Non-invasive respiratory monitoring in surgical intensive care

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Non-invasive respiratory monitoring in surgical intensive care

Niet-invasieve respiratoire bewaking in chirurgische intensive care

Proefschrift

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Paranimfen: Steven Buijk
Jasper van Bommel

To my parents

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GENERAL INTRODUCTION

The need to monitor postsurgical patients for signs of respiratory deterioration was recognized long before the first intensive care units were introduced during World War II(1). In the early days of the intensive care unit, reports were published about the high incidence of postoperative mortality which was often heralded by the onset of apnea or airway obstruction(2). Soon it became clear that these effects were induced by either the surgical procedure itself, or by the type of anesthesia used. It was demonstrated that these potentially lethal conditions could be easily prevented and treated if patients were monitored scrupulously in the early postoperative period for signs of respiratory failure and rapid action was taken if pulmonary deterioration occurred(2). These experiences probably mark the beginning of the development of techniques to monitor the respiratory condition of patients after surgery.

Another important advance in the field of postoperative respiratory monitoring which has had considerable impact on the reduction of mortality and morbidity has been the use of mechanical ventilators, which changed the type of anesthesia that could be attained during surgery. From then on it was possible to anesthetize patients for an extended period of time using other types of anesthetic agents such as muscle relaxants, without further compromising their condition. The application of mechanical ventilation increased the time available to perform the surgical procedure and protected patients from postoperative apnea. The introduction of blood gas measurement further improved the accuracy with which the oxygenation in the perioperative period could be measured and established the use of supplemental oxygen therapy for a wide range of conditions(3, 4).

Despite the fact that mechanical ventilators are now commonly used in the perioperative period in developed countries, their application still faces important problems. These include the risk of hyperinflation and subsequent barotrauma to the lungs, atelectasis, dehydration of the respiratory mucosa and ventilator-associated pneumonia(5). It is also known that mechanical ventilation affects the cardiac output and may therefore cause hypotension and may compromise tissue oxygenation(6). Patients who suffer from the acute respiratory distress syndrome (ARDS), asthma or chronic obstructive pulmonary disease (COPD) are of specific concern during artificial respiratory support due to their high impedance to ventilation(7-9). Recent studies have applied new techniques for

monitoring respiratory mechanics in mechanically ventilated COPD patients(10-15). Although the study of respiratory mechanics has advanced since the first use of mechanical ventilation, due to a lack of clinically applicable techniques it is still difficult to tailor the ventilator settings to the needs of the individual patient.

A number of techniques are available which enable monitoring of several aspects of the respiratory system. These techniques include pulse oximetry, measurement of end-tidal CO_2, the display of pressure-flow waveforms, and the calculation of work of breathing (16). The use of computer technology in respiratory monitoring has provided tools to indicate the onset of potentially dangerous complications during mechanical ventilation including apnea and excessive airway pressure by means of electronic alarms(17). It also has facilitated application of algorithms to characterize the degree of ventilation inhomogeneity of the lungs(18) and has aided in the study of decision support systems in mechanical ventilation(19, 20).

To further develop respiratory monitoring in mechanically ventilated patients, several studies were initiated at the surgical intensive care unit of the University Hospital Rotterdam. In the present thesis, the development and evaluation of several techniques are presented which have the potential to improve respiratory monitoring in mechanically ventilated intensive care patients. We have focused on techniques which can be applied continuously and are non-invasive in nature. These requirements are needed to protect the already heavily burdened intensive care patient from further invasive procedures, and to enable early detection of changes in the pulmonary condition. Techniques especially suited for this purpose are based on gas exchange measurement, due to its non-invasive character. These techniques were developed and tested for use in an intensive care department to contribute to respiratory monitoring in general.

The thesis is divided in three sections: In **section I**, **chapter 1**, a review of the literature concerning postoperative pulmonary complications is presented. These complications may lead to life-threatening conditions that often necessitate admission to an intensive care unit where endotracheal intubation and mechanical ventilation may be necessary.

Section II, development of devices and measurement techniques, consists of three chapters: In **chapter 2**, a flow-proportional gas injector system is described which was developed in our institution. In many gas exhange techniques, a non-toxic tracer gas is delivered to the respiratory system to study characteristics of uptake and elimination.

From these characteristics, it is then possible to extract information about the studied respiratory system. However, the delivery of the gas to the respiratory system may face specific problems. In our institution, the development of the gas injector system was initiated to enable performance of multiple breath indicator washout tests in mechanically ventilated patients in spontaneous, assisted and mandatory breathing patterns. The multiple breath indicator washout technique can be used to calculate the end-expiratory lung volume. Until now, the application of multiple breath indicator washout tests remains cumbersome in patients with spontaneous breathing patterns, because of the lack of (commercially available) tracer gas injection systems which can inject tracer gas in the breathing circuit when irregular or erratic breathing flow pattern is present. The chapter describes several aspects of the design and validation of the indicator gas injector as well as results of tests of the sensor in experimental measurement settings.

In **chapter 3** the development of an analyser to measure SF_6 gas in breathing circuits is presented. Previous studies indicated the need for compactly designed analysers for indicator gas (SF_6) washout tests which enable inline breathing circuit measurements. Mass spectrometry has often been used to measure SF_6 concentrations in the breathing circuit, using sample capillaries to transport the sampled gas from the breathing circuit to the measurement unit of the mass spectrometer. Despite the high accuracy of the gas fraction measurement using mass spectrometry, the use of sample capillaries causes a delay in the measurement time because the sample gas has to be transported into the measurement unit. For adequate interpretation of these measurements, correction of the delay time is needed with data from a simultaneous flow measurement. Another drawback of mass spectrometers is their large size, which complicates routine placement in the intensive care ward, where space for experimental equipment is limited. In order to facilitate its use, the analyser presented in this study has been designed compactly, employs an inline SF_6 measurement transducer and its operation is user-friendly. The development strategies used in designing the sensor and the test results which include calibration procedures, accuracy of concentration measurement, and signal stability are presented in this chapter.

In **chapter 4** a setup is described to measure end-expiratory lung volume (EELV) in mechanically ventilated patients in a non-invasive way. The setup includes the flow proportional gas injector and the SF_6 gas analyser which are described in the previous

chapters. The measurement system obtains signals of SF_6 gas and breathing flow by using a personal computer. This computer was configured to initiate measurements automatically and to perform calculation of the end-expiratory lung volume. To ensure accuracy, online detection of signal disturbance was performed which enables prediction of EELV measurement accuracy. For this purpose, dedicated software was developed in our clinic. The setup was tested in a model lung and demonstrated in a mechanically ventilated patient.

Section III, experimental studies, consists of three chapters: **Chapter 5** reports on the results of the application of the alveolar amplitude response technique in which forcing gas sinusoids are used to enable calculation of the blood flow of ventilated alveoli. The described technique may aid in the adequate adjustment of ventilator settings such as positive end expiratory pressure (PEEP) by indicating the change in blood flow of functioning alveoli. The study was conducted in mechanically ventilated pigs that underwent surfactant depletion to mimic the acute respiratory distress syndrome (ARDS).

In **chapter 6**, the results of a study into the efficacy of three different types of commonly used heat-moisture exchangers (HMEs) are presented. In vivo, the inspired air is heated and humidified by the mucosa lining the nasopharyngeal tract. HMEs are used to heat and humidify the air presented to the lungs when the nasopharyngeal tract is bypassed after endotracheal intubation. The technique used to compare the different HME types was developed in our clinic, and is here introduced in an experimental, comparative study. The HMEs were tested during the application of different breathing frequencies and tidal volumes in a patient model to study the influence of different ventilator settings on the heat and humidity output of each particular HME.

Chapter 7 reports on the results of an experimental study to measure EELV in mechanically ventilated patients of the intensive care unit using the setup described in chapter 4. The EELV equals the volume of air remaining in the lungs after a normal expiration. This volume has been shown to be reduced in the case of restrictive lung disease and to be increased in the presence of obstructive pulmonary disease. Despite the fact that previous studies suggest that the EELV may serve as an indicative parameter of the onset of respiratory disease, no data is available to ascertain if routine measurement of EELV in mechanically ventilated patients is feasible and useful for monitoring purposes. Therefore, a study was designed to perform non-invasive EELV measurements in

mechanically ventilated patients and to discuss the results. The thesis is concluded by a summary and recommendations for future research.

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SECTION I:

RESPIRATORY PROBLEMS AFTER SURGERY

"It is not uncommon, in small country hospitals, to have a recess or small room leading from the operating theatre in which the patients remain until they have recovered, or at least recovered from the immediate effects of the operation"

Florence Nightingale, 1863

CHAPTER 1
Perioperative risk factors for postoperative pulmonary complications

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Aim

This review article aims to give an overview of the current literature on postoperative pulmonary complications (PPC). Individual risk factors for the development of PPC are discussed. Limitations of previous studies are identified and goals for future research are suggested.

INTRODUCTION

Pulmonary complications, such as atelectasis, productive cough and pneumonia constitute the major part of postoperative complications. It can be expected that the incidence and severity of PPC will increase in future, as an increasing number of patients with significant comorbidities will have to undergo surgery. The advent of advanced monitoring techniques and treatment has enabled major surgery even in severely ill and debilitated patients. This practice will increase the need for intensified postoperative care and artificial respiratory support.

A wide variety of definitions for PPC have been used and the incidence of PPC has been determined in diverse patient populations with large differences in preoperative health status. As a consequence, the incidence of PPC varies between 20 and 69% (1) in the current literature. Definitions for PPC range from inclusion of signs of mild or transient respiratory impairment (e.g. radiological evidence of atelectasis), to inclusion of only pulmonary infection or exacerbation of pre-existing lung disease. The lack of uniformity in the definitions of postoperative respiratory impairment impedes comparisons between the studies conducted thus far. A consensus should be reached for the definitions that will be used in future.

Pre-operative factors	Intra-operative factors	Post-operative factors
Smoking	Anesthesia	Hypoventilation
COPD	Thoracic surgery	Pain and sedation
Astma	Upper abdominal surgery	Pneumonia
Obesity	Type of incision	
Critical illness	Fluid overload	
Neuromuscular disease	Hypothermia	
Age	Aspiration of gastric contents	
Cancer		

Table 1. Risk factors for postoperative pulmonary complications in the postoperative period

It is important to distinguish between severe and mild respiratory complications. Loss of respiratory function postoperatively can be acceptable in some cases, because the loss is transient, and it will not cause a significant deviation in the normal postoperative course. Thorough analysis of predisposing factors for postoperative respiratory complications may lead to identification of patient characteristics which influence duration and need of preoperative pulmonary medication and postoperative mechanical ventilation. Knowledge of these characteristics is essential to reduce the incidence of PPC, or to predict when complications are likely to occur. This article reviews the current literature on perioperative risk factors for development of pulmonary complications after surgery (table 1).

PREOPERATIVE RISK FACTORS

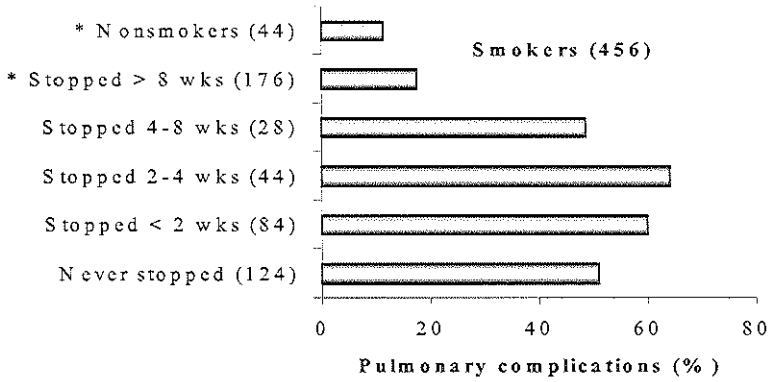
History

Cigarette smoking, chronic obstructive pulmonary disease (COPD), obesity and advanced age have traditionally been cited as being correlated with a higher incidence of PPC (2-4). Therefore, the presence of these factors is routinely assessed preoperatively, and studies of their influence on postoperative recovery have been made. A history of cancer has recently also been proposed as a risk factor for developing PPC(1). The importance of assessment of preoperative health status is evident in critically ill patients. Without meticulous attention to preoperative care this patient group is not likely to survive. It is essential that the presence of these factors is documented during preoperative assessment, and the severity of possible predisposing conditions is assessed, and the proper care is given to increase the pulmonary reserves.

