspiratory and mid-expiratory volumes were 2 versus 2.2 cmH_20s/L (ratio 1:1.1), in patients with ARDS 3.4 versus 3 cmH_2Os/L (ratio 1:0.9) and in COPD patients 20 versus 50 cmH_2Os/L (ratio 1:2.5) [131,132].

How is Mechanical Ventilation Employed in the ICU?

What ventilatory treatment do patients receive today and how do we monitor respiratory mechanics after more than 30 years of profound research on the subject and known risk factors of ventilator-induced lung injury?

Esteban [154] recently carried out a one-day prevalence study in 412 intensive care units in South and North America, Spain and Portugal to study administration of ventilator treatment (data from 1996 and 1997). This involved 1,638 patients, 197 (12%) of them having ARDS. In this study, mechanical ventilation was delivered via an endotracheal tube in 75% of the patients, a tracheostomy in 24% and a facial mask in 1%. The ventilatory modes were assist/control ventilation (volume-limited, constant flow) in 47% of the patients, 15% received pressure support ventilation (pressure-limited, decelerating flow) and the rest synchronised intermittent mandatory controlled ventilation (SIMV), alone or in combination with pressure support ventilation (PSV). This indicates that pressure-limited ventilator modes with

decelerating flow are only used in minority of patients. The median tidal volume was 9 and 7 mL/kg for VC and PC modes respectively. In spite of similar tidal volumes, the median peak pressure for the VC modes was much higher than the PC modes, or 30 cmH_2O versus 19 cmH_2O. This was explained by their different flow patterns, demonstrating the unreliability of airway pressure measurements at the Y-piece or ventilator caused by endotracheal tube resistance. The PEEP levels used were low and 31% of the patients did not receive any PEEP at all. In 47% of the patients the PEEP was between 1 and 5 cmH_2O and in 18% between 6 and 10 cmH_2O.

Luhr [155] also recently (data from 1997) studied the impact of respiratory variables on mortality in 520 non-ARDS patients and 95 ARDS patients (15%) receiving mechanical ventilation in 78 intensive care units in Sweden and Iceland (non-ARDS patients; all intubated patients receiving mechanical ventilation more than 24 h and not fulfilling criteria for ARDS). The ventilator settings at admission to the ICU for the survivors and non-survivors were almost identical. For the non-ARDS group, peak inspiratory pressure was 26 cmH_2O, PEEP 5 cmH_2O and tidal volume 8 mL/kg. The corresponding values at admission for the ARDS group were peak inspiratory pressure 29 cmH_2O, PEEP 7 cmH_2O and tidal volume 8 mL/kg.

Both studies present the upper pressure level as peak inspiratory pressure (PIP), which will mainly reflect the endotracheal tube resistance if measured at the Y-piece or ventilator. Both studies indicate that low levels of PEEP are generally used in ventilator-treated patients and in one of them [154] a third of the patients did not receive PEEP at all. Even in patients with ARDS, only modest levels of PEEP seem to be employed. These studies indicate a somewhat gentler approach to ventilator treatment, with lower tidal volumes, than what has been considered as traditional in recent studies [1,5]. However, the trend in the literature towards higher PEEP levels [60] seems not to have had a clinical impact.

The great diversity of ventilatory modes and settings and the limited features of monitoring respiratory mechanics make it virtually impossible to identify actual differences between ventilator therapies in the current literature and their effect on respiratory mechanics. This is reflected in the studies discussed above as respiratory mechanics are estimated with rather simple and somewhat misleading parameters. Further, in the study by Luhr [155] no association was found between either oxygenation or ventilator settings and mortality in ARDS patients. However, differences in occurrence of ventilator-induced lung injury may

appear which the conventional crude monitoring methods of respiratory mechanics are not able to reveal. More sophisticated and correct methods of monitoring respiratory mechanics are not available clinically. Still, the mortality of both ventilator treated non-ARDS and ARDS patients is high, 41 and 44 % respectively according to Luhr [155], giving every reason to improve monitoring of respiratory mechanics. All previous methods of static measurement are intermittent, difficult to apply clinically and not readily available. The methods presented in this thesis are an attempt to solve these problems.

Aims of the thesis

The overall aim of this thesis was to develop and evaluate a safe and accurate method of monitoring respiratory mechanics during on-going ventilator treatment that could also partition the total respiratory system into its lung and chest wall components.

The specific aims were:

- To develop and validate the use of a double-lumen liquid-filled tube for measurement of oesophageal pressures (a surrogate for pleural pressure) (Paper I)

- To evaluate the effect of endotracheal tube resistance on dynamic measurements of respiratory mechanics (Paper II)

- To develop and validate an algorithm with which to calculate alveolar pressure and display alveolar pressure/volume curves during on-going ventilator treatment, based on direct measurements of tracheal pressures (Paper III)

- To evaluate methods of direct measurement of tracheal airway pressures (Paper IV)

- To combine these methods to monitor respiratory mechanics in patients with ALI and ARDS (Paper V)

Subjects and Methods

The fundamental idea of these studies was to utilise basic equipment at hand in every intensive care unit to improve the accuracy of monitoring respiratory mechanics bedside. The monitoring methods presented evolved from studies in mechanical models and in patients. Most of the research equipment was therefore used both during bench tests and in patients.

Patients

Studies on patients were approved by the Ethics Committee of the Medical Faculty in Göteborg. All patients were intubated and ventilator treated. They were either anaesthetised or sedated and all were muscle relaxed during measurements. In Paper I the use of a double-lumen liquid-filled oesophageal tube was evaluated regarding position in 6 ICU patients and compared with an oesophageal balloon catheter in another 5. Respiratory mechanics and the effect of endotracheal tube resistance were evaluated in 12 patients during open abdominal surgery. In Paper II the influence of endotracheal tube resistance on airway pressure measurements was estimated in 10 patients with ALI/ARDS. In Paper III the feasibility of continuous calculation of the alveolar pressure applying an algorithm developed by the research group, *the dynostatic algorithm*, was studied in the same patients. In Paper V the monitoring methods were combined to apply the dynostatic algorithm to both the total respiratory system and the lung to calculate volume-dependent compliance at different ventilatory settings in 10 patients with ALI/ARDS, 5 of them also studied in Papers II and III.

Equipment

Ventilators: Siemens UV-705, Servo 900C and Servo 300 ventilators (all from Siemens Ltd., Solna, Sweden) were used. All ventilators were connected to a standard breathing circuit. A variety of ventilator settings were used both during bench tests and in patients. Basically, three different settings of tidal volume, PEEP, end-inspiratory pause and inspiratory time were used to grade the response.

Lung model: A Biotek adult ventilator tester, model VT-1 (Bio-Tek Instruments Inc, Vermont, USA), was used as a lung model. The lung model was fitted with an artificial rigid plastic trachea (inner diameter (i.d.) 22 mm, length 25 cm). The compliance of the lung model was varied between 20, 35 and 50 mL/cmH_2O.

Endotracheal tubes: Standard endotracheal tubes with i.d. 6, 7 and 8 mm and tracheostomy tubes with i.d. 7 and 8 mm (SIMS Portex Limited, Hythe, Kent, UK) were used during studies in the bench test and in patients.

Basic monitoring unit: An AS/3 multi-module monitor (Datex-Ohmeda Ltd, Helsinki, Finland) was used to obtain spirometric and pressure data with a sampling frequency of 20 Hz.

Spirometry: Airway pressure, volume and flow were measured at the Y-piece with a D-lite Side Stream Spirometer (Datex-Ohmeda Ltd, Helsinki, Finland) based on the principle of a Pitot tube.

Airway pressure measurements: In the lung model reference airway pressure was measured through a side-hole in the tracheal model, 2 cm beyond the tip of the tube, and in the bellows of the lung model, presenting tracheal and alveolar pressures. Different-sized, low-compliant, catheters were introduced through the endotracheal tube and used for direct measurement of tracheal pressures both in bench tests and in patients. These were filled with either air or saline and had either an end hole or a side hole. The reference pressure site and tracheal catheters were connected to standard pressure receptors (PVB Medizintechnik GmbH, Germany). Spirometry measurements provided the airway pressure at the Y-piece.

Oesophageal pressure measurements: For oesophageal pressure measurements in patients, a Salem™ stomach tube no.16, 120 cm long (Argyle ™ , Sherwood Medical Ltd., Belgium) with two lumens, diameters 3 and 0.75 mm, was used. The tube was passed through the nose into the stomach, a site identified by suction of gastric contents or auscultation while injecting air through the tube. A pressure line with a slow continuous flow of isotonic saline of 3 mL/h was connected to the narrow lumen of the stomach tube. The larger lumen was filled with water and kept so by occluding the outer end. The tube was then withdrawn slowly from the stomach into the oesophagus until the pressure curves showed maximal respiratory related pressure fluctuations and minimal pressure variations related to cardiac activity. This method of positioning the tip of the oesophageal tube was validated against the rib cage compression occlusion test, i.e. during a prolonged end-expiratory pause the rib cage is externally compressed and pressure fluctuations in the airway and oesophagus observed. These should agree within 10% to be accepted, as there is no change in volume during the test [156]. The fluid-filled catheter was also validated against a traditional oesophageal balloon catheter. In the last study the methods were combined, first positioning according to pressure variations and then the right position verified with the occlusion test.

Response time: When testing the response time of catheters used for direct measurement of tracheal pressures via the endotracheal tube lumen, a sampling frequency of 1000 Hz was accomplished by means of a bridge amplifier (Linear Technology Corporation, Milpitas, California, USA).

Flowmeter: A Calibration analyser RT-200 (Timeter Instrument Corporation, Pennsylvania, USA) was used to measure constant flow.

Data acquisition: In the first paper data were recorded on a flat-bed recorder (Multitrace 4, Lectromed, St. Oven, Jersey, Channel Islands). In the others data were sampled via an A/D converter (DI220, DATAQ instruments, Akron, Oklahoma, USA) to a portable computer. Data were analysed in a TestPoint™ application designed by the research group (Capital Equipment Corporation, Burlington, Massachusetts, USA).