Smoking

Of all factors, the two most important preoperative risk factors are a history of smoking and obstructive lung disease(5). The beneficial effects of cessation of smoking before surgery have been documented repeatedly(6-8). However, only 10 in 50 patients stop smoking before an operation after being advised by their physician(9). Smoking 20 cigarettes per day or a history of 20 pack-years is regarded to be the border of increased risk(8) of developing PPC. Although the mucociliary clearing system recovers within days after cessation of smoking, the risk of developing PPC only decreases significantly 8 weeks after cessation of smoking(6) (figure 1). This period of eight weeks is needed for the improvement of other lung functions such as sputum production and small-airway function. Thus, discouragement of smoking is advisable during any stage, but surgeons should realize that the incidence of PPC will only decrease significantly after a cessation period of 8 weeks preoperatively.

Figure 1. Preoperative duration of smoking cessation and pulmonary complication rates in 500 CABG patients. *P < 0.001 compared with patients who never stopped smoking preoperatively (Reprinted with permission of Anesthesiology (6))



Obstructive lung disease

From many studies it has become clear that the incidence of PPC is higher in patients with clinical or subclinical lung disease(10-12). Compared to controls, an increase in severe respiratory complications (respiratory failure, pneumonia) and death was found in COPD patients after thoracic and major abdominal surgery(13). Also, COPD patients have a

higher incidence of normal to moderate respiratory complications (atelectasis, sputum retention) postoperatively. Surgery in these patients, with low pulmonary reserve, is likely to worsen lung function parameters even further, and is therefore often feared. Therefore, several studies have been conducted to assess to which extent the risk of developing PPC is higher in patients with obstructive lung disease. Kroenke et al. examined the incidence of PPC after surgery in patients with severe chronic obstructive pulmonary disease (forced expiratory volume in 1 second, less than 50% of predicted). They concluded that the risk of developing PPC following abdominal surgery in patients with severe obstructive pulmonary disease is acceptable(14). A comparatively high mortality and morbidity in COPD patients undergoing coronary artery bypass grafting has been reported(13). Thoracotomies in these patients are associated with a higher incidence of PPC. Asthmatics are at increased risk of developing PPC compared to control patients(15). Bronchospasm is easily provoked by endotracheal intubation and manipulation of viscera(16). However, Oh and Patterson have shown that major surgery in steroid dependent patients can be successful if proper perioperative care is given(17). To our knowledge, this finding has never been reproduced in the literature. Corticosteroids are routinely given as preoperative preparation in COPD patients, but further studies are required because few studies exist on the relationship between the application of corticosteroids and the incidence of PPC.

Obesity

Incidence of PPC in obese individuals range between 3.9 % and 95 % (18). These numbers clearly illustrate that different definitions for obesity and/or PPC have been used. As obesity itself is associated with considerable comorbidity, exacerbations of concomitant disease by surgical trauma can be expected. Vaughan et al. have documented lower baseline and postoperative oxygenation in obese patients undergoing surgery for morbid obesity(19). The incidence of atelectasis and hypoxemia after surgery is increased in obese patients, but the incidence of severe respiratory complications (respiratory failure, pneumonia) is generally not increased.

Age

Whether advanced age is a risk factor for postoperative pulmonary complications does not become clear from reviewing multiple studies(11). It has been suggested that advanced

age alone is not a good indicator of risk(20, 21). Therefore, a decision to withhold potentially beneficial surgery should not be based solely on age. The presence of comorbidity seems responsible for the higher incidence of PPC found in the elderly. In a recent multivariate analysis where a variety of possible risk factors were weighed, a significant contribution to PPC was suggested by age above 60 years. However, in this study many older patients with cancer were included. Which of these two risk factors is the most important for the development of PPC remains unclear(1).

Critically ill

An increasing number of patients in intensive care units demand surgery. Wolfe et al.(22). classified these patients into three categories according to the need for surgery. The first group needs surgery immediately for survival, the second allows some preoperative delay, so evaluation and preparation is possible, and the third group has no emergency indication for surgery. This classification can aid in weighing the risks and benefits of immediate versus delayed operation. In the first group, the risk of organ failure during operation is a minor consideration in the decision to operate. In the second group, the focus of decision making should be on timing of operation. In the third group of patients, surgery can be delayed until the conditions that necessitated intensive care have somewhat improved. Preparation of critically ill patients for surgery should be focused on optimizing ventilatory and hemodynamic parameters next to metabolic and nutritional status. In this group, respiratory failure can occur even if no previous pulmonary problems are present. This group of patients is particularly at risk of deteriorating during transport between operating room and intensive care unit, so the organization of transportation must be carefully planned.

ASA class

For classifying the preoperative health status the ASA risk classification can be used (table 2). This score has made a significant contribution in the classification of patients at risk(23). The ASA scoring system has shown to be a powerful predictor of both cardiac and pulmonary complications (14), especially in patients with poor exercise capacity(24). An extended use of this score is the identification of patients who might benefit from improving lung function by pharmacological measures(13, 14).

ASA class	Description
I	No organic disease
II	Mild or moderate systemic disease without functional impairment
III	Organic disease with functional impairment
IV	Severe disease that is life-threatening
V	Moribund patient, not expected to survive

Table 2. American Society of Anesthetists (ASA) physical status classification

The ASA scoring system is one of the best predictors of PPC probably because it includes pulmonary as well as non-pulmonary factors(25). Perhaps the greatest value of the ASA classification in research is making patient populations and clinical studies comparable.

Diagnostics

Preoperative pulmonary assessment should include 1) history taking, 2) physical examination and 3) chest X-rays in specific patient groups. During taking of history, attention should be focused on preexistent (lung-) disease, use of medication and should be determined if any of the previously mentioned risk factors are present. Physical examination should ascertain the following points: 1) If the patient can ascend a staircase without needing to rest because of dyspnea, 2) If signs of emphysema and prolonged expirium exist, 3) If active inflammation or congestive heart failure are present.

Preoperative arterial blood gas measurements detect respiratory impairment and are essential when lung disease is present, and render guidelines for postoperative endpoints of weaning from mechanical ventilation. Derangement of any the mentioned tests before surgery indicates increased risk of developing PPC. Chest X-rays are definitely indicated in patients with a history of cancer, lung disease and a higher ASA class. Radiological chest abnormalities increase with age, so preoperative chest X-rays are routinely recommended in patients over 45 years of age. Routinely made preoperative chest X-rays lead to interventions (which would otherwise not have happened) in only a fraction of all cases. However, an undoubted value of the preoperative X-ray is that it provides a baseline to compare postoperative chest films with.

Lung function tests have long been regarded as essential in preoperative evaluation when pulmonary risk factors are present. The value of monitoring lung function in the perioperative period has been strongly established(22, 26). These tests should be used to

optimize preoperative lung function and to determine if lung function has responded to preoperative preparation. Furthermore, results of spirometric measurement should be interpreted with respect to pulmonary disease, age, height and sex. The efficacy of lung function tests in predicting postoperative respiratory complications has been rightfully questioned. In a recent study by Lawrence et al(23) no single spirometric variable was found to be associated with PPC after elective abdominal surgery. Other evidence indicates spirometry may be overutilised(27). It may not be accurate to expect spirometry to predict PPC with high accuracy. Some of the postoperative complications are caused by unpredictable factors: unexpectedly long anesthesia time, hypothermia, etc. The data presented so far on spirometry should be corrected for unexpected events.

Preoperative lung function tests should be instituted when the following characteristics are present: over 60 years of age, 20 pack years or more, productive cough, history or physical findings of cardiopulmonary disease, or obesity(11). Finally, ventilation-perfusion scanning is not routinely indicated preoperatively, and should only be performed when pulmonary embolism is suspected.

Preoperative preparation in the presence of risk factors

When lung disease is present, improvement of airflow and clearance of secretions are the most important preoperative measures to be taken. Elimination of wheezing in patients with asthma diminishes the incidence of PPC. Antibiotic prophylaxis during surgery is given to counteract bacteremia and to prevent inoculation of bacteria at the surgical site. Peroperative bacteremic pulmonary inoculation is extremely rare and pulmonary compromised patients are not specifically at risk. Therefore, the use of systemic antimicrobial prophylaxis to prevent postoperative pneumonia is not justified. The exception to this rule is emergency surgery in the septic patient. Here, diffuse hematogenic bacterial spread can cause pulmonary infiltrates, in which case a single dose of aminoglycosides (4-7 mg/kg) next to the standard prophylaxis is warranted. In case of established pulmonary infection treatment should be started based on culture results and surgery should be postponed (if possible) until resolution of infection.

Bronchodilator therapy and chest physiotherapy reduce the incidence of PPC in COPD patients. Also, a vigorous pulmonary toilet in the 48 to 72 hours before surgery has shown

to be beneficial. One study showed that bronchodilator therapy, combined with chest physiotherapy resulted in a decrease in PPC with 40%(28).

Risk factors	Measures
Smoking	Cessation > 8 weeks before surgery, chest physiotherapy
COPD	Bronchodilators, chest physiotherapy
Asthma	Bronchodilators
Obesity	Weight reduction, chest physiotherapy

Table 3. Therapeutic measures the pre-operative period

Preoperative pulmonary training increases respiratory muscle strength(29), and may prevent PPC (table 3). Pharmacological preparation consists of methylxantines, β_2-agonists, and corticosteroids. Methylxantines, e.g. theophylline are long acting agents with weak bronchodilator capabilities. They are not suited for relieving acute exacerbations of bronchospasm. The risk of overdosing these toxic agents warrants careful monitoring of administration. β_2-agonists are short acting agents, which are primarily indicated for counteracting bronchospasm. The largest benefit from these agents is found in acute exacerbations of bronchospasm, and side effects occur mostly in large doses. Corticosteroids reduce inflammation of the respiratory mucosa and are most beneficial in acute illness, when airway obstruction is not resolving to optimal bronchodilator therapy, or in chronic disease when previous regimens fail with recurrence or exacerbation of symptoms. An adequate increase in airflow is generally achieved by combining β-agonists with corticosteroids. Finally, response to preparation should be monitored with lung function tests, as patients with increases in lung volume have a better prognosis.

INTRAOPERATIVE RISK FACTORS

Anesthesia

It is commonly known that induction of general anesthesia produces pronounced changes in lung volumes, especially a reduction in functional residual capacity. This is due to changes in position of the diaphragm, and alteration of motion of the chest wall. Mucociliairy transport decreases due to analgesics, prolonged immobilisation and ineffective coughing. Anesthesia during a period longer than 3.5 hours has been associated with increased PPC(8, 30).

Inhalation anesthetics inhibit hypoxic pulmonary vasoconstriction(31). This can cause hypoxia when a ventilation/perfusion mismatch is present. However, most postoperative pulmonary effects due to anesthesia are gone within 3 to 4 days after surgery.

Prevention of PPC has been attempted by substituting general for epidural anesthesia. A considerable reduction in postoperative pulmonary complications has been found(32, 33) when epidural rather than general anesthesia is used. In elderly patients, epidural anesthesia during lengthy procedures is thought to improve safety(32). Although epidural anesthesia is suggested to play a significant role in the prevention of postoperative pulmonary complications, an increased incidence of systolic hypotension has been documented(34). However, this hypotension is uncommon when epidural opiates are used and fluid status is carefully monitored.

Site of surgery

Clinically significant respiratory complications are rarely seen after surgery outside chest or abdomen(10, 35). Respiratory complications have been reported after 30-40 % of thoracic and upper abdominal operations whereas surgery outside the thoracic or abdominal cavity is associated with an pulmonary complication rate less than 10(36). Surgery of the lower abdominal cavity has a less great effect on lung volumes an surgery close to the diaphragm. Dureuil et al. measured diaphragmatic function and vital capacity after lower and upper abdominal surgery(37). Vital capacity was more impaired after upper abdominal surgery, and took longer to recover. Diaphragmatic function was reduced for a week after upper abdominal surgery, whereas no impairment was found after lower abdominal operations.

Type of incision

The type of incision performed is known to influence the incidence of PPC. Lateral thoracotomies have a stronger association with postoperative hypoxia than sternotomies. This is due to the lower risk of inducing compression and trauma to the lung during median thoracotomies(38-40). The incidence of pulmonary complications after vertical laparotomies is found to be higher than after horizontal incisions(41, 42). A randomized prospective comparison of retroperitoneal and transabdominal incision for abdominal aortic surgery yielded no difference in incidence of pulmonary complications. Overall

though, significantly fewer complications occurred in the retroperitoneal incision group(43). A shortcoming of this study is that it included a significantly higher percentage of COPD patients in the group that underwent transabdominal incision. Diaphragmatic dysfunction after abdominal surgery is thought to result from a reflex that originates in abdominal receptors inhibiting respiratory center activity(37). Induced hypothermia during cardiac surgery can lead to respiratory failure due to phrenic nerve injury(44). The physiological response to anesthesia and the supine position during surgery, significantly diminish lung volume(45-47). The diaphragmatic shift which occurs during induction of general anesthesia is thought to decrease lung volume and especially functional residual capacity and can be worsened by an increase of the intraabdominal pressure (e.g. ileus). The small airways of the dependent areas of the lung tend to close under these circumstances, which results in a relatively increased ventilation of the non-dependent regions. This causes a ventilation-perfusion mismatch leading to hypoxemia.

Type of surgery

Little information exists about surgical procedures that cause pulmonary failure and necessitate ventilatory support. It has been suggested that long lasting intraoperative manipulation of viscera may worsen the intraoperative health status, for example by precipitating bronchospasm in asthmatics(17). Laparoscopic procedures are now practiced widely, on an increasing number of patients. These procedures are often thought to be harmless due to their minimal invasiveness. As more experience is obtained with these techniques, it is likely that more patients with significant cardiorespiratory diseases will be exposed to these procedures. However, the effects of the pneumoperitoneum on cardiorespiratory parameters have still not been studied extensively. It was recently shown by Feig et al.(48) that CO_2 insufflation during laparoscopic procedures significantly affects hemodynamic parameters in these patients. Fluid or nitroglycerin administration could largely counteract the effects of insufflation in this study. The authors concluded that volume expansion during these procedures could be an effective intervention to achieve hemodynamic stability. During insufflation of the abdomen a decrease in pH due to respiratory acidosis was induced. Also, an increase in pulmonary dead space was noted. On desufflation, the bulk of these changes were reversed to baseline values. It seems likely that long insufflation periods or high insufflation pressures will compromise

respiratory function. Intraoperative pulmonary dysfunction is more pronounced during laparoscopic surgery than in laparotomy procedures because of increased intraabdominal pressure and CO_2 load(49). The intraoperative risk of inducing acute effects due to insufflation is present during laparoscopy. However, the minimized trauma in laparoscopic surgery lowers the overall chance of postoperative pulmonary dysfunction(50). Lung volumes after laparotomy are more diminished than after laparoscopy(51) and laparoscopic procedures are associated with faster recovery. Current studies in relatively healthy populations show a reduced incidence of PPC when laparoscopy rather than laparotomy is performed. In conclusion, as abdominal gas insufflation may cause intraoperative cardiopulmonary dysfunction in a population with preexistent cardiac disease, further studies are needed to verify if this population will also benefit from laparoscopy.

Few studies have assessed the relation between surgery and the need for postoperative mechanical ventilation. Several authors(2, 52) found that patients who required postoperative mechanical ventilation after abdominal aortic surgery, had suffered a greater blood loss intraoperatively. They also found that the volume of fluid infused was significantly greater in patients which needed a longer intubation period. No relation was found between the time of aortic cross-clamping and mechanical ventilation postoperatively.

Fluid overload

Parameters which guide volume suppletion are blood loss, hemodynamic instability, wedge pressure, type and duration of the operation, and urine production. However, excessive administration of fluid is known to be associated with PPC. Patients with severe fluid overload (10-20 % increase in body weight) were found to have a higher mortality rate and a longer period of intubation(53). It may be concluded from these data that loss of blood or volume infused during surgery can be used as predictors of postoperative need and duration of mechanical ventilation.

In patients who underwent thoracic surgery, increases in CO_2 production have been documented, thought to be due to the metabolic stress of the operation(54). Fever and shivering during rewarming contribute to this increase, together with an increase in oxygen consumption. Under these circumstances, the development of blood gas

abnormalities seems inevitable, unless oxygen consumption is reduced, or supplemental oxygen is given.

POSTOPERATIVE FACTORS

Within few hours after the operation, most effects of anesthesia have subsided. Pain, the operative lesion and impairment of the cough mechanism cause reduction in vital capacity in this phase. Adequate pain relief and mobilization increase lung volume and improve clearance of bronchopulmonary secretions. Hypoxemia, pain, nosocomial pneumonia and hypothermia are the main problems in the early postoperative period.

Hypoxemia

Hypoxemia after surgery can be caused by hypoventilation, ventilation-perfusion mismatch and aspiration (table 4). Also increased lung water, the systemic inflammatory response syndrome, cardiogenic or non-cardiogenic pulmonary edema and bronchospasm are prominent causes of a decreased arterial oxygen tension. Extrapulmonary causes of hypoxemia are: decreased mixed venous oxygen content because of a decrease in cardiac output, increased oxygen consumption or severe anemia and leftward shift of oxyhemoglobin dissociation curve when hyperventilation is used to decrease arterial CO_2 tension.

Intra-pulmonary causes	Extrapulmonary causes
Hypoventilation	Increased oxygen consumption
Ventilation-perfusion mismatch	Low cardiac output
Aspiration	Severe anemia
Pulmonary edema	Hyperventilation
Bronchospasm	

Table 4. Common causes of hypoxemia after surgery

After abdominal or thoracic surgery, disturbances of lung function are seen up to 4 to 5 days(46). This is generally caused by the surgical trauma itself, and the presence of intraoperatively developed microatelectases. One of the most frequent problems in the immediate postoperative period is hypoventilation. This is caused by the respiratory depressant effects of narcotics, benzodiazepines, and volatile anesthetics have on CO_2 responsiveness of the medullary respiratory center. These effects can be present up to

several hours after surgery. Prolonged muscular paralysis is also an important cause of hypoventilation. A recent study from our clinic (Peters RF et al., unpublished data) which classified patients undergoing abdominal surgery shows that surgical, non-pulmonary complications are followed by pulmonary complications, increasing hospital stay.

Pain

Pain is the main cause of the inability to take deep breaths and sigh after surgery. If narcotic analgesics are administered, sighs and coughs are often eliminated unless the patient is specifically instructed. Reduced mobility due to pain may increase the incidence of deep vein thrombosis and pulmonary thromboembolism.

Postoperative pain also affects many body systems. Tachycardia and hypertension can lead to increased oxygen consumption, while diaphragmatic dysfunction and impaired intercostal muscle function cause decreased oxygen and high CO_2 levels. According to current views, sedation should be instituted to a level where patients are lightly asleep, but easily roused(55, 56). However, no ideal regimen can be prescribed. Burns et al. have shown that more sedatives are given in understaffed hospital units(56). Also, a general tendency towards oversedation exists in intensive care units, because patient comfort is hereby assured, and unresponsive patients present a lower workload. Total eradication of pain does not seem desirable, since patients are comfortable if their pain is controlled rather than absent(57). Several trials have been conducted to assess the best route of administration for analgesics. Epidural catheter analgesia has been shown to significantly reduce the amount of analgesic to reach excellent pain relief compared to intramuscular analgesia and patient controlled analgesia. When compared to intramuscular injection and patient controlled analgesia, epidural catheter injection was found to be associated with a significant reduction of the incidence of PPC(58). Furthermore, Yeager et al.(59) found an overall reduction in overall postoperative complications when epidural anesthesia and postoperative analgesia was compared to standard anesthesia and analgesia. Neuromuscular blocking drugs should only be given in specific circumstances; only when patients are asleep and free of pain. The indications for instituting deep sedation and neuromuscular blocking agents are limited to painful muscular spasms, severe cranial injuries and as a general measure to decrease oxygen consumption, or to prevent barotrauma.

Nosocomial pneumonia

Postoperative pneumonia accounts for 30-38% of all postoperative deaths (60). Postoperatively, the presence of a nasogastric tube, prolonged intubation, sustained immobilization, the use of antacids and inadequate analgesia all contribute to an increased risk of pneumonia (61, 62). Ventilator circuit contamination has little or no influence on the incidence of nosocomial pneumonia (63). Therefore, frequently changing ventilator tubes or the use of heat moisture exchangers (to prevent circuit colonization) fail to reduce this incidence (64, 65).

Preventive measures include aggressive pulmonary toilet, strict bedside hygiene and restricted use of gastric alkalizing agents. The use of selective decontamination of the digestive tract remains controversial. Recent meta-analyses of clinical studies comparing decontaminated patients with controls showed a significant reduction in respiratory infection rate (66-69). However, the beneficial effect on survival was less clear. In cases of high colonization and infection rates on admission to the surgical intensive care unit, the preventive benefit of selective decontamination is highly debatable (70). Whether the reduction in respiratory tract infection rates will counterbalance the emergence of resistant microorganisms remains to be seen.

Hypothermia

Postoperative hypothermia is often seen after extended periods of anesthesia and major abdominal operations(71). A beneficial effect of moderate hypothermia is the delay of tissue ischemia(72, 73), by reducing metabolic requirements and oxygen consumption. Long periods of postoperative hypothermia are correlated with a high mortality rate(74). Heat loss is particularly prominent after induction of anesthesia and when body cavities are exposed to the ambient temperature in the operating room(75-77). Shivering in the immediate postoperative period can increase oxygen consumption dramatically. This can be averted by instituting low dose morphine or ventilating the patient with higher levels of oxygen to compensate for the increased demand. Hypothermia can be relieved by application of heated blankets, and generally simple measures. Extubation of a hypothermic patient should not be attempted until the body temperature has been normalized (above 36 °C).

Weaning and endotracheal extubation

The complications associated with endotracheal intubation are widely recognized. Policies to shorten the overall intubation period could reduce the incidence of aspiration of gastric contents, endotracheal tube-related infections and injuries. Weaning patients off the ventilator can be instituted with a variety of methods(78). However, before starting the weaning process, physiologic readiness has to be established(79) (table 5). Caldwell(80) et al. showed that extubation within 24 hours after oesophagectomy does not increase the incidence in PPC. These data suggest that extubation could be executed sooner after surgery. The risk of acquiring ventilator induced lung damage may also be diminished, and possibly speed discharge from the (surgical) intensive care unit which will most likely reduce the risk of infection. Ideally, administration of anesthetics and analgesia should be done with weaning endpoints in mind.

Reversal of indication for mechanical ventilation
P_aO_2[a] > 60 mmHg with FiO_2[b]<0.5 and PEEP[c]< 5 cmH_2O
Intact ventilatory drive
Cardiovascular stability
Normal electrolytes
Normal body temperature
Adequate nutritional status
Absence of other major organ system failures

[a]arterial oxygen tension; [b]inspiratory oxygen fraction; [c]positive end-expiratory pressure

Table 5. Readiness to wean

Conclusion

When a patient with risk factors faces surgery preoperative evaluation and preparation are warranted. Preparation should entail cessation of smoking, bronchodilators, corticosteroids and chest physiotherapy. If it is not possible to screen patients before surgery, or if the surgical procedure is complicated according to the abovementioned points, postoperative care should be intensified, to assure hemodynamic stabilization and swift extubation. The choice of incision should be considered when risk factors are present. Judgment of fluid status postoperatively and measures to correct fluid overload should be aggressively instituted. Anesthesia should be instilled according to the time spent on the operation table, and with evaluation of postoperative consequences. Current views plead judicious use of sedation and neuromuscular blocking drugs during the perioperative period, to

enable extubation in the early postoperative period. The need for clear and uniformly accepted criteria for PPC has been stated in this chapter. Only then can these complications be addressed in multi-center trials that will be needed to correct for the influence of the skill of individual surgeons on the incidence of PPC and variation of postoperative care from hospital to hospital. Finally, extubations should only be attempted when anesthetic, surgical technique and postoperative management are balanced and properly executed.