Statistics

Statistical analyses were performed using Winstat software (Kalmia Company, Cambridge Massachusetts, USA). Values are given as mean ± standard error in Papers I, II, III and V. In Paper IV, a pure model study, ± standard deviation is used except in some of the bench test studies, where the deviation was so low that they were not of interest. During dynamic flow produced by ventilators both in patients and in model studies, three breaths were analysed at each ventilator setting and averaged.

A paired t-test was used to evaluate differences. Pearson's correlation coefficient was used to study relationships. Repeated measures analysis of variance was used to estimate differences in series of measurements with a Bonferroni correction when appropriate. A P-value less than 0.05 was considered statistically significant. Coefficients of variance were calculated to study the reproducibility of the monitoring methods.

Pressure vectors were compared by linear regression and the results expressed in terms of the equation of linear regression and the coefficient of regression. A best linear curve fit with the method of least squares was also performed and the slope of the curve used for comparisons.

Summary of Papers

Paper I

A simplified method for separate measurements of lung and chest wall mechanics in ventilator-treated patients

Aim

To evaluate the use of a liquid-filled, double-lumen stomach tube for measurement of oesophageal pressures (a surrogate for pleural pressure) to enable the partitioning of respiratory mechanics into its lung and chest wall components.

Methods

Pressures were measured simultaneously at the Y-piece, trachea and oesophagus. Volume and flow were measured at the Y-piece. The oesophageal-catheter was a double-lumen, liquid-filled Salem^{TM} stomach tube or a traditional oesophageal balloon catheter with a 10 cm latex balloon.

Results

After positioning the double-lumen, liquid-filled oesophageal tube in six ventilator-treated ICU patients at maximal respiratory related pressure fluctuations and minimal pressure variations related to cardiac activity, the rib cage compression occlusion test was performed and pressure fluctuations in the airway and oesophagus compared. These agreed within 10% or 0.97 ± 0.09 (Fig.2).

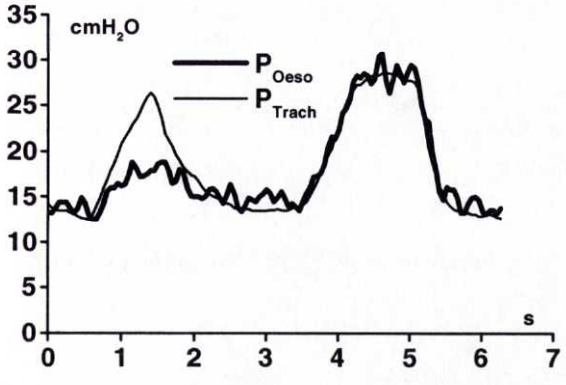


Fig. 2. *Rib compression occlusion test. After a ventilato- induced breath (left in figure) a prolonged end-expiratory pause is performed. The rib cage is then compressed manually, causing pressure fluctuations (right in figure) in the oesophagus (P_{Oeso}) and airways (P_{Trach}) that follow each other closely.*

In five ventilator-treated patients the double-lumen, liquid-filled oesophageal tube and the traditional oesophageal balloon catheter were inserted in random order and positioned with the above-described methods. The pressure fluctuations during normal respiratory treatment were 4.6 ± 0.8 cmH_2O with the liquid filled catheter and with the balloon catheter 4.4 ± 0.8 cmH_2O (ns).

In 12 patients undergoing open abdominal surgery, using VC ventilation without an end-inspiratory pause, the differential peak airway pressure was significantly higher at the Y-piece than at the trachea, 18 ±1.4 cmH_2O versus 11 ±1.2 cmH_2O ($p < 0.001$), reflecting the effect of tube resistance. With increasing tidal volume, the total respiratory system compliance increased ($p < 0.001$), the chest wall compliance increased ($p < 0.01$) and the lung compliance increased first and then decreased (ns). With increasing PEEP the total respiratory system compliance decreased ($p < 0.05$), the chest wall compliance increased slightly (ns) and the lung compliance decreased (ns). Coefficients of variance for measurements repeated 3 times at the same ventilatory settings during the measurement period were for the total respiratory system compliance 8%, for chest wall compliance 11% and for lung compliance 22%.

Conclusions

- The use of a double-lumen, liquid-filled oesophageal tube for measurement of oesophageal pressures gives similar values as the conventional oesophageal balloon catheter. It is more convenient to insert and probably available in every ICU.
- The oesophageal catheter should be positioned according to pressure variations in muscle-relaxed patients and then the correct placement verified with the rib cage compression occlusion test.
- The endotracheal tube resistance has a significant influence on measurements of peak inspiratory pressure.
- Total respiratory system compliance increased significantly with increasing tidal volumes but decreased significantly with increasing PEEP. No definitive pattern of chest wall and lung compliance was identified.
- The coefficients of variance for compliance calculations were influenced by the unstable conditions during measurements.

Paper II:

Evaluation of pressure loops based on intratracheal pressure measurements during dynamic conditions

Aim

To investigate the influence of the endotracheal tube resistance on dynamic measurements of respiratory mechanics.

Methods

In patients, endotracheal tubes with 7 mm i.d. and tracheostomy tubes with 7 and 8 mm i.d. were used. An airfilled end hole catheter with 3 mm outer diameter (o.d.) was inserted through the tube lumen for direct measurements of tracheal pressures. In the lung model, endotracheal tubes with 6 and 7 mm i.d. and a tracheostomy tube with 8 mm i.d were studied to cover the range of endotracheal tube resistances in patients. The effect on endotracheal tube resistance of inserting catheters with 2 and 3 mm o.d. inside the tube lumen was evaluated (Fig. 3).

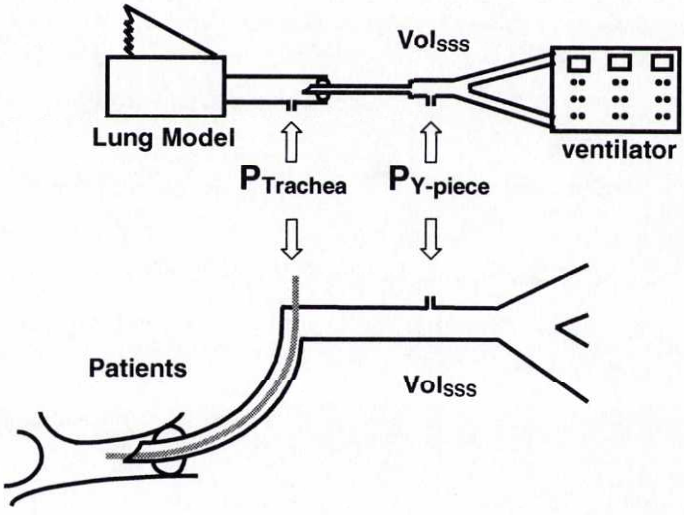


Fig. 3. *Tracheal pressures* ($P_{Trachea}$) *were measured via a side hole in the artificial trachea in the lung model but in patients via an end-hole catheter inserted through the lumen of the endotracheal tube. Airway pressures and volumes were measured simultaneously at the Y-piece with side stream spirometry* ($P_{Y\text{-}piece}$, Vol_{SSS}).

Both volume-controlled (VC) and pressure-controlled (PC) ventilation were used and the respiratory settings were varied with three values of PEEP, tidal volume, end-inspiratory pause and inspiratory time. Three different compliance values in the lung model were also used. While one feature was varied the others were kept at a basic level.

Results

Lung model: The average endotracheal tube (ETT) resistance during the constant inspiratory flow of VC ventilation at the different ventilator settings was calculated. The results in order of increasing resistance were: 8 mm i.d. tracheostomy tube + 3 mm intraluminal catheter (8 ± 0.3 cmH_2Os/L), ETT 7 mm i.d. (10 ± 0.4), ETT 7 mm i.d. + 2mm intraluminal catheter (14 ± 0.6) ETT 6 mm i.d. (16 ± 1.2) and ETT 7 mm i.d. + 3 mm intraluminal catheter (22 ± 1.2). The areas of P/V-loops originating from pressure measurements at the Y-piece and trachea at all the ventilator settings were calculated and averaged and showed a statistically significant difference at all ventilatory settings ($p < 0.001$). Y-piece P/V-loop areas increased in size with increasing resistance while the trachea P/V-loops decreased. The size of the tracheal P/V-loop areas compared to the Y-piece P/V-loop areas was 42 %, 34%, 25%, 20% and 16% in the same order as the ETT resistance increased. There was an inverse correlation between ETT resistance and Y-piece/trachea P/V-loop area ratio ($r = 0.96$).

Patients: There was a statistically significant difference at all ventilator settings between Y-piece and tracheal P/V loops ($p < 0.05$-0.001). It was easy to identify endpoints of inspiration and expiration and the formation of intrinsic PEEP. Signs of overinflation could also be observed with increasing PEEP, tidal volume and inspiratory time (fig. 4).

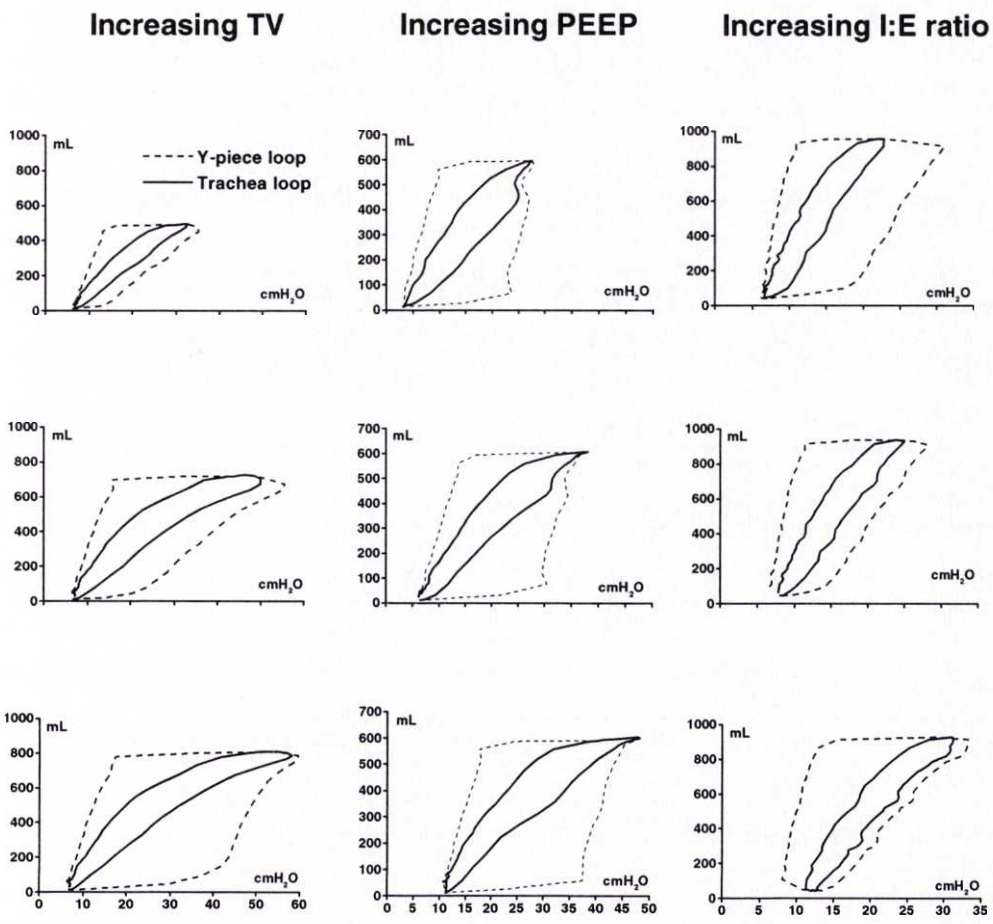


Fig. 4. *Results from three of the patients. Left column increasing tidal volume during VC ventilation. Middle column increasing PEEP during PC ventilation. Right column increasing inspiratory time during VC ventilation. The tracheal P/V-loop readily reveals endpoints of inspiration and expiration (all patients), development of overdistension (all patients) and the formation of intrinsic PEEP (patient to the right). These phenomena are not obvious in the Y-piece P/V-loop.*

Conclusions

- There is a statistically significant difference between P/V-loops originating from the Y-piece and trachea at all ventilatory settings.
- The resistance of the endotracheal tube conceals how airway pressure develops beneath the tube, in the lungs, when pressures are measured at the Y-piece.
- Y-piece airway pressure reflects mainly the high endotracheal tube resistance during inspiration and the low resistance of the ventilator outlet valve during expiration.
- Direct measured tracheal airway pressures *exclude* endotracheal tube resistance during inspiration and *include* it during expiration.
- Direct measured tracheal pressures allow easy identification of:
    1. *End points* of inspiration and expiration, even at ventilatory settings without end-inspiratory pause
    2. Development of *overdistension*
    3. Formation of *intrinsic PEEP*

Paper III

A new method for non-invasive, manoeuvre-free determination of "static" pressure-volume curves during dynamic/therapeutic mechanical ventilation

Aim

To validate the use of the dynostatic algorithm in calculating the alveolar pressure during dynamic conditions in a lung model and to evaluate its use in patients with ALI/ARDS

Methods

The dynostatic algorithm: A whole trachea P/V-loop is analysed. Pressure *(P)*, flow *($\dot{V}$)* and volume *(V)* are registered at each measurement point. The inspiratory and expiratory limbs are identified. For each point on the inspiratory *(insp)* and expiratory limbs *(exp)*, a corresponding point, at the same volume on the opposite side is identified with the help of a computer program. At each volume level (isovolume levels), there is a pair of measurement points on each limb. The alveolar/dynostatic pressure lies within the points as:

$$R_{insp} = (P_{insp} - P_{dyn}) / \dot{V}_{insp}$$

$$R_{\exp} = (P_{\exp} - P_{dyn}) / \dot{V}_{\exp}$$ *Note that the flow is negative during expiration*

Assuming that airway resistance is the same during inspiration and expiration at isovolume levels, the alveolar/dynostatic pressure can be calculated with the formula:

$$P_{dynostatic} = (P_{insp} \times \dot{V}_{\exp} - P_{\exp} \times \dot{V}_{insp}) / (\dot{V}_{\exp} - \dot{V}_{insp})$$ *(see Fig. 5)*

Lung model:

1. Directly measured alveolar pressures during dynamic conditions were compared with calculated dynostatic pressures during the same inspiratory and expiratory resistances at different ventilator settings during both VC and PC ventilation.

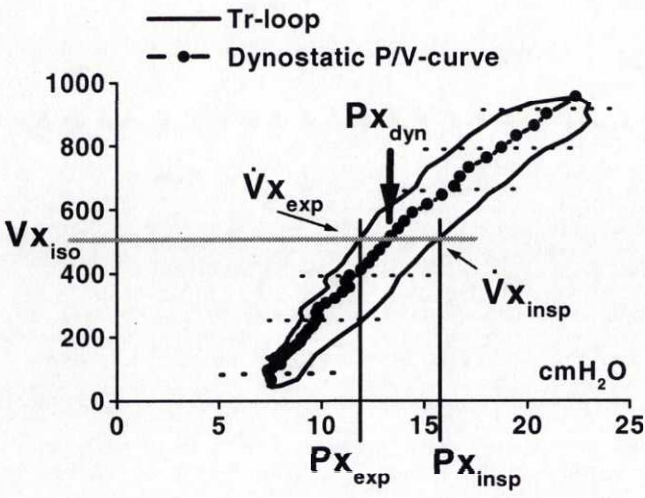


Fig. 5. *Schematic illustration of the mathematical background to the calculation of the dynostatic P/V-curve. Every point (Px_{dyn}) on the curve is calculated according to the dynostatic algorithm using pressure (P) and flow ($\dot{V}$) values at isovolume levels (Vx_{iso} indicated by the grey line and the broken lines) during inspiration and expiration.*

2. Directly measured alveolar pressures under dynamic conditions were compared with calculated dynostatic pressures at different inspiratory and expiratory resistances, which were varied in a one-way circle system in series with the lung model and trachea (fig 6). The resistance was varied in either the inspiratory or expiratory limb of the one-way circle by inserting resistance blocks with different diameters. The mean inspiratory/expiratory resistance ratios of the resistance blocks at flow velocities between 10 and 60 L/min were 4.6:1, 2.3:1, 1.4:1, 1:1, 1:1.4, 1:2.3 and 1:4.6.
3. Static alveolar pressures produced with the super syringe method were compared with calculated dynostatic pressures achieved during dynamic conditions at different compliance values in the lung model.

Patients:

The same patients as in Paper II were studied to demonstrate the clinical use of the dynostatic curve at various ventilator settings.

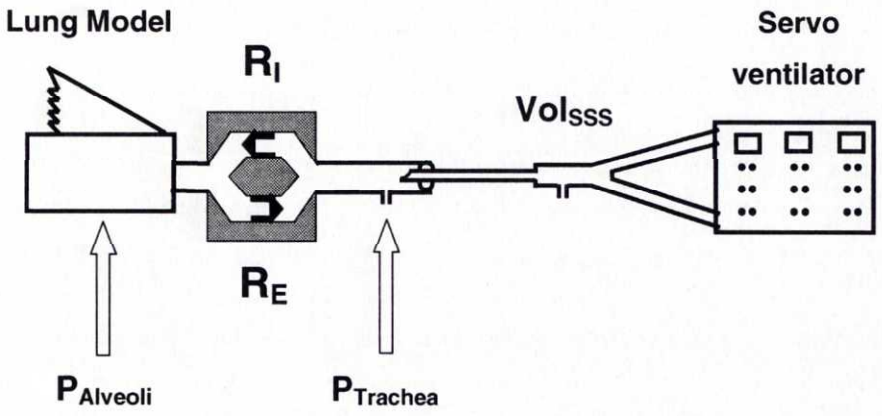


Fig. 6. *During measurements of tracheal ($P_{Trachea}$) and alveolar pressures ($P_{Alveoli}$) in the lung model, inspiratory (R_I) and expiratory resistances (R_E) were varied by inserting a one-way circle system between the artifical trachea and the lung model with different resistance blocks.*

Results

Lung model: Comparisons of *direct measured alveolar pressure* and *calculated alveolar pressure,* using the dynostatic algorithm.

1. During dynamic conditions at different ventilator settings with both VC and PC ventilation and the same inspiratory and expiratory resistances, the coefficients of regression (r^2), for comparisons of directly measured and calculated alveolar pressures were between 0.981 and 0.999. The regression equations differed very little from the line of equality, being $P_{dyn} = 0.98\ P_{alv} - 0.02$ for VC ventilation and $P_{dyn} = 0.95\ P_{alv} + 0.05$ for PC ventilation.
2. When inspiratory and expiratory resistances were varied between 2.3:1 and 1:2.3 during dynamic conditions with VC and PC ventilation and the same ventilator settings, the coefficient of regression (r^2) for comparisons of directly measured and calculated alveolar pressure remained above 0.95, the slope (α) varied from 0.8 to 1.2 and the constant (K) between –0.09 and 1.42.
3. When static and dynostatic P/V-curves were compared at different compliance in the lung model, the compliance of the static P/V-curves was 49, 35 and 20 mL/cmH_2O and that of

the corresponding dynostatic P/V-curves during VC ventilation 49, 34 and 20 and during PC ventilation 50, 34 and 20 mL/cmH_2O (fig. 7).

Patients:

No lower inflection point was seen in patients during normal ventilator treatment. Overdistension was easily detected with increasing tidal volume and PEEP but occurred successively, so an upper inflection zone would be a better description than a point. Development of intrinsic PEEP with increased inspiratory time was also easily detected. The behaviour of the dynostatic P/V-curve within the tracheal P/V-loop is dependent on the flow velocity and lies closer to the inspiratory/expiratory limb, which has a lower flow velocity (fig. 7).