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SECTION II:

DEVELOPMENT OF DEVICES AND MEASUREMENT TECHNIQUES

CHAPTER 2

A fast, digitally controlled flow proportional gas injection system for studies in lung function

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Abstract

An injector is described which enables injection of indicator gas at a predetermined concentration in a breathing circuit. The presented setup uses a control computer to produce steering signals to a multi-valve array in proportion to the input breathing signals. The multi-valve array consists of 10 valves, each with a different diameter, which can be opened or closed individually according to the input signal of the array. By opening of a certain combination of valves an amount of sulphur hexafluoride gas proportional to the inspiratory breathing signal is released.

The rate of transmission between the components of the injection system was 80 Hz. The injector has a full flow range between 0-10 L/min. The delay time between the breathing signal and the flow response was 70 ms. The study describes the results of tests to determine valve-flow ratios, step response and dynamic response of the injector.

We conclude that the delay time of the injector is sufficiently low to achieve a stable concentration of indicator gas in a breathing system. The results of the study indicate that the injector may be of use in other application fields in respiratory physiology in which breathing circuit injection of indicator gas is required.

Introduction

Gas injection systems are commonly used in lung function studies when uptake and elimination of tracer gases are investigated. Data of uptake and elimination of tracer gas by the lungs enable calculation of end-expiratory lung volume, pulmonary dead space,

pulmonary diffusion characteristics and non-shunted pulmonary capillary blood flow. Examples of these techniques include the multiple breath indicator washout technique which is used to measure functional residual capacity, or the gas forcing sinusoid technique which is used to measure non-shunted pulmonary capillary blood flow or alveolar volume(1-8). In our institution, the application of multiple breath indicator gas washout tests and the gas forcing sinusoid technique is studied. To expand the application of these techniques to mechanically ventilated patients, and especially in those exhibiting unpredictable patterns of breathing, a suitable injection system is necessary. A requirement for such a gas injector is that it can administer a tracer gas at a rate proportional to the inspiration flow of the ventilated patient to achieve stable tracer gas washin concentrations. Furthermore, the gas injection system has to adapt fast and automatically to changes in breathing circuit flow. These demands result from the fact that variations in breathing-flow-dependent intrapulmonary tracer gas concentrations hamper calculation of the previously mentioned parameters. A further requirement for a dynamically adapting gas injection system is that it should be electrically controllable with a sufficiently fast response time (time constant less then 100 ms) in order to follow changes in air flow during inspiration. Various gas injection methods have been described which enable performance of tracer gas washout measurements:

Jansen et al.(9) described a system in which gas injection is achieved by the simultaneous use of 2 ventilators, one fed with a tracer gas-free gas mixture and the other with a tracer gas supplied from a premixed, bottled gas. At the start of the washin and washout periods, the tubing of the low-pressure breathing gas circuit at the patient-side is switched between the two ventilators. A different approach was taken by Huygen et al.(10) whom described a system in which the supply gas is mixed by using a mixing device at the input-side of a ventilator. At the start of washin period, the mixing device injects a constant flow of tracer gas into a steady stream of supply gas. The resulting pre-mixed gas flow is offered in excess to a Siemens 900 series ventilator, which dispenses the excess gas in a pressure-stabilised buffer. Drawbacks of these two methods are that they are limited in their use to non-spontaneously breathing individuals and that during the execution of these techniques (costly) tracer gas is spilled.

Another approach was described by East et al.(11-13) whom employed a system in which the composition of the inspired flow at the breathing side of the ventilator is dynamically

controlled. The amount of tracer gas injected is constantly matched to the ambient inspiratory flow in the breathing circuit of the patient to achieve a constant inspiratory gas fraction even if changes in the magnitude of the inspiratory flow occur. In order to employ this method, a flow proportional gas injector is needed to administer tracer gas at a rate proportional to the time-varying inspiration. Compared to the previously mentioned methods, this is attractive to use for our purpose, as only one ventilator is needed and tracer gas is used economically. Other authors devised fast responding gas dosing systems by modulating the gas flow passing through a single on/off solenoid valve, which was rapidly pulsed open and closed (14, 15). A similar technique employing a fast switching piezo valve (100-400 Hz) was used in a proportional gas injection system specially designed for a washout method(11, 12). Lundsgaard et al. described a digital principle of linear regulation of gas flow rates by using a set of laminar flow resistors (16). Except for the piezo-valve based injection technique, these abovementioned methods were not reported to be applied in study settings that resemble ours. To our knowledge, commercially available gas injectors which can provide the desired flow range (0-1 L/min) and which fulfil our requirements do not exist despite the considerable number of studies which describe flow proportional injection methods. Commercially available thermal mass flow controllers are too slow (time response 0.5 to 3 seconds) to be suitable for our use. Voice-coil actuated flow control valves, such as used in some types of mechanical ventilators (Evita series, Dräger, Lübeck, Germany) are fast enough, but the flow range in which they can be operated is too high to be suitable for our purpose. We are not aware of the existence of valve types with a flow range that is sufficiently low to fit our demands. The main requirements for a gas injection system are that it can inject the measurement gas accurate enough to perform washout measurements and that it can be integrated in a measurement unit which can be used in the intensive care setting, where space for experimental equipment is limited.

Because there is a lack of tracer gas injection systems which can provide stable tracer gas concentrations in the presence of fluctuations in breathing flow, we tested a system to inject tracer gas flow-proportionally in a lung function measurement system to apply in mechanically ventilated patients. We evaluated the use of a computer controlled tracer gas injection system, which includes a small sized ventilator (Babylog® 8000 ventilator, Drägerwerk AG Lübeck, Germany) which was especially modified for this purpose. The

ventilator was originally designed to artificially ventilate newborns and small infants. It uses nozzles as flow resistors and fast-switching solenoid valves to enable a quick flow response. Its flow range is low enough for use as a flow-proportional gas injection system in washout methods. The description of the presented gas injection system maybe of use to those who seek to perform respiratory monitoring techniques that require the injection of tracer gas for washout tests, but also in other methods including the gas sinusoid forcing technique, and the intratracheal administration of nitric oxide (17, 18).

Materials and methods

Proportional gas injection system: The gas injection system (figure 1) consists of the gas injector valve array (modified Babylog® 8000 ventilator, Drägerwerk AG Lübeck, Germany), a laminar flow sensor (Fleisch type No. 1, MEC, Brussels, Belgium), a differential pressure transducer (pressure range 0-2 cm H_2O, LCVR/010 transducer (figure 1, marked "P") and a carrier demodulator LCCD, (Celesco, Canoga Park, CA, USA (figure 1, marked "DEMOD")), an external analog-digital (A/D) converter (ADC16, Pico Technology Ltd., Hardwick, Cambridge, United Kingdom), and a dedicated control computer (PC-AT IBM-compatible 386 SX). The A/D converter has an input range of ± 2.5 Volts, a resolution of 9 bits, and communicates through a serial port of the PC. The PC controls the gas injector by transmitting data through a second serial channel. The control of data acquisition, processing and output of the measurement signals are operated from the PC using software written in Turbo Pascal® 5.5 (Borland, Scotts Valley, CA, USA). This software is programmed to steer the valves according to significance of flow output. For example, during gas injection the least significant valves in terms of flow output are opened more frequently compared to larger valves in the array. The injection system was tested using sulphur hexafluoride (SF_6) as the tracer gas, because of its non-toxic and non-soluble characteristic and because of the successful use of the gas was reported in previous lung function studies in similar study settings(3, 12, 19-25).

The gas injector contains a bank with 10 valves (numbered 1-10), each consisting of a solenoid valve containing a built-in orifice with bore diameters between 40 and 820 μm (nominal values) varying in steps of approximately a factor 1.41 ($\sqrt{2}$). The gas supply (2-8 bar) is connected to an internal pressure controller, which reduces the pressure to 1.5 bar prior to exposition of the gas to the inlet of the valves. The gas flow-rates through the

open valves vary in steps of approximately a factor 2. The valves have a common exit, so the output gas flow equals the sum of the flows through the opened valves, allowing for 1024 (2^7) combinations of different flow values. As the flow through the orifices is turbulent, the actual flow rate delivered by the injector depends on the physical density of the gas used. The generated SF_6 flow is injected into the breathing circuit through a 2 m long tube (inner diameter 1 mm) to produce a constant SF_6 concentration during the inspiration phase of the breathing cycle. The volume of this tubing causes a delay time (50 ms) between the signal of the airflow and the SF_6 flow.

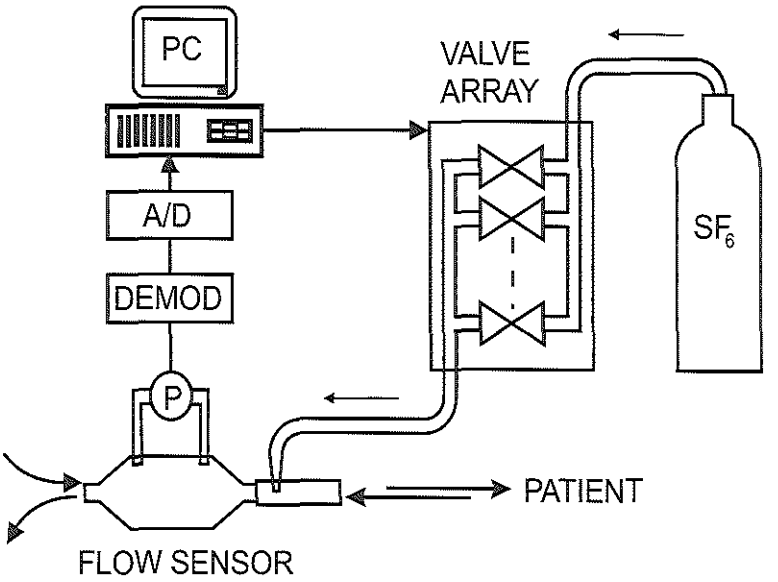

Figure 1. Schematic of the proportional gas injection system. The flow sensor is connected to a differential pressure transducer (marked "P"). The signal of the pressure transducer is converted into an analog signal by a carrier demodulator marked "DEMOD". The output signal of the demodulator are fed into an A/D converter (marked "A/D") which presents the obtained digital output signal of the pressure transducer to the injection computer. The injection computer determines the appropriate number of valves to be opened. This is signalled to the valve array. A SF_6 gas cylinder is connected to the valve array of the modified Babylog. The gas dispensed from the valve array is injected at the patient's side in the breathing circuit.

The full flow range of the injector (with all valves open) was determined to be 10 L/min. In order to reach a concentration of approximately 1% SF_6 (This is the selected concentration for our washout experiments) in an inspiratory flow with peak values of up

to 60 L/min, an injection flow of 0-0.6 L/min SF_6 is required. This low flow range is covered by the 6 valves (No 5 to 10) which control the generation of the smallest flows.

Measurement parameter: The performance of the described gas injection system was evaluated in a measurement unit to determine end-expiratory lung volume. The end-expiratory lung volume can be determined by means of a tracer gas washout method. A prerequisite for correct application of this method is that at the end of the washin period the concentration of the tracer gas is equal in all parts of the rest volume of the lung. This homogeneous mixing state can be achieved by ventilating the subject for a sufficiently long period with a gas mixture that contains a constant concentration of tracer gas. After completion of a washin period the washout is started, during which a tracer-gas free gas mixture is inspired and the amount of expired tracer gas is measured. By calculation of the expired volume of indicator gas and subsequent summation of the expiratory volumes of tracer gas during the entire washout, the end expiratory volume is estimated(10-12).