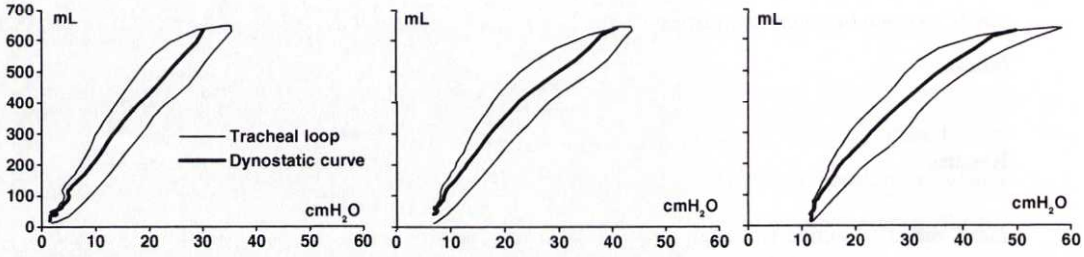


Fig. 7. *Successive increase of PEEP from 4 to 8 and 12 cmH_2O caused development overdistension. The ventilator mode is VC ventilation and the tidal volume was kept the same.*

A mathematical manipulation of the dynostatic algorithm in one of the patients revealed that on doubling the expiratory resistance in relation to the inspiratory resistance the dynostatic curve was shifted to the left (closer to the expiratory limb because of lower flow velocity) by less than 3 cmH_2O. A corresponding less than 3 cmH_2O shift to the right was seen when the inspiratory resistance was calculated at double the expiratory resistance (fig. 8).

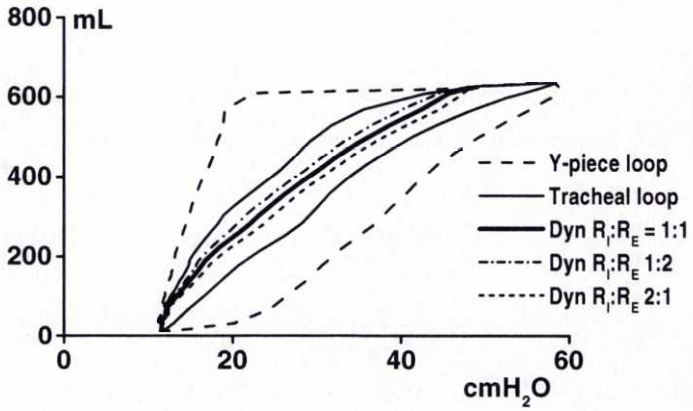


Fig. 8. *The dynostatic algorithm is based on R_I:R_E = 1:1. The figure shows the effect of mathematically manipulating the dynostatic curve assuming the R_I:R_E is either 1:2 or 2:1, creating a shift of less than 3 cmH_2O to the right and left respectively.*

Comparison of a semistatic P/V-curve, constructed from end-inspiratory plateau pressures at different tidal volumes during VC ventilation, and dynostatic P/V-curves showed a greater tendency to overdistension which the static curve did not reveal. (fig. 9).

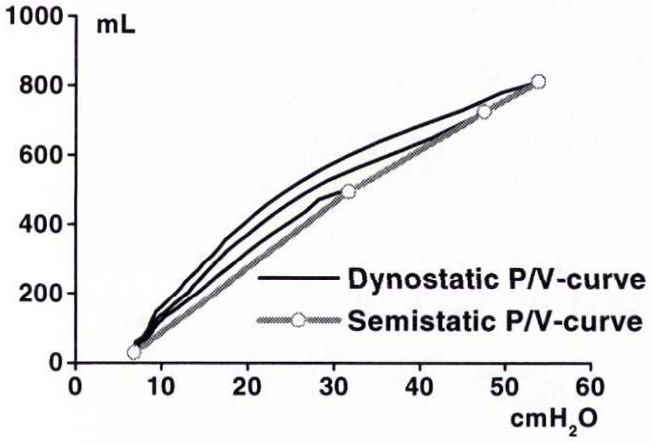


Fig. 9. *Tidal volumes were increased during VC ventilation with inspiratory time 25% and end-expiratory pause 10%. The difference in the shape of the dynostatic P/V-curves is caused by the increase in flow velocity and reveals a much greater tendency to overdistension than the semistatic P/V-curve created with end-expiratory pauses.*

Conclusions

- There was excellent agreement between calculated alveolar pressures acquired with the dynostatic method and directly measured alveolar pressures when the inspiratory and expiratory resistances were equal in a lung model.
- When the inspiratory and expiratory resistances were varied in a lung model, a difference of 2.3 times did not cause a serious deterioration of the correlation and regression between the directly measured alveolar pressure and the calculated dynostatic pressure.
- There was excellent agreement between static and dynostatic P/V-curves in a lung model.
- In patients, a lower inflection point could not be identified with the dynostatic curve during normal tidal breathing at 20 breaths/min. Overdistension and intrinsic PEEP were easily seen. Overdistension was more clearly detected than with a semistatic P/V-curve.
- The dynostatic method is capable of providing breath-to-breath analysis of alveolar pressures during dynamic conditions.

Paper IV:

Direct tracheal pressure measurements, essential for safe and accurate dynamic monitoring of respiratory mechanics. A laboratory study.

Aim

To investigate factors that may influence the resistance between the Y-piece and trachea causing difficulties in interpreting values obtained during dynamic conditions at the Y-piece or ventilator, and to evaluate a clinical method for direct measurement of tracheal pressures to overcome these problems, i.e. by introducing a catheter through the lumen of the endotracheal tube.

Method

Influences on tube resistance: The effect on the pressure drop between the Y-piece and trachea of connecting a swivel connector and a humidification device to an endotracheal tube with 7 mm i.d. was studied during constant flow, between 10 and 100 L/min, in both the inspiratory and expiratory direction. The effect of secretions inside the endotracheal lumen on resistance was investigated during dynamic conditions by injecting 1 and 2 mL of gel into an endotracheal tube with an i.d. of 6, 7 and 8 mm (fig. 10).

Intraluminal catheters for direct measurement of tracheal pressures: A catheter with o.d. 2 mm and i.d. 0.9 mm was used for the studies. The catheter response time was studied by measuring the pressure fall after bursting a balloon and comparing it with a control pressure in the trachea. The effect of the position of an end-hole or side-hole catheter's tip in relation to the tip of the endotracheal tube was investigated during constant flow between 10 and 100 L/min in both the inspiratory and expiratory direction. The catheter tip was positioned 4 and 2 cm below the endotracheal tube tip, at the tip and 2 and 4 cm above the tip (fig.10).

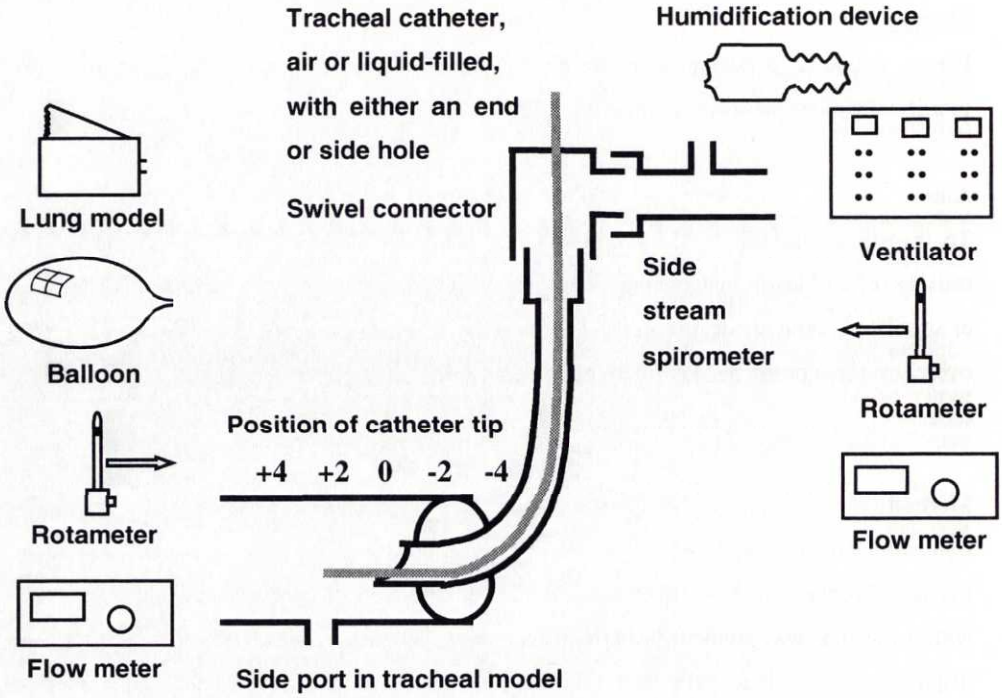


Fig. 10. *The set-up used during the experiments. The pressure difference between the trachea and Y-piece was measured with different connectors and gel injected in the tube lumen. A tracheal catheter was inserted through the tube lumen with either an end-hole or a side-hole and either air or liquid-filled and studied regarding response time and position. The airway pressures measured with the tracheal catheter were compared with a reference pressure measured through the side hole in the tracheal model.*

Results

Influences on endotracheal tube resistance:

1. *Influence of different connectors:* The mean pressure difference between the Y-piece and trachea increased 15 ± 10 % (over a flow range of 10 – 100 L/min) as the swivel connector and humidification device respectively were connected to the endotracheal tube. The mean pressure difference over the endotracheal tube and connectors was 32 ± 19% greater during flow in the expiratory compared to the inspiratory direction.