SF_6 gas measurement system: To measure SF_6 gas in the breathing circuit, an analyser was developed in our clinic which makes use of near-infrared spectroscopy. The design and validation of this sensor was performed in our institution and will be described elsewhere.

Gas injection system: The gas injection system operates as follows. First the computer reads a value of the measured breathing flow. From this value the software program determines the combination of valves to be opened in order to deliver a proportional tracer gas flow that would produce a ~1% SF_6 concentration when injected into the inspiration flow. Next the pertinent valve data combination is transmitted to the gas injector which actuates the selected valves. Different switch-on and hold-on voltages are applied to actuate the valves, thereby lowering their electrical power dissipation. This scheme of actuation needs 2 bits of information for each valve. Thus 3 bytes are sufficient to specify the actuation state of all 10 valves. After these bytes have been transmitted, the operation cycle is repeated. The transmission rate depends on the A/D conversion time (9 ms) and computer processing time. In practice, a transmission rate of 80 Hz (0.0125 s) was reached.

Performance: To study the gas injection system response in terms of flow output, delay time and the amplitude response, the output flow signal of the injector was measured after a triangular, block or sine wave was presented as A/D input. Wave form signals used for testing the gas injector response were either obtained from a function generator (PM 5132,

Philips, Eindhoven, The Netherlands) or from a mechanical ventilator (Evita 4, Dräger, Lübeck, Germany). To mimic the clinical setting, the ventilator was set to deliver mandatory breaths to a dummy lung (Demonstrations Thorax, Drägerwerk, Lübeck, Germany). Flow output response was measured at the end of the 2 m long injection tube. A precision wet gas meter (1 L volume, Schlumberger b.v., Dordrecht, The Netherlands) was used to measure steady SF_6 injection flow. Varying SF_6 injection flow was measured by a fast (60 ms) micro bridge mass airflow sensor with a range 0-5 L N_2/min (AWM5101, Micro Switch, USA). Signals were sampled at 200 Hz and monitored, stored and plotted by using an in-house developed data acquisition programme (MKR (multi-channel registration system), Central Instrumentation Department, Erasmus University Rotterdam, The Netherlands).

Results

Valve flow ratios. The injector was fed with SF_6 gas with an inlet pressure of 2-6 bar. The valves were switched on and off individually using a software programme, and the gas flow through each of the valves No. 5 to 10 was measured using the wet gas meter. The results are displayed in figure 2 on a logarithmic scale.

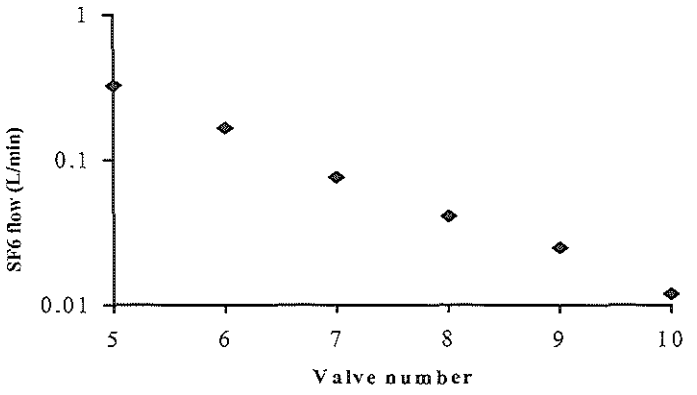

Figure 2. Flow output of the individual valves. The individual SF_6 flow of the smallest valves No. 5 to 10 is depicted.

Especially the smallest valves, No. 9 and 10 have a proportionally higher relative deviation in terms of flow output compared to the larger valves being approximately 0.005 L/min (+25%) and 0.002 L/min (+20%), respectively. However, due to the minimal contribution of these valves to the overall SF_6 flow of the injector, the effect of these deviations can be considered negligible.

Linearity of composed flow. The A/D converter input was fed with a triangular wave form voltage with a period of 10 s and 1 V in amplitude as displayed in figure 3, marked "A". With this amplitude the desired flow range (0-0.65 L/min, all 6 lower-flow valves switched on) was covered. The measured flow output of the gas injector during this experiment is shown in figure 3.

The spikes superimposed on the SF_6 signal (marked "B") are also observed during the washin procedure (figure 4). Judging from their repetition frequency they arise from the

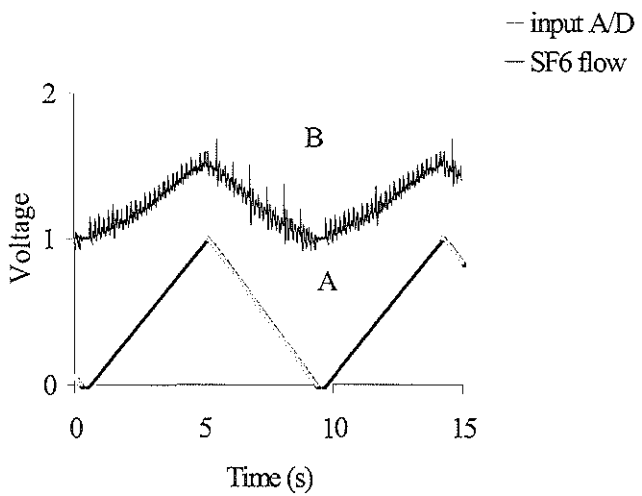

Figure 3. Linearity of the flow injector. The inlet triangular wave (marked "A") and the resulting SF_6 concentration (marked "B", in L/min) are depicted.

most frequently oscillating valves, being No. 9 and 10. The flow spikes are caused by deviations from the required valve flow ratios, the opening and closing transients of the valves, and by overshoot behaviour of the valves. The spikes in the SF_6 injection flow give

rise to inequalities in the produced SF_6-concentration in the inspiration gas during the washin phase of the multiple breath gas technique (figure 4).

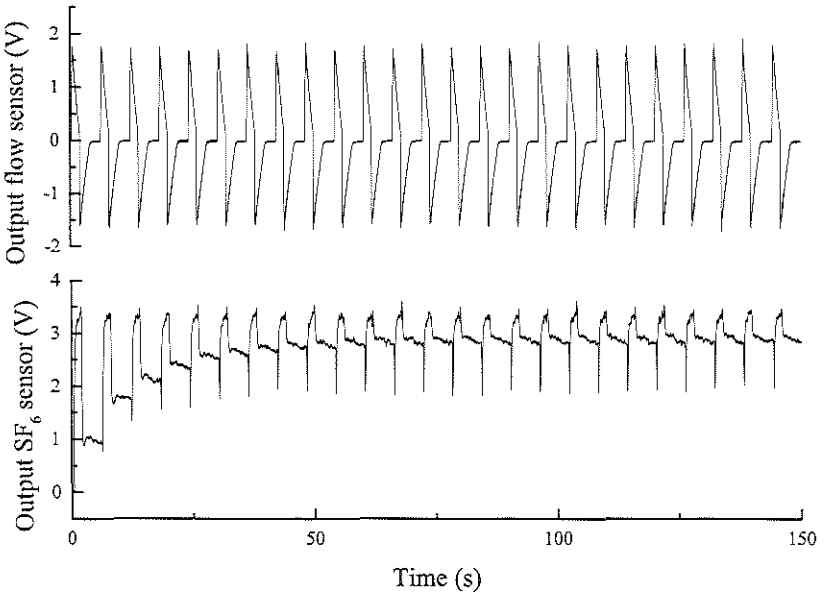

Figure 4. SF_6-concentration and breathing circuit flow during a washin experiment. The upper plot depicts the SF_6 concentration (in V) after the initiation of a washin. The lower plot depicts the concomitant breathing flow (in V) during the washin.

In summary, the results of these tests indicate that during a washin procedure the SF_6 concentration during the inspiratory phase displays spikes, which can be attributed to oscillation artefacts that arise from the valves with the smallest diameter.

Step response. The A/D inlet was fed with a step voltage with a time period of 0.5 s and an amplitude of <1 V, in such a way that only one selected valve (No. 6) could open and close. The measured SF_6 injection is displayed in figure 5. The flow output of the flow proportional gas injector was determined by measuring the flow output at the end of the 2 m tubing of the injector. This shows that after opening or closing of the valve the flow oscillates during 0.2 s with an overshoot of approximately 100%. The overshoot seen in the graph is most likely due to the presence of SF_6 gas in the compartment at the exit of the valves. Resonance during the initiation of the valve opening may also contribute to the

overshoot of SF_6 gas. The delay time between the steering signal and the flow response, measured at the end of the tubing was approximately 70 ms.

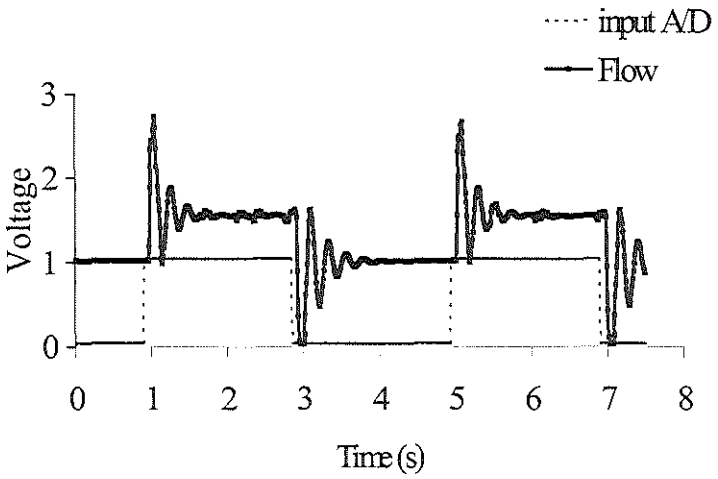

Figure 5. Step response of the flow injector. The SF_6 flow output (in V) of the flow proportional gas injector to an input block wave is shown. Note the oscillation in the SF_6 flow signal after a change in input voltage is induced. The delay time (Δ t) between the input signal and the injector flow output signal was 70 ms.

Dynamic response. Figure 6 depicts the flow-response of the SF_6 injector and the input signal when the frequency of the A/D input signal was slowly swept from 0 to 10 Hz. The figure shows the results of a fast Fourier transform (FFT) of both signals of which the flow amplitude response increases for frequencies above 3 Hz. The graph shows that at 10 Hz the amplitude response of the injector has increased by a factor 3. FFT of a typical breathing pattern obtained from a mechanically ventilated patient, together with the input breathing flow signal is shown in figure 7, shows that the larger part of the frequency spectrum of the breathing signal is contained in the interval between 0 and 3 Hz. This finding suggests that within the frequency range of a typical breathing pattern, the injector will not display possibly unwanted increases in SF_6 flow in the breathing circuit.