2. *Influence of secretions on resistance:* At a constant inspiratory flow of 39.4 ± 0.5 L/min, the resistance of all the endotracheal tubes increased significantly ($p < 0.05$) when 1 and 2 mL of gel were injected into their lumens. Intrinsic PEEP developed with a 6 mm i.d. tube with 2 mL of gel in the lumen. The pressure drop over a 7 mm i.d. endotracheal tube at a flow of 40 L/min was 6.5 ± 0.5 cmH_2O without gel and 14.4 ± 1.7 and 33 ± 4.4 cmH_2O with 1 and 2 mL of gel respectively.
3. *Calculation of tracheal pressures from Y-piece pressure measurements:* It was not possible to calculate the tracheal pressures from Y-piece pressures using a published algorithm and constants [149] for this purpose after injection of gel into the tube lumen (fig 11).

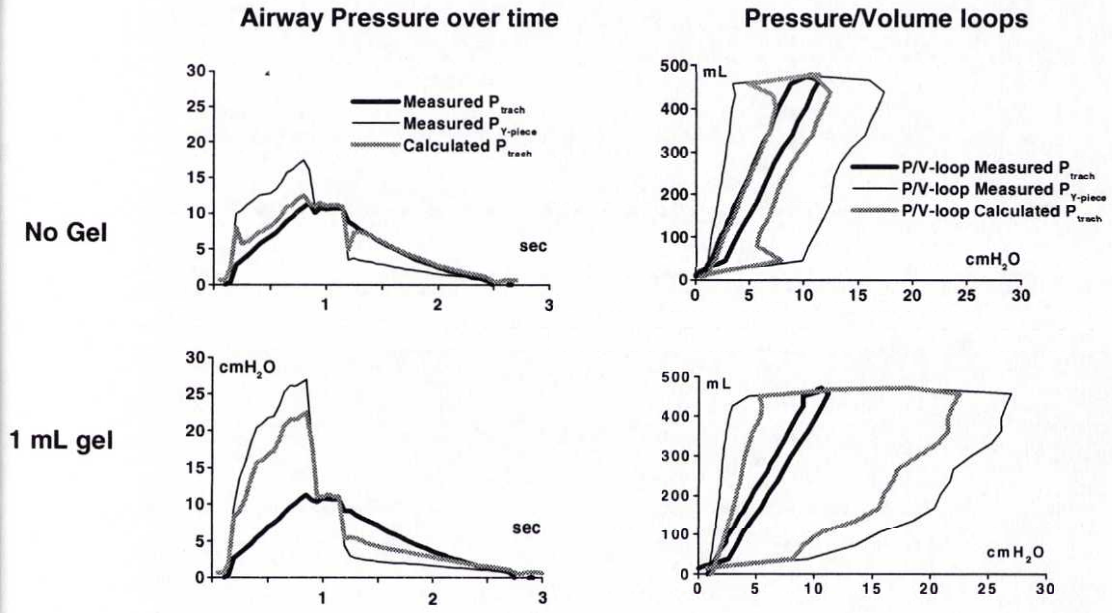


Fig. 11. *The right column shows the directly measured tracheal pressure (thick black line) and the calculated tracheal pressure (grey) from pressure (thin black line) and flow measurements at the Y-piece according to Guttmann [149] in an ETT with i.d. 7 mm without and with 1 mL of gel deposited in the tube. The corresponding P/V-loops are shown in the column to the right. With 1 mL of gel inside the tube lumen, the calculated tracheal pressure showed a marked false increase during inspiration and a false decrease during expiration.*

Direct measurements of tracheal pressures

1. *Catheter response time:* There was no delay between the catheter and the reference pressure measured in the tracheal model. The 10 – 90% response time of the different catheters was 4 msec for the air-filled catheters and 12 msec for the liquid-filled ones. There was no difference between catheters with an end hole and a side hole.
2. *Influence of catheter position:* Pressure measurements with an end-hole catheter were less sensitive to position than those with a side-hole catheter. The pressure difference between an end-hole catheter positioned 2 cm above the endotracheal tube tip and 4 cm below the tip was less than 1.5 cm H_2O (fig. 13).

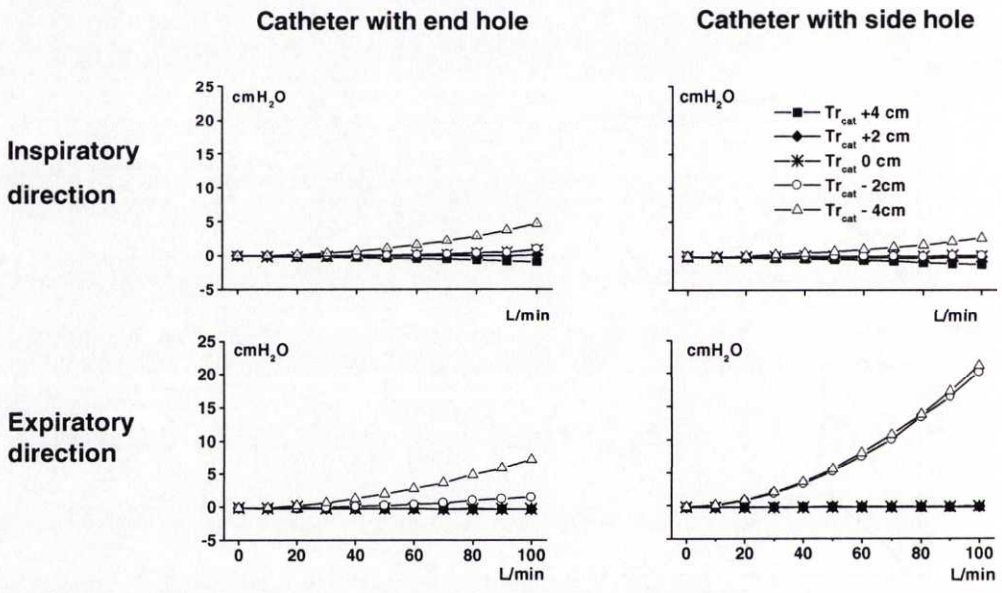


Fig. 13. *Pressure differences between reference pressure in the tracheal model and a tracheal catheter inserted through the ETT with either an end hole or a side hole during constant flow in either the inspiratory or expiratory direction. The tracheal catheters were positioned 4 and 2 cm below the tip (+4 and +2, solid symbols) of the endotracheal tube, at the tip of the tube (0, star symbol) and 2 and 4 cm above the tube tip (-2 and -4, open symbols) inside the tube lumen. The range in pressure differences between the end-hole catheter and the reference pressure is very small from 2 cm above the ETT tip to 4 cm distal to it (-0.07 ± 0.37 cmH_2O, range –0.9 – 1.5 cmH_2O).*

The difference between end and side-hole catheters is explained by their difference in measuring kinetic and static airway pressures. When air flow passes a central constriction as during expiration (trachea to tube), static energy will be converted to kinetic energy according to the increase in flow velocity. This will cause a side-hole catheter, which only measures static energy, to show a larger pressure drop than an end-hole catheter, which measures static plus kinetic pressures during expiration.

Conclusions

- Different tube connections and secretions inside the tube lumen cause variances in the endotracheal tube resistance. The influence of secretions is much greater than that of connections.
- Calculation of tracheal pressures from pressure measurements at the Y-piece may lead to considerable errors as the flow profile may be affected by connectors and secretions of the endotracheal tube.
- Direct tracheal airway pressure measurements can be accomplished with high precision by simple means and can be used in combination with Y-piece pressures to detect tube obstruction.
- Direct tracheal pressure measurements can be performed with an end-hole catheter, either air or liquid-filled, positioned from 2 cm above to 2 cm below the tip of the endotracheal tube.

Paper V

Manoeuvre-free, on-line, "static" respiratory system, lung and chest wall mechanics during on-going ventilator treatment

Aim

To evaluate the use of the dynostatic algorithm to describe changes in respiratory mechanics in patients with ALI and ARDS at different ventilator settings during on-going ventilator treatment and to validate its reproducibility.

Methods:

Ten patients with ALI and ARDS were studied. The same ventilator setting during both VC and PC ventilation was repeated three times during the measurement period to validate the reproducibility of the measurements (VC: Tidal volume 8 mL/kg, PEEP 8 cmH_2O, inspiratory time 25%, end-inspiratory pause 10%, 20 breaths/min. PC: Tidal volume 8 mL/kg, PEEP 8 cmH_2O, inspiratory time 33%, no end-inspiratory pause, 20 breaths/min). Respiratory mechanics were studied by successively increasing tidal volume (4, 8 and 12 mL/kg) and PEEP (4, 8 and 12 cmH_2O). In four of the patients respiratory mechanics were studied during low flow inflation. i.e. VC ventilation, 50% inspiratory time, respiratory rate 6/min, TV between 1000 and 1500 mL (giving a flow rate of 12 –18 L/min) at zero end-expiratory pressure.

Calculation of respiratory mechanics

The total respiratory system: A complete dynamic tracheal P/V-loop was analysed using the dynostatic algorithm, creating a dynostatic P/V-curve representing alveolar pressure. This curve was then used for calculation of compliance in two ways: A *single-value compliance* (SVC) for the entire breathing cycle was calculated by best linear fit of the whole dynostatic P/V-curve using the least square method. The slope of the best linear fit curve provided the compliance value. A *volume-dependent compliance* (VDC) for the initial, middle and final parts of the dynostatic P/V-curve was determined by analysis of alveolar pressure differences at 5-15%, 45-55% and 85-95% of the tidal volume (fig. 14).