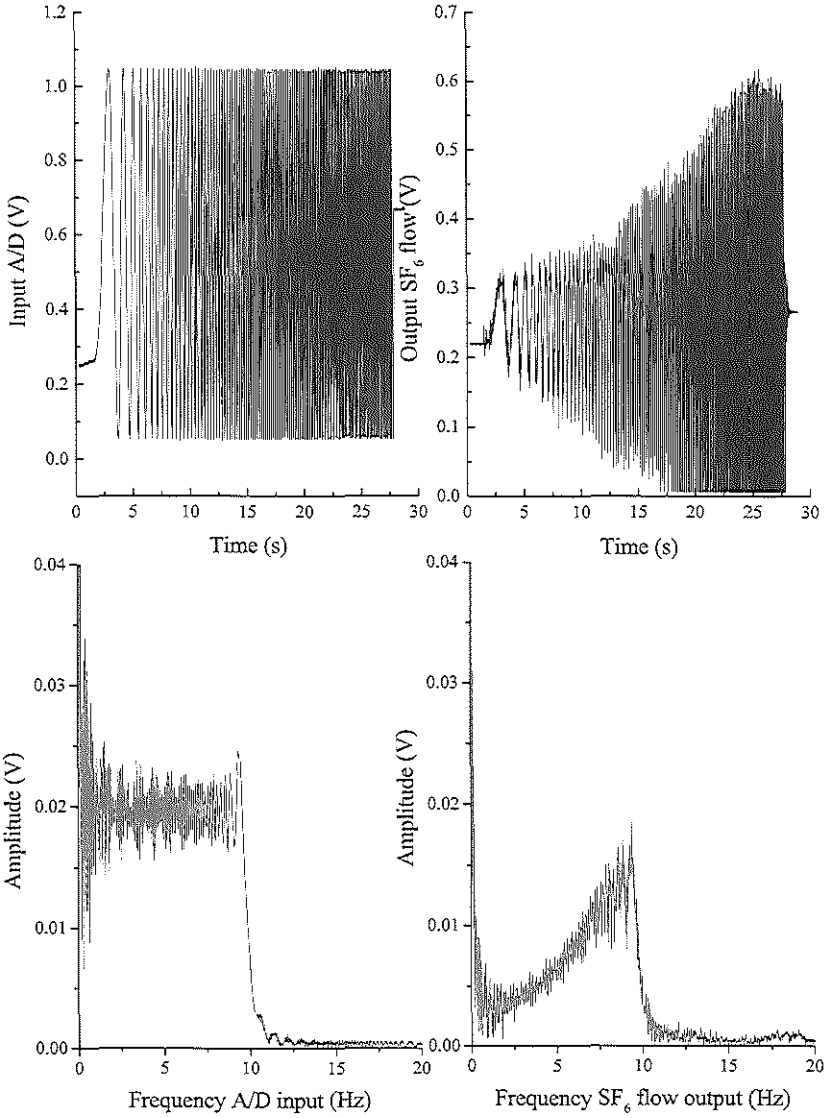

Figure 6. Response of the flow injector to an inlet sine wave swept from 0 to 10 Hz. The lower part of the graph shows a FFT of the sweeps obtained from the A/D input as well as the SF_6 flow output of the injector.

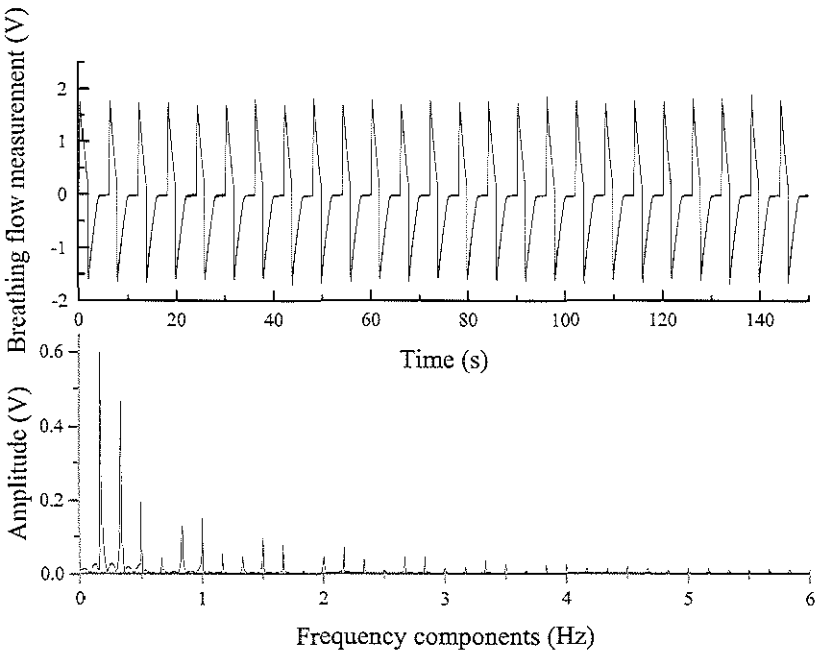

Figure 7. Frequency components of a typical breathing pattern from a mechanically ventilated patient. The data of the bottom graph was obtained by performing a FFT on the breathing flow signal (top graph). The predominant frequency components of the breathing signal are seen between 0 and 3 Hz.

Discussion

This study describes a digitally controlled gas injector, aimed for use in lung function studies, which enables flow proportional injection of tracer gas on breathing circuits. It consists of a valve array, a flow sensor, and an injection computer. The gas injector was submitted to tests to determine rate of injection, transmission speed of the steering signal within the injection system circuit, and to compare the obtained tracer gas signal in the breathing circuit to the input steering signal. These tests indicate that the described gas injector can deliver SF_6 gas in a breathing circuit at a stable fraction of 1% (which concentration was set by manipulation of the computer software). These findings suggest

that the injector can be used to obtain intrapulmonary tracer gas fractions suitable for the execution of multiple breath inert gas washout tests.

Measurement of the gas flow rate of the individual valves of the flow proportional gas injector by a wet gas meter show that flow rates double with increasing valve size. This only with the exception of the two smallest valves of which the contribution to the error in the overall output flow of the injector is in the range of 0.002-0.005 L/min (figure 2). The current settings of the software used to operate the valve array cause the two smallest valves to open more frequently than the larger valves in the array during gas injection. Therefore, the oscillatory error observed in the flow output of the injector results in part from the way we chose to set the operating software. Since these settings can be modified, further research may indicate which alterations in the current software may further increase the stability of the injector gas output. However, the current system does display a satisfactory level of accuracy in terms of tracer gas fraction to be suitable for use in the previously described multiple breath inert gas washout technique.

In this setup, a Fleisch pneumotachograph is used as a flow meter. In principle any type of fast responding pneumotachograph may be incorporated in this setup. The tests of the linearity of composed flow indicate that the use of the flow proportional injection system generates spikes during washin of the SF_6 gas which is caused by the oscillation of the smallest valves of the array. If not filtered out, these spikes may destabilise the SF_6 washin concentration, and subsequent analysis. Further study is necessary to develop techniques to eliminate the occurrence of these artefacts during tracer gas washin. However, the influence of these disturbances on the washout signal can be expected to be minimal because the gas will mix in the respiratory tree and lungs during washin and therefore spike-induced variations of gas fraction will be attenuated in the lungs and therefore in the washout.

The step response of the flow proportional gas injector was determined in this study by presenting a block wave as an inlet signal to a single valve and measuring the subsequent flow output. It was observed that the flow output oscillates during a 0.2 s time period. This oscillation probably arises from at least three factors: the volume of dead space which the injected gas has to traverse after passing through the valve, the resistance encountered in the breathing circuit, and the mass inertia of the gas present in the dead space which is thrusted forward by the SF_6 gas leaving the valve. Further study is necessary to determine

if reduction of the dead space compartment in the injector can lead to a decrease in oscillation time.

The delay in response seen in the gas flow output of the flow proportional gas injector as measured at the exit tubing of the, after a block wave was presented to the valve array, was 50 ms (figure 5). This means that after initiation of a opening impulse, no tracer gas will be detected in the breathing circuit during the first 70 ms. This delay is primarily caused by the time needed by the injection system to detect the inspiratory flow, feeding of the flow signal to the injector, opening of the valves and travel of the injected SF_6 gas stream to the end of the tubing of the injector. Linnarsson et al. described a flow proportional injection unit employing a piezo valve which with a delay of 90 ms (13). The delay time of the injector described in this paper is lower than the previously stated demands for our investigation purpose (time constant less than 100 ms).

Dynamic response of the flow proportional gas injector was determined by presenting a sinusoidally varying input voltage to the flow proportional gas injector (figure 6). The test was done to study the relationship between input signal frequency and the amplitude response of the flow proportional gas injector. The experiment shows that the amplitude response increases above 3 Hz and that it doubles at frequencies above 10 Hz. These data suggest that the SF_6 flow output magnitude increases when signals with modulations exceeding a frequency of 3 Hz are presented to the injector. It is unclear to us what causes this phenomenon. To study if breathing flow patterns as seen during mechanical ventilation increase the amplitude response of the injection system, the magnitude of frequency components of these breathing patterns were determined (figure 7). These data show that the frequency components of normal breathing flow patterns lie in the interval between 0 and 3Hz, which implies that no increase in amplitude response of the flow proportional gas injector is expected under these circumstances.

The control software of the described injection system is set to deliver a constant gas fraction prior to initiation of the washout. However, modification of the operating software would enable application of different injection characteristics of the tracer gas. This may expand the use of the flow proportional gas injection system from our described particular application to other techniques in respiratory physiology which depend on such a system such as the sine-wave measurement of alveolar volume and pulmonary capillary

blood flow(5-7, 26-31) or improve measurement systems which also measure end-expiratory lung function(20, 23).

This injection system has the potential to inject other types of tracer gases during respiration. The use of gases that are similar to SF_6 in terms of inertia and insolubility such as helium, xenon etc. would require little or no modification to the injection system. Use of water-soluble gases would require modification of the described gas injection system such as adding a separate valve sealed circuit containing the water-soluble gas. The gas flow from the gas injection system presented to the valve sealed circuit will result in delivery of the water-soluble gas with the same injection characteristics as the gas flow presented at the inlet of the valve sealed circuit. Recently, an injection unit with components based on the Babylog ventilator technology (Dräger) was modified to administer nitric oxide (NO-DOMO, Dräger, Lübeck, Germany). This system uses the internal inspiratory flow measurement data of the ventilator to determine the proportion of nitric oxide to be injected. In our system we use an external flow meter which enables application of the injection system also in spontaneously breathing individuals. However, the current study has focused on the efficacy of the flow proportional gas injector in service of a measurement system to study SF_6 gas washout. Further research is necessary to expand the use of this injector to other applications. This gas injector system can inject SF_6 gas flow proportionally with the aid of a pneumotachograph. It is now used in our institution to perform SF_6 washout measurements in mechanically ventilated patients to determine functional residual capacity or end-expiratory lung volume, independent of the mode of mechanical ventilation or breathing pattern.

Acknowledgements

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CHAPTER 3

Design and validation of an analyser to measure sulphur hexafluoride gas during respiration

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Abstract

This study presents the results of the development of an analyser to measure sulphur hexafluoride (SF_6) gas in breathing circuits, for the application of studies in lung function. The analyser consists of an inline breathing circuit measurement transducer and a compact unit for signal treatment. The detector unit of the analyser consists of a near-infrared light source, a band pass filter and a pyroelectrical detector. When incremental steps of SF_6 gas between 0 and 2 % were presented to the analyser, the maximum deviation from the theoretical calibration curve using was calculated to be 0.01 %SF_6. The step response of the analyser (10-90%) was 250 ms. The sensitivity to ambient temperature of the analyser was 0.01 %SF_6/°C in the range between 0 and 2 %SF_6. We conclude that the presented analyser is accurate, has a sufficient response speed to be used in clinical measurement settings. Furthermore, the analyser is resistant to changes in temperature, gas flow and changes in orientation and movement, which are likely to occur in clinical measurement settings.

Introduction

Sulphur hexafluoride (SF_6) is an inert non-toxic gas which is applied in a wide range of medical applications which include pulmonary physiology studies. Measurement of SF_6 in such studies is usually performed by mass spectrometry or infrared (IR) spectroscopy(1-5). Previous studies recognise the potential advantages of SF_6 gas in pulmonary physiology studies over other types of tracer gases(1-9), but the application of SF_6 gas

based techniques in the clinical setting is often hampered by the complexity and/or size of the measurement devices which are needed to perform SF_6 measurement. In our clinic, SF_6 gas is used to perform inert gas washout experiments in mechanically ventilated patients to study the end-expiratory lung volume (EELV) and ventilation inhomogeneity(10, 11). Previous studies suggest that EELV measurement may be a powerful tool to monitor the lung function of critically ill, mechanically ventilated patients and may improve the efficacy of therapeutic regimens at the bedside(6, 12-18). However, for routine study of the EELV in the intensive care unit employing SF_6 gas, small, easy-to-use devices are needed.

In order to study the EELV in critically ill mechanically ventilated patients we developed an experimental setup which can measure sulphur hexafluoride (SF_6) washout. An important part of this setup was the design and development of a compact analyser to measure SF_6 concentration in the expired air. The measurement of EELV using SF_6 washout employs the fact that SF_6 is a non-soluble non-toxic gas which can be safely administered to human subjects and is not taken up by the body tissues. When the SF_6 washout technique is used, low dose SF_6 gas is injected in the inspiratory tube of the breathing circuit of the subject. The wash-in of the gas leads to an equilibrium in the lungs, which is characterised by an identical expiratory and inspiratory SF_6 concentration. By simultaneous flow measurements, the volume of SF_6 gas inspired from baseline to equilibrium can be calculated (or the volume *expired* from equilibrium to baseline). This volume of SF_6 gas corresponds with the end-expiratory lung volume (1-9). The inert gas washout method (using SF_6 gas) is an attractive way to measure the end-expiratory lung volume because no co-operation of the subject is required and the tracer gas is non-toxic.

An analyser to measure SF_6 gas for the purpose of measurement of EELV in the intensive care setting has to comply with several demands. The instrument should measure the SF_6 concentration accurate enough to be able to allow determination of clinically relevant changes in EELV. In the literature, the reported range of reproducibility of EELV measurement systems is 2 to 12%(19). The sensor has to respond fast to indicate the abrupt changes in gas concentration induced by the transition from inspiration to expiration and vice versa. Since the analyser is to be used in the intensive care setting where space for experimental equipment is limited, such a measurement device has to be user-friendly and compact.

A technique which is particularly suited to devise fast, compact SF_6 gas concentration sensors is based on the absorption of infrared light(5, 7, 8). In the past, several manufacturers have designed in-line (flow-through) IR-analysers to measure carbon dioxide in the breathing gas flow (capnographs) (20-22). An IR-analyser to measure SF_6 gas during wash-out tests was described previously by Jonmarker (7). The design was derived from a commercially available in-line type capnograph (CO_2-analyzer 130, Siemens-Elema,, Solna, Sweden). In the Jonmarker study, the original operating wavelength of the capnograph was changed from the 4.2 μm wavelength band where CO_2 absorbs, to the 10.6 μm band where SF_6 has a strong absorption band by changing the IR band pass filters. This prototype infrared sensor was demonstrated to enable measurement of SF_6 gas, but never became commercially available. The sensor we developed was initially based on the Jonmarker concept, but has resulted in a product which differs in several aspects from the original concept. The main differences between our design and the Jonmarker model that we could determine from their report from the literature at least include a different design of the in-circuit SF_6 transducer and the application of a 20 Hz filter on the output SF_6 signal. In contrast to other studies, we present a detailed description of the technique and the measurement components itself. The description and validation of the design may be of use to those designing or using such a sensor. We have aimed at the application of standard commercially available components in our design. This study addresses the technical development and presents test results concerning accuracy, linearity, response time and stability of the SF_6 analyser.

Principles of measurement of the analyser

IR radiation from a heat source (figure 1) reaches the interior of a flow-through cuvette through a window, where the radiation around 10.6 μm is attenuated by the SF_6 molecules within the breathing gas mixture. The attenuated radiation departs from the cuvette via a second window. The IR radiation outside the area of 10.6 μm is blocked using an optical band pass filter that suppresses interference by other respiratory gases (H_2O, CO_2), which absorb elsewhere in the IR spectrum. Furthermore, the optical filter reduces the electronic noise to which the detector is exposed, which increases stability of the detector and prevents overranging. The IR detector (Hamamatsu, Hamamatsu City, Japan) makes use

of the pyroelectrical effect: polarisation currents are evoked as a consequence of changes in temperature of a thin plate of pyroelectrical material (Lithium tantalate).

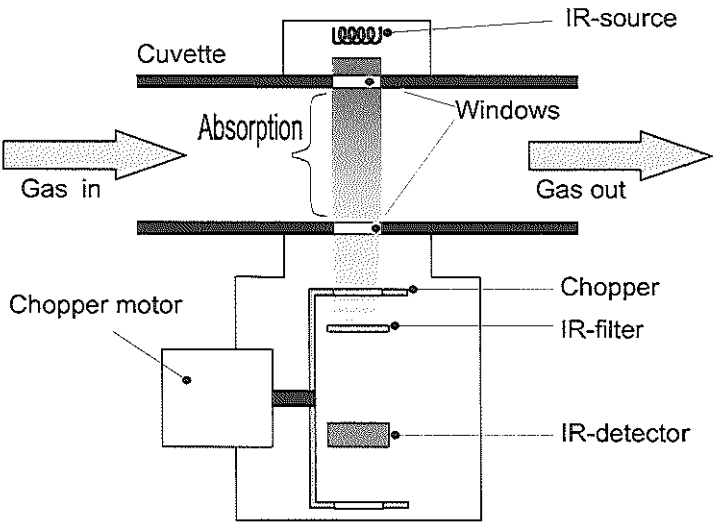


Figure 1. Schematic drawing of the components of the SF_6 analyser

The sensitivity of this type of detector for a wavelength of 10.6 μm is already good at room temperature, thus eliminating the need for additional cooling (noise equivalent power: $1.0 \cdot 10^{-9}$ $W/Hz^{-½}$, Fachnormenausschuss Elektrotechnik im Deutschen Normenausschusses, Berlin, Germany). As the pyroelectric is "blind" to steady or low frequency radiation, it is necessary to interrupt the IR beam periodically with a chopper if constant or slowly varying radiation intensities (i.e. SF_6 concentrations) have to be measured. In this way, the detector delivers an alternating current (a/c) carrier wave on which the intensity of the received radiation is amplitude-modulated. Amplitude demodulation of this signal yields information of the concentration of the absorbing SF_6 in the gas mixture of the cuvette.

Figure 2 shows a drawing of the components in the breathing circuit transducer head and the signal processing unit of the analyser. The μV-level detector output signal is a/c pre-amplified in the transducer head. In the main signal-processing unit the signal is further a/c amplified, band filtered around the chopper frequency, then full-wave rectified and low-pass filtered. The obtained d/c output voltage then varies in proportion with the detected radiation intensity. An adjustable offset is used to move the zero point in such a way that SF_6-free gas mixture in the cuvette corresponds to 0 volts output voltage. The presence of SF_6 gas in the cuvette will cause an increase in the output voltage. After calibration, the sensor is ready to measure the SF_6 concentration in the cuvette.

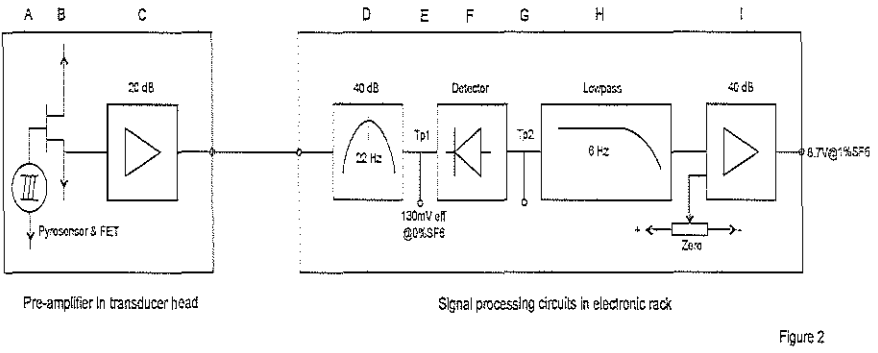


Figure 2. Electronic circuitry for signal processing in the transducer head and the component rack of the SF_6 analyser.

Construction of the analyser

The SF_6 analyser consists of a flow-through transducer (fig 3a) (dimensions: 33 x 62 x 74 mm; weight: 0.28 kg) which is connected to the main signal processing unit by means of a cable (with a of length 3 m) containing signal, control and power lines. The transducer contains a detachable measuring flow-through cuvette (see fig 3b), which can be locked in place using a metal hood (not drawn in figures). The metal hood also acts as a protecting heat shield to protect the user from components that heat up during use. After unbolting of the hood, the cuvette can be detached for cleaning or replacement.

A part of the flow-through transducer head is made of synthetic material (PTFE) which contains an IR light source, consisting of a cone-shaped reflector (inner dimensions: 7 mm

diameter, 12 mm height), and which is internally gold-plated. The reflector was obtained from a flow-through transducer of a commercially available CO_2 analyser (type 930, Siemens-Elema AB, Solna, Sweden). The heat source is a ceramic encapsulated PT100 resistor element (maximally admissible temperature 600°C, 1.6 mm in diameter, 12 mm in length, RTD element/cell 1PT00R669, Newport Electronics b.v., Amstelveen, The Netherlands.) The heating element is attached to the top of the cone with silicone rubber (type E41, Viba, Zoetermeer, The Netherlands) and the cone is secured with a screw through the synthetic encasing. The PT100 element was connected to a stabilised voltage supply, of which the voltage slowly increases to 24 Volt DC in 30 s after the device is switched on. In stationary state the current through the element was measured as 93.74 mA. The dissipation of the element was 2.3 W, and its resistance during operation was 256.0 Ω. Using a table for the resistance-temperature values of PT100 elements, provided by the manufacturer, the internal temperature of the element was estimated to be 420 °C.

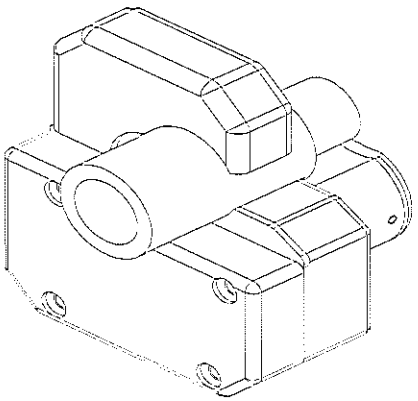


Figure 3a. The breathing circuit transducer

The measurement cuvette (see figure 3b) consists of two symmetrical aluminium parts which were glued together. The cuvette is equipped with standard 22 mm ID/OD connections. The lumen of the cuvette is narrowed to achieve a rectangular profile (8 x 8 mm) at the position of the windows. Round spaces of 9 mm in diameter were cut in both halves of the cuvette to create chambers to place the germanium windows (10 mm in diameter x 1 mm in thickness). The windows were glued to the cuvette using silicone rubber (E41, Wacker, Viba, Zoetermeer, The Netherlands). The windows were supplied

with a single layer antireflection coating applied to both sides of the window (Germanium, NOC, Jarrow, Tyne & Wear, United Kingdom). The transmission of light through each window, as specified by the manufacturer, was 90% at 10.6 μm.

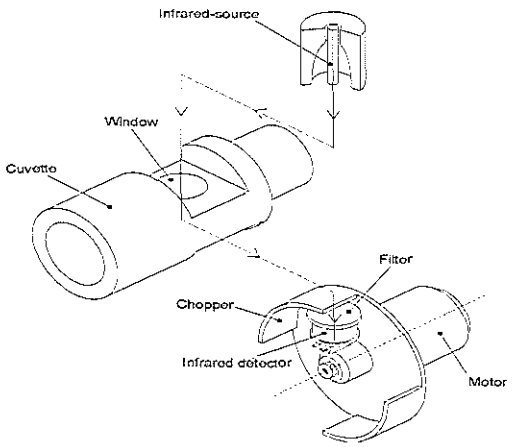


Figure 3b. The measurement cuvette (left) and the chopper and detector (right). The arrows indicates the path the IR beam traverses towards the detector

The IR-filter (10 mm diameter x 1 mm thick) is a di-electric narrow band pass filter; the central wavelength (CWL) is specified as 10.6 μm ± 0.5% and the band width at half height is 0.22 μm (NOC, Jarrow, Tyne & Wear, United Kingdom). The transmission of the band pass filter measured by the manufacturer is 60% at 10.6 μm. The filter was glued to the top of the detector with silicone rubber (E41, Wacker, Viba, Zoetermeer, The Netherlands).

The detector is a thermally compensated pyroelectrical detector (type P3782-01, Hamamatsu, Hamamatsu City, Japan). The spectral response range (7-20 μm) is determined by its window material. The thermal time constant is 100 ms. The pyrosensitive element is integrated with a FET source follower and is contained within a standard transistor TO5 housing. The diameter of the sensitive surface is 2 mm and the entrance diaphragm of the detector housing is 2.5 mm diameter. The entrance lumen of the transducer head is 3x3 mm. Figure 3 shows an outline of dimensions and geometric configuration of the optical design together with the pathways of some limiting IR radiation rays. Because the detector is sensitive to microphonics, a rubber ring was placed

around the encasing of the detector to prevent transmission of vibrations from the rotating motor and chopper.