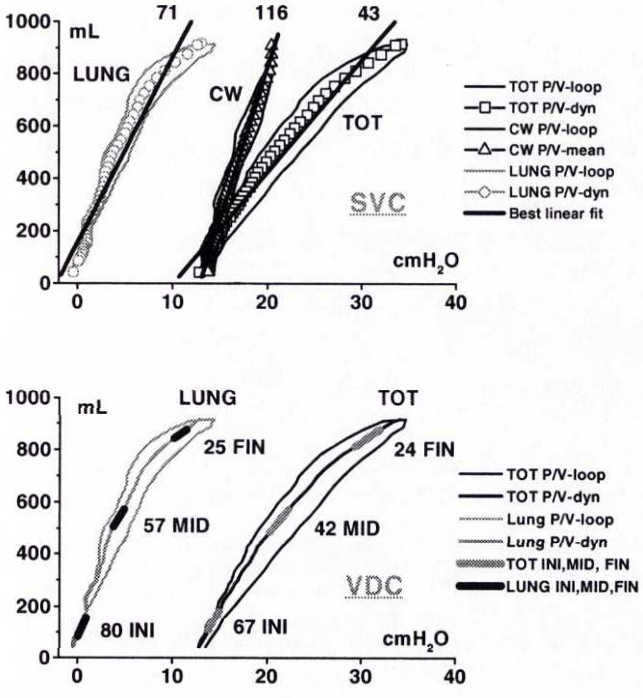


Fig. 14. *The upper figure shows an example of single value compliance (SVC) for the whole breath, for the total respiratory system (TOT), the chest wall (CW) and the lung (LUNG) calculated as the best linear fit of the P/V-curves using the least square method. The slope of the best linear fit curve gives the compliance value (mL/cmH_2O) shown by the figures above each curve. The lower figure shows an example of initial (INI), middle (MID) and final (FIN) volume-dependent compliance (VDC) within the breath for the total respiratory system (TOT) and the lung (LUNG). The corresponding compliance values are also shown. The same breath is analysed in both figures.*

The chest wall: The oesophageal pressure curve was smoothed over sections of 8 measurement points to decrease pressure variations caused by heart oscillations. As we did not observe any hysteresis in the oesophageal P/V-loop, a mean value of the inspiratory and expiratory limbs at isovolume levels during inspiration and expiration was calculated, producing a *mean chest wall P/V-curve*. To obtain a *single compliance value* for the chest wall compliance, a best linear fit of this curve using the least square method was calculated. As the pressure changes of the mean chest wall P/V-curve were less than 4 cmH_2O within the breath in all of the patients, and because it was susceptible to cardiac oscillations, it was not considered of value to calculate volume-dependent compliance values for this P/V-curve (fig. 14).

The lung: A lung pressure curve was calculated as the pressure differences between the tracheal and the smoothed oesophageal pressure curves and displayed as a lung P/V-loop. This lung P/V-loop was then used for calculation of a lung dynostatic P/V-curve using the dynostatic algorithm. This dynostatic lung P/V-curve was then treated in the same manner as described above; a best linear fit curve using the least square method was calculated to get a *single compliance value* for the whole breath and the *volume-dependent compliance* values of the initial, middle and final parts of the tidal volume were also calculated (fig. 14).

Results

Single-value compliance:

The reproducibility of SVC was excellent, as shown by coefficients of variance of 3.1 - 6.6%. Both total respiratory system and lung compliance decreased significantly ($p < 0.05 - 0.01$) with increasing PEEP and tidal volume while the changes in chest wall compliance did not change (ns). Large differences in individual responses were noted. Chest wall compliance was approximately twice as high as the lung compliance, 159 ± 6 vs. 80 ± 5 mL/cmH_2O during VC ventilation and 157 ± 7 vs. 74 ± 4 mL/cmH_2O during PC ventilation ($p < 0.001$) at all ventilator settings.

Volume-dependent compliance

1. Total respiratory system: The reproducibility of volume-dependent compliance measurements was satisfactory as shown by coefficients of variance of 5.1 – 9.2%. At all ventilator settings, the total respiratory system compliance was highest at the initial segment and decreased successively through the middle and final parts of the dynostatic P/V-curve ($p < 0.01 - 0.001$). This successive decrease in compliance became more prominent with increasing PEEP and increasing tidal volume. A lower inflection point above 4 cmH_2O was not detected in any of the patients during normal ventilation and there was no definitive point of overinflation but a gradual decrease in compliance.

2. The lung: The coefficients of variance for the lung volume-dependent compliance were higher than for the total curve (8.7 – 18%). There was a statistically significant successive decrease of the volume-dependent compliance from the initial segment through the middle and final parts of the lung dynostatic P/V-curve at all ventilator settings ($p < 0.05 - 0.001$).

There was also a successive decrease in compliance in the final and middle segments with increasing PEEP and tidal volume but not as prominent as in the total dynostatic P/V-curve.

Respiratory mechanics during low flow inflation

Lower inflection "points" were detected in three, and an upper inflection "point" in one, of four patients. However, they were positioned at different levels in the dynostatic P/V-curve and the inspiratory limb of the tracheal P/V-loop. The low flow inflation method, based only on the inspiratory limb of the tracheal P/V-loop, is subject to errors because of the pressure drop from the trachea to the alveoli. In contrast the dynostatic algorithm utilises the whole tracheal P/V-loop to calculate the dynostatic P/V-curve. Due to low inspiratory flow, the pressure increase is very slow during the start of inspiration giving ample time for the alveoli to collapse, possibly explaining the difference between respiratory mechanics during normal tidal breathing and low flow inflation (fig. 15).

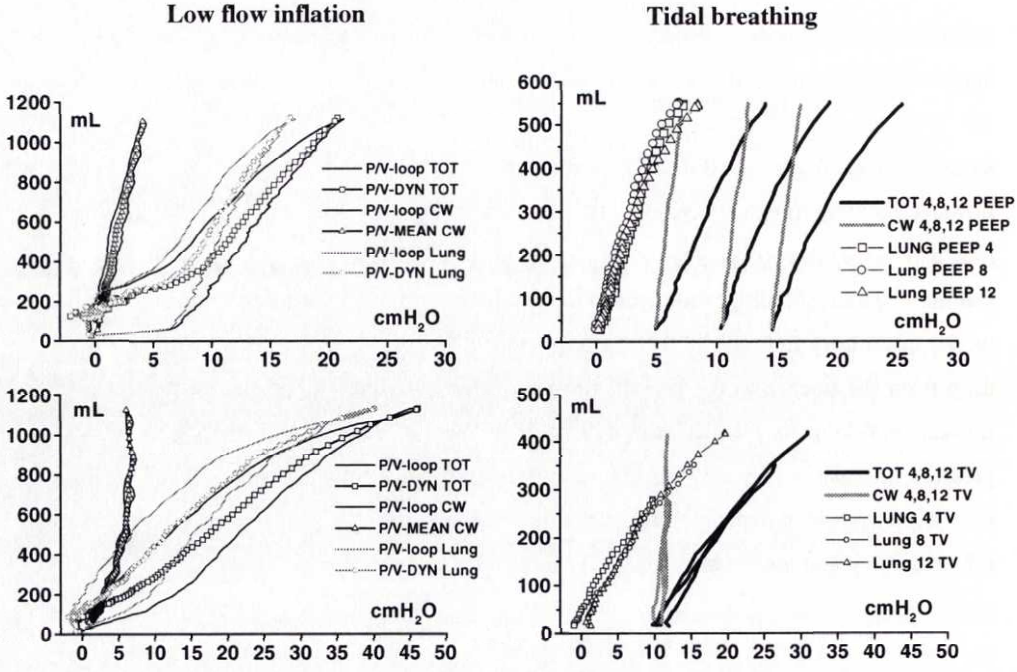


Fig 15. *The left hand column shows development of respiratory mechanics in two patients during low flow inflation. Signs of lower inflection "points" are evident at different sites in the total respiratory system dynostatic P/V-curve* (P/V-DYN TOT) *and the inspiratory limb of the tracheal P/V-loop. The P/V-curves of the chest wall* (P/V-MEAN CW) *and lung* (P/V-DYN Lung) *are also shown. In the lower figure, the lower inflection point of the total respiratory system P/V-dynostatic curve is due to a lower inflection in the chest wall, which is not seen in the lung. In the right hand column respiratory mechanics during normal tidal breathing in the same two patients are shown, displaying the P/V-curves for the total respiratory system* (TOT), *chest wall* (CW) *and lung* (Lung). *The upper figure during increasing PEEP (4, 8 and 12 cmH_2O) and the lower during increasing tidal volume (TV 4, 8 and 12 mL/kg). Both figures reveal the successive decrease of volume-dependent compliance in the total respiratory system and lung dynostatic P/V-curves within each breath and the enhancement of this phenomenon with increasing PEEP and tidal volums.*

Conclusions

- The monitoring methods presented allow partitioning of total respiratory system mechanics into their lung and chest wall components and reveal changes in compliance within each breath, on-line, during normal ventilator therapy.
- Low coefficients of variance during repeated measurements at the same ventilator settings indicate a good accuracy of the monitoring method.
- Single-value compliance for the entire breath, using the least square method to obtain a best linear fit of the dynostatic P/V-curve, is a valid method of evaluating respiratory mechanics in a simplified manner.
- Volume-dependent compliance revealed a statistically significant successive decrease in compliance from the initial segment through the middle and final parts in both the total respiratory system and the lung.
- No lower inflection was detected in the dynostatic P/V-curves during normal tidal breathing with a respiratory rate of 20.
- A lower inflection appeared during low flow inflation, indicating the time dependency of respiratory mechanics.
- Because of the high individual variation in respiratory mechanics, which can reflect both the underlying pathology and the different stages of the disease, all patients with ALI/ARDS should be monitored thoroughly during the course of their disease to optimise ventilator settings and avoid ventilator-induced lung injury.

Discussion

The studies presented have demonstrated the possibility of utilising common equipment to monitor respiratory mechanics, on-line, without interrupting or altering the ventilator treatment. The patient's response to different ventilator settings can be followed on-line and the total respiratory system partitioned into its lung and chest wall components. Such a system has a great potential as an aid in the clinical decision process of choosing the most appropriate ventilator settings to individualise treatment and minimise the risk of producing ventilator-induced lung injury.