The chopper consists of an aluminium wheel (34 mm in diameter) equipped with two flange pieces. The chopper is directly connected to the shaft of the driving 15 VDC collector motor with is equipped with a ball-bearing spindle (Escap 16C2R18-204.30, API Portescap, Telerex b.v., The Netherlands). The revolution speed of the motor spindle is kept at a constant rate of 11 revolutions per second (rps) by a proportional closed loop control circuit. The feedback signal (i.e. the chopper speed) is obtained from the chopped detector output signal. In the Jonmarker model, another type of chopper is used, with a rotating speed of 300 Hz(7). This rotating speed is much higher than the chopper speed in our study which causes, as the authors indicate, an increase in signal noise. We found that a sufficient signal to noise ratio could be obtained with a significantly lower chopper speed. Furthermore, our tests indicate that a reduction in detector response occurs at higher frequencies which is caused by the thermal inertia of the pyrodetector which amounts to a reduction of -6dB per octave above the thermal cut-off frequency. Another difference in the analyser compared to the Jonmarker model is that we implemented a 22 Hz band pass filter to the output signal of the analyser to reduce signal noise.

Aspects of design and tests of behaviour

During the tests both a/c signals (on test point 1, tp1) as well as d/c signals (the circuit output) were fed into the schematically displayed electronic rack (figure 2).The tests were performed using the following instruments:

The amplitude of the a/c chopper signal on tp1 was measured using an analog volt meter (3400B, Hewlett Packard, Englewood CO, USA)) in a range of 300 mVrms. The output of this volt meter (0-1 VDC) was amplified 10 times. The a/c amplitude was measured with a digital multi-meter (8842A, Fluke, Everett, Washington, USA). The carrier wave frequency was measured and recorded using a programmable frequency voltage converter (type D421.3, Braun GMBH, Waiblingen, Germany), with a setting of 15-35Hz = 0-10V. The temperature in the surrounding air and in the sensor head was measured with a digital thermometer (DU-3, Ellab, Copenhagen, Denmark, output 100 mV/°C). The air flow through the cuvette was measured with a Fleisch type flow head No 1 and a differential pressure transducer (Selesco LCVR transducer 0-2 cm H_2O and a LCCD carrier

demodulator, 0-10V line out voltage). The signals were monitored in real time, stored and printed using a personal computer with an added 16 channel A/D converter (PCL-812 Advantech, Advantech Benelux b.v., Roosendaal, The Netherlands) with a range of 0-10 VDC, which was operated using a PC data acquisition programme (MKR (multi-channel registration programme) Central Instrumentation Department, Erasmus University, Rotterdam, The Netherlands).

1) SF_6 detector calibration. Figure 4 shows the results of 4 sets of measurements in which the detector output was measured as a function of SF_6 concentration. A gas mixture containing SF_6 was purged through the cuvette of the transducer. Gas mixtures with incremental SF_6 concentrations between 0 and 2% were generated by a gas mixing pump (Westhoff 1m300/a-F, Bochum, Germany).

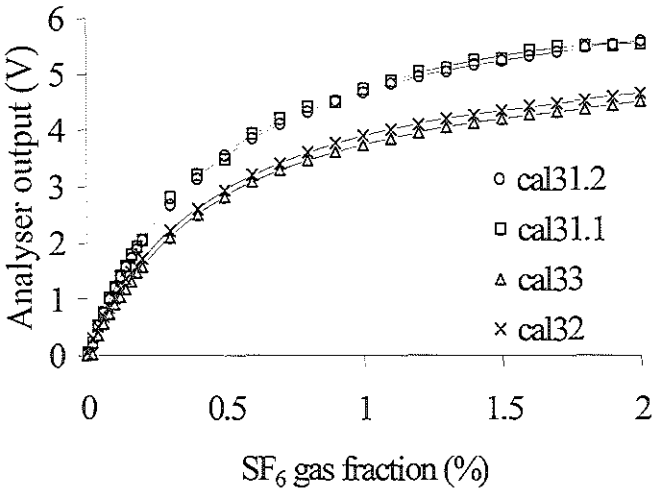


Figure 4. Calibration curves of the SF_6 analyser obtained with two different sets of germanium windows in the measurement cuvette (cal31.1 and cal31.2) and after substitution (cal32 and cal 33).

The difference between the upper two curves (cal31.1 and cal31.2) and lower two curves (cal33 and cal32) is caused by replacement of one set of the germanium windows of the

measurement cuvette by another set. Lambert-Beer's law, which applies to the absorption of monochromatic light by gases and liquids at low densities, predicts a saturated negative exponential relationship as a relationship between concentration and detector output, which is a linear function of the IR radiation incident and the IR radiation incident on the detector. Detector output D in the present setup can be characterised by:

$$D = c_1 - c_2 \cdot I$$

Applying Lambert-Beer's law this becomes:

$$D = c_1 - c_2 \cdot I_0 \cdot e^{-c_3[SF_6]}$$

c_1, c_2, c_3: constants

I: 10.6 μm radiation incident on detector

I_0: 10.6 μm radiation incident on detector in absence of SF_6.

The result of a best-fit procedure with such a curve is shown in figure 4 (drawn lines). It can be seen that the theoretical curve does match the measured points well but not perfect: the curve crosses between two adjacent calibration points of which the maximum deviation from the theoretical curve amounts to approximately 0.01% SF_6. This slight deviation results from the fact that the signal is the result of the detection of radiation in a wavelength interval (determined by the band pass filter) in which the absorption coefficient of SF_6 strongly varies (figure 5). In practice, we chose to use a 6^{th} order polynomial function to obtain a close fit of the calibration points.

2) Optical band pass filter. The transmission characteristic of the optical band pass filter and the absorption curve of 1% SF_6 in air are shown in figure 5. The filter transmission curve of the optical band pass filter was measured and supplied by the manufacturer. SF_6-absorption was measured using a Fourier type infrared spectrometer with a resolution of 4 cm-1 (FTS-7, Bio-Rad Laboratories b.v., Veenendaal, The Netherlands). With this spectrometer, an absorption curve was obtained with 100% SF_6 present in the measurement cuvette. The path length of the cuvette was 0.5 mm. Applying Lambert-Beer's law, the measured absorption values were then converted to obtain the expected absorption of 1% SF_6 gas through a path length of 8 mm. Figure 5 shows that the transmission curve of the band pass filter (CWL 10.60 μm) and the absorption maximum of SF_6 (CWL 10.55 μm) do not exactly coincide. However, the two curves still overlap sufficiently. The filter bandwidth (BWHH 0.22 μm) is somewhat wider than that of the

SF_6 absorption curve (BWHH 0.10 μm) implying that the full SF_6 band is used, whereas the quantity of transmitted background radiation is kept to a minimum.

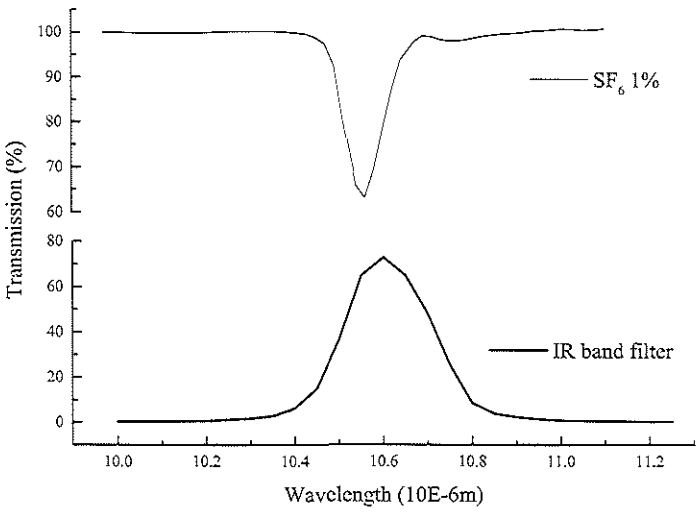


Figure 5. Transmission characteristic of the optical band filter and absorption spectrum of SF_6.

The narrow band pass filter used to isolate the SF_6 absorption band and the fact that this band lies in a spectral region (referred to as the N-band in atmospheric and IR-astronomy measurements), which is characterized by the virtual absence of any H_2O-absorption (See Lord, S.D. 1992, NASA Technical Memor. 103957; also available from http://www.gemini.edu/sciops/ObsProcess/obsConstraints/ocTransSpectra.html) renders the measurements immune to water vapor present in the exhaled air.

3) SF_6 detector response speed. The step response of the analyser was obtained by suddenly purging a 2% SF_6 gas mixture through the cuvette, and recording the subsequent d/c output of the analyser. The obtained step response in figure 6 shows a 10-90% rise-time of 250 ms.

This final rise time can be attributed to the thermal inertia of the pyrodetector element (100ms), and the electronic filters in the signal pathway (See figure 2). These filters contain the band filter displayed in figure 2, as well as the low pass filter which flattens

the remnants of the rectified carrier wave. The 10-90% rise time of this filter (4^{th} order, 3 dB cut-off frequency at 6 Hz) is 70 ms. The remaining parts of the rise time (80 ms) is caused by the influence of the band filter. A faster response can be reached by increasing chopper frequency and the thereby adjusted increase of pass- and cut-off frequencies of the band filter and the cut-off filter. However, a higher chopper frequency will lead to a reduction in signal amplitude (with -6 dB per octave) and an expected reduction in the signal to noise ratio. We chose a chopper frequency of 22 Hz as a useful compromise between response speed and signal to noise ratio. A fast response speed is demanded by the fact that the washout method is sensitive to time delay between the signals of the SF_6 gas concentration sensor and the gas flow sensor.

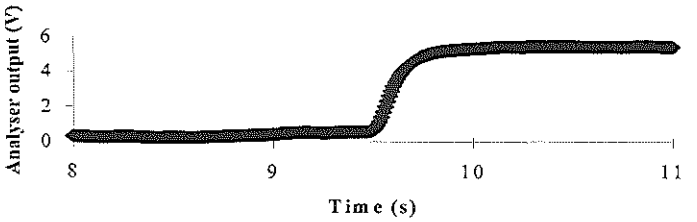
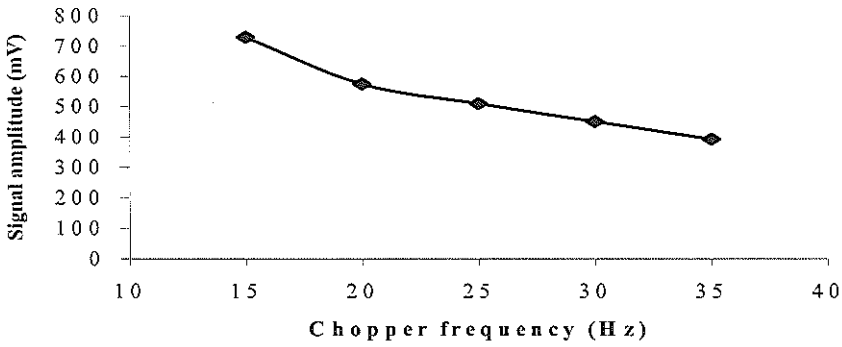


Figure 6. Step response of the SF_6 analyser

4) Chopper speed. Figure 7 shows the change in a/c chopped signal amplitude (measured on tp1 in figure 2) which was measured when the chopper frequency was varied between 15-35 Hz by varying the motor speed. The graph shows a maximum response at about 22 Hz. The position of the rising flank and the orientation of the maximum of this curve is primarily determined by the presence of two single-pole high pass filters (with a cut-off frequency of 25 Hz) in the a/c amplifier stages. The reduction in response at higher frequencies is caused by the thermal inertia of the pyrodetector which causes a reduction of -6dB per octave above de thermal cut-off frequency, which is about 1.5 Hz. The angle of the curve