Airway Pressure Measurements

About two-thirds of the resistance between the Y-piece and alveoli is caused by the endotracheal tube. This will not have any effect on airway pressure measurements during static conditions, but static methods of measuring P/V-curves are seldom applied clinically. During dynamic conditions, airway pressures measured at the Y-piece will be distorted by the resistance of the endotracheal tube. All monitoring of dynamic respiratory mechanics should therefore be based on tracheal airway pressures as they will exclude endotracheal tube resistance during inspiration and include it during expiration. Two ways have been proposed to accomplish this, *calculation of tracheal pressures* by using pressure values at the Y-piece and known resistance factors of the endotracheal tube [149] and *direct measurement of tracheal pressures* by introducing a pressure line through the lumen of the endotrachel tube [150].

A group led by Guttmann has advocated calculating tracheal pressures continuously for the purpose of compensating for the endotracheal tube resistance during ventilator treatment using coefficients measured in vitro for calculation of tube resistance [149]. This method has also been used with the aim of monitoring respiratory mechanics [157]. However, not only the endotracheal tube will affect airway pressure measured at the Y-piece or ventilator. It will also be influenced by different tube connections and highly affected by secretions inside the tube lumen. Changes in the position or angulation of the distal endotracheal tube may also

cause profound changes in its resistance [158]. All this makes it difficult, if not impossible, to calculate endotracheal tube resistance reliably from pressure measurements at the Y-piece and implies that direct measurement of tracheal pressures is necessary to obtain correct values. However, this necessitates insertion of a pressure line through the lumen of the endotracheal tube and positioning its end close to the tip of the tube, which has certain technical implications.

Theoretically, a side-hole catheter has been preferred as it will measure static pressure in all circumstances. Navalesi [150] evaluated the use of a side-hole catheter for this purpose and found a large difference when the catheter tip was positioned above the tip of the endotracheal tube compared to below it, or an 8% overestimation during inspiration and 41% underestimation during expiration. This is due to the fact that when flow passes a central constriction, as during expiration (trachea to tube), static energy will be converted to kinetic energy according to the increase in flow velocity, causing a side-hole catheter to measure a lower airway pressure when positioned inside the tube (the mean velocity will be about ten times higher in an ETT with i.d. 7 mm than in a trachea with i.d. 22 mm). The pressure difference between trachea and Y-piece will therefore seem less and tube resistance will be underestimated.

End-hole catheters have been used to some extent for direct measurement of tracheal airway pressures for research [131] but have not been evaluated as extensively as side-hole catheters. Holst [159] reported less than 3% difference in pressure values between end-hole and side-hole catheters when positioned below the tip of a tracheostomy tube during sinusoidal flow in a lung model, however.

We have used end hole catheters in our studies as they are easier to obtain than side hole catheters. They are also easier to flush clean than side hole catheters if obstructed by secretions. The influence of the 3 and 2 mm o.d. catheters on endotracheal tube resistance in corresponding tubes used in the patients was measured in a model and confirmed that a 2 mm o.d. and 0.9 mm i.d. catheter had sufficient response time for airway pressure measurements both when air or liquid filled.

We found end-hole and side-hole catheters to give similar pressure values when positioned at or below the tip of the endotracheal tube. However, when inside the tube lumen and during

expiration the end-hole catheter gave pressure values closer to a reference value in the trachea, than a side-hole catheter. The difference was less than 1.5 cmH_2O at flow values of 10 – 100 L/min. The reason for this is that an end-hole catheter will measure static pressure minus dynamic pressure during inspiration but static pressure plus kinetic pressure during expiration. Tracheal pressure can therefore be measured accurately by using an end-hole catheter with its tip placed 2 cm above or below the tip of the endotracheal tube.

The method presented here to measure tracheal pressures directly can certainly be improved and it would be a great advantage if a lumen in the wall of the endotracheal tube could allow for direct measurements or insertion of a pressure line.

The use of Dynamic Pressure/Volume Loops

The combination of volume and direct tracheal pressure measurements to display P/V-loops gives valuable information about respiratory mechanics and enables visual identification of their features. Directly measured tracheal pressures will provide correct end-inspiratory and end-expiratory pressures, irrespective of the ventilatory mode, enabling correct calculations of conventional single-value compliance without end-inspiratory and end-expiratory pauses. A prolonged end-expiratory pause to measure intrinsic PEEP is therefore unnecessary, as are end-inspiratory pauses, which are hardly utilised except during VC ventilation. During PC ventilation, the end-inspiratory flow will not be sufficiently low to allow determination of static pressures. Further, dynamic P/V-loops based on tracheal pressure measurements will also reveal the development of overdistension within the breath independent of the ventilatory mode.

P/V-loops based on Y-piece pressure measurements mainly reflect the endotracheal tube resistance during inspiration and the low resistance of the outlet valve in the respirator during expiration. In our studies, we mimicked the effect of secretions inside the endotracheal tube lumen by injecting clinically relevant amounts of gel into it. P/V-loops based on Y-piece pressures measurements became highly distorted and calculation of tracheal pressures using the algorithm and coefficients suggested by the Guttmann group [149] became erroneous and

were much more similar to the Y-piece pressures than the directly measured tracheal pressures.

Just by measuring tracheal pressures, instead of Y-piece pressures, a major improvement in monitoring of respiratory mechanics is achieved and an important step towards alveolar pressures is taken.

Calculation of Alveolar Pressure – the Dynostatic Algorithm

The respiratory system is undisputedly a dynamic system. However, static or semistatic methods have been considered the most appropriate way to describe its behaviour even though the dependence of respiratory mechanics on volume, flow and frequency has been well established [118-123,151]. However, static measurement methods have seldom been used clinically because of their slowness and technical complexity. It therefore seems reasonable that dynamic measurements might be of more value than static ones. The term "dynostatic pressure" is used as a description of what static measurements have only been able to identify before, namely the alveolar pressure, but during dynamic conditions.

The dynostatic algorithm was developed to calculate alveolar P/V-curves and enable visualisation of them on-line. It is based on the assumption that at isovolume levels during inspiration and expiration the inspiratory and expiratory resistances are equal [160]. Isovolume planes of inspiration and expiration are created at all sampling points during a breathing cycle, creating pairs of points on the inspiratory and expiratory limbs, holding information on flow and tracheal pressure, beside the volume, at each point. For each isovolume plane, the alveolar pressure is calculated according to the dynostatic algorithm: $P_{dynostatic} = (P_{insp} \times \dot{V}_{\exp} - P_{\exp} \times \dot{V}_{insp}) / (\dot{V}_{\exp} - \dot{V}_{insp})$. All the isovolume planes provide one point and together they create the dynostatic alveolar P/V-curve.

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The most important question concerning the dynostatic algorithm is the assumption of equal resistance at isovolume values during inspiration and expiration. There are various methods of measuring/calculating airway resistance but no consensus as to which one reflects the "true" situation in the respiratory system most accurately. Studies using a method based on rapid

occlusion at mid-inspiratory and mid-expiratory volumes differ between inspiratory and expiratory resistances at an isovolume level. They have shown that in healthy patients and in patients with ARDS the values of inspiratory and expiratory resistance are almost identical, only higher in ARDS patients. In patients with chronic obstructive pulmonary disease, the expiratory resistance was 2.5 times higher than the inspiratory resistance [131,132].

Evaluation of the performance of the dynostatic algorithm at different inspiratory and expiratory resistances in a lung model verified that at inspiratory/expiratory resistance ratios between 2.3:1 and 1:2.3 the algorithm calculated alveolar pressures highly satisfactorily [160]. These resistance ratios are well above the ratios that healthy individuals and ARDS patients had and close to the ratio in COPD patients. If a reliable method of calculating the volume-dependent airway resistance becomes available, a correction factor might easily be included in the dynostatic algorithm.

The dynostatic algorithm provides the possibility of viewing the development of the dynostatic alveolar P/V-curve on-line, during on-going ventilator treatment, and even following how it changes instantaneously with changes in ventilator settings.

The dynostatic alveolar P/V-curve describes the behaviour of the respiratory system during on-going ventilator treatment and therefore not only represents the compliance of the respiratory system but is also influenced by its inhomogeneities and viscoelastic components, which depend on flow, respiratory rate and volume [119,120,122].

In contrast to this, static or semistatic alveolar P/V-curves represent the behaviour of the respiratory system at zero or continuous low flow, a state that is never encountered during normal breathing or ventilator treatment. This information is then used to predict the behaviour of the respiratory system during dynamic conditions. However, it is not clear what information such data provides [113].

It is therefore probably not appropriate to compare measurements acquired during on-going ventilator treatment in patients with the dynostatic method with static/semistatic methods obtained during a state of no flow/low flow as they will be measuring a dynamic system under different conditions.

Partitioning of the Respiratory System – the Chest Wall and Lung

In spite of the fact that valuable information about respiratory mechanics can be obtained by separating lung and chest wall mechanics, such measurements are rare in clinical practice [110]. This is probably due to problems encountered in measuring pleural pressure, which is difficult to obtain in patients [161], or its surrogate, oesophageal pressure, when using the conventional method of a balloon catheter. The correspondence between pleural pressure and oesophageal pressure has been debated through the years, especially measurements in the supine position, which will be influenced by the weight of the mediastinal structures on the oesophagus [162-168]. It is generally accepted, however, that even if the oesophageal pressure might be overestimated in the supine position, a correctly positioned catheter will reflect intrathoracic pressure changes appropriately [169].

The conventional method of measuring oesophageal pressure is by introducing a 10 cm long balloon with a circumference of 1 cm, sealed over a thin catheter, into the mid part of the oesophagus and filling it with 0.5 to 1 mL of air [169]. Correct positioning is evaluated by measuring airway and oesophageal deflections simultaneously during an inspiratory effort against an occluded airway [156]. The use of balloon catheters has certain disadvantages. The introduction and manipulation of a balloon catheter in the unconscious and muscle-relaxed patient is difficult but has been partly solved by attaching the balloon to a normal stomach tube [170] or providing a protecting tube around the balloon catheter during insertion [145]. The pressure measurements may differ in vitro and in vivo and the amount of inflated air may have an effect on pressure measurements, the balloon may cause contractions of the oesophageal wall, leading to artefacts, and the adequate balloon characteristics are still debated [171,172]. Although the balloon catheter is 10 cm long, it does not measure "average" pressure over its length as the air bubble will migrate to the area were the pressure is lowest and thus only measure pressure over a short section in the oesophagus [173]. An advantage of the air-filled balloon catheter is that it provides relative pressure values directly and does not require positioning of the pressure receptor at zero level, i.e. the same height as the catheter tip. However, the balloon catheter has never gained popularity in the intensive care unit.

Fluid-filled catheters have been used both in adults and in infants to measure oesophageal pressure but have never gained widespread acceptance [10,161,174]. A disadvantage of fluid-filled catheters is that it can be difficult to obtain relative pressure values because of hydrostatic factors requiring the pressure receptor to be at the same height as the catheter tip. Fluid-filled catheters will also show larger artefacts from cardiac oscillations as they do not have the same damping mechanisms as balloon catheters. An advantage is that their response time is inherently high [169].

We have improved the liquid-filled catheter methodology by using a liquid-filled double-lumen stomach tube (Salem^{TM}) to measure the oesophageal pressure through its narrower lumen. This type of catheter is easy to insert, cheap and probably available in every intensive care unit. It allows pressure measurements over only a small section of the oesophagus but such measurements have been proved to give reliable results [175,176].

As a dynamic occlusion test to verify the position of the oesophageal catheter is not possible in muscle-relaxed patients, we positioned the catheter in the oesophagus where the pressure curve showed maximal respiratory-related pressure fluctuations and minimal pressure variations related to cardiac activity, as has been described previously [173,176]. We then learned about the rib cage compression occlusion test to verify the position of the oesophageal catheter which has been used in humans and animals [145,177] and been compared with the dynamic occlusion test [178]. We compared the pressure fluctuation method and the rib cage compression occlusion test to position the oesophageal catheter and found good agreement. With these positioning methods, there is no need to disconnect the patient from the ventilator or change the PEEP level the patient is treated with. We also compared the fluid-filled, double-lumen stomach tube to with an oesophageal balloon catheter and found them of equal value.

In Paper I we studied patients during an open abdominal operation. Repeated measurements were performed at the same ventilator settings on three occasions. The resulting coefficients of variation were fairly high 8, 11 and 26 % for the total respiratory system, chest wall and lung compliance respectively. The open abdominal cavity and on-going surgery influenced the compliance values obtained and might have led to variations in pressure measurements. In Paper V studies were performed on ventilator-treated ICU patients with the oesophageal catheter positioned first according to pressure fluctuations and then its position verified by the

rib cage compression occlusion test. Here the mean corresponding coefficients of variance at all ventilator settings were considerably lower, 3.4, 5.4 and 5.7 % for the total respiratory system, chest wall and lung compliance respectively, indicating a high accuracy and reproducibility of the measurement methods.

Integration of Monitoring Methods - On-line Respiratory Mechanics of the Total Respiratory System, Chest Wall and Lung

The monitoring methods presented in this thesis, i.e. calculation of dynostatic P/V-curves and the simplified method of monitoring oesophageal pressures, were combined to study respiratory mechanics in patients with ALI/ARDS. This enabled on-line monitoring of the total respiratory system compliance and its chest wall and lung components within every breath.

The results are expressed as *single-value compliance* for the whole breath, calculated as the best linear fit using the least square method of the P/V-curves, and as *volume-dependent compliance* for the total respiratory system and lung separating the compliance of each breath into initial (5-15% of tidal volume), middle (45-55% of tidal volume) and final (85-95% of tidal volume) compliance values for the total respiratory system and lung. Only single-value compliance was calculated for the chest wall as oesophageal pressure variations were low and a subject to artefacts caused by cardiac oscillations.

Using these methods, large individual variations in this group of patients were detected, both in compliance values and in responses to different ventilator settings. The accuracy of the measurement methods was verified by low coefficients of variance in both single-value and volume-dependent compliance values during repeated measurements at the same ventilator settings.

Single-value compliance was presented as an attempt to create a more accurate analogue to conventional compliance, which is only calculated between endpoints of inspiration and expiration without considering the development of compliance between them. This method showed the same development as volume-dependent compliance, i.e. a statistically significant

successive decrease in compliance of the total respiratory system and lung with increasing PEEP and tidal volume. Changes in chest wall compliance were not significant but its values were approximately twice as high as lung compliance. Chest wall compliance thus plays a minor role when lung compliance is low, which will become more prominent in later phases of ARDS. The transmission of airway pressure to the pleural space will also decrease with decreasing lung compliance, causing the chest wall compliance to be overestimated [179].

Volume-dependent compliance describes the development of compliance within the breath. No lower inflection point was detected during normal tidal breathing in any of the patients included in the studies. There was a statistically significant successive decrease in compliance from the initial segment through the middle and final parts which came more prominent with increasing PEEP and tidal volume indicating an increase in overdistension .

Similar results were observed in 8 out of 14 patients by Mols et al [157], who used the recently introduced SLICE method [180], for volume-dependent compliance values, obtained during dynamic measurements. He also showed a large variance between patient values. The SLICE method is based on an enhanced linear multiregression analysis.

Dynamic versus Static/Semistatic Measurements of Alveolar Pressure

Static/semistatic methods do not reflect the "only true" pressure/volume relationship in the respiratory system as their results will be influenced by the volume history and recruitment [131,147]. They probably only describe the behaviour of the respiratory system during the state of no flow/low flow at the time the measurements are performed.

In contrast to this, the dynostatic alveolar P/V-curve represents the behaviour of the respiratory system during on-going ventilator treatment and will reflect the influences of volume, flow and time dependence of the respiratory system [119,120,122].

No lower inflection point in the dynstatic P/V-curve was identified in any of the patients studied during normal tidal breathing, at a frequency of 20 breaths/min. However, during low flow inflation lower inflection points were detected in the dynostatic P/V-curve in three of

four patients tested. The slow rise in pressure during low flow inspiration gives ample time for the alveoli to collapse but this might be hindered during normal tidal breathing because of the short time between end-expiration and start-inspiration [181]. The lower inflection point might thus be an artefact due to the measurement technique itself, i.e. low flow inflation.

In a recent animal study, low flow inflation was used to identify respiratory mechanics and measurements performed at different PEEP levels. The authors found no correlation between oxygen transport and respiratory mechanics (i.e. a lower inflection point and static compliance) and concluded that there was no PEEP value that was optimal with respect to ideal mechanical stress and oxygen delivery [67]. Identification of a lower inflection point with static methods is therefore no guarantee for optimal ventilator settings and dynamic parameters might therefore be a more appropriate guideline for setting the ventilator.

The effect of PEEP is often unpredictable in individual patients and depends on a variety of factors that are poorly understood and determination of the optimal PEEP requires careful ventilatory and hemodynamic evaluation [68]. This emphasises further the need for continuous monitoring of respiratory mechanics to follow the interaction between ventilation and circulation in critically ill patients as the respiratory mechanics vary markedly between patients and change over time, as does circulation.

The need to monitor circulation continuously has been understood and the term hemodynamics is well known. In this thesis, a new term for the continuous monitoring of ventilation, based on the monitoring methods presented, is proposed: *Spirodynamics*.

Clinical Implications

Spirodynamics, the monitoring concept presented in this thesis, is based on continuous and simultaneous sampling and display of data during on-going ventilator treatment.

- It uses ordinary monitoring equipment with the addition of simple and inexpensive methods for direct monitoring of the tracheal and oesophageal pressures and a straightforward algorithm to analyse the data.
- It allows for monitoring of the alveolar P/V-curve on-line and partitioning of the total respiratory system in its lung and chest wall components.
- It creates a possibility to individualise ventilator treatment and has the potential to reduce the risk of ventilator-induced lung injury.

In current editorials and opinion papers in the literature, the risk and consequences of ventilator-induced lung injury have been emphasised, as has the need for simple, rapid, safe and reproducible bedside monitoring methods to provide information on how to set the ventilator based on analysis of the P/V-curve [6,20,21,50,104,182,183]. The monitoring concept presented in this thesis has the potential to fulfil these requirements.

General conclusions

- Oesophageal pressures can be easily and accurately measured with a liquid-filled, double-lumen stomach tube.
- Tracheal pressures can be measured directly with an end-hole catheter introduced through the endotracheal tube lumen with its tip positioned 2 cm above or below the tip of the endotracheal tube.
- It is difficult, if not impossible, to estimate tracheal pressures from pressure measurements at the Y-piece or ventilator.
- The dynostatic algorithm provides a reliable estimate of alveolar pressures during dynamic conditions between inspiratory/expiratory airway resistance ratios of 2.3:1 and 1:2.3.
- The dynostatic algorithm reveals a successive decrease of compliance through the initial, middle and final parts of a volume-dependent dynostatic P/V-curve at all ventilatory settings in patients with ALI/ARDS.
- The successive decrease in volume-dependent compliance increases with increasing PEEP and tidal volumes, indicating increased overdistension.
- No lower inflections points were seen during normal tidal breathing but were detected during low flow inflation, indicating that the low flow inflation method itself might give rise to its formation.

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Original Papers

Paper I

A simplified method for separate measurements of lung and chest wall mechanics in ventilator-treated patients.

Paper II

Evaluation of pressure/volume loops based on intratracheal pressure measurements during dynamic conditions.

Acta Anaesthesiol Scand 2000: 44: 571-577.

Paper III

A new method for non-invasive, manoeuvre-free determination of "static" pressure-volume curves during dynamic/therapeutic mechanical ventilation.

Paper IV

Direct tracheal airway pressure measurements, essential for accurate and safe monitoring of dynamic respiratory mechanics. A laboratory study.

Paper V

Manoeuvre-free, on-line, "static" respiratory system, lung and chest wall mechanics during on-going ventilator treatment.

På grund av upphovsrättsliga skäl kan vissa ingående delarbeten ej publiceras här.
För en fullständig lista av ingående delarbeten, se avhandlingens början.

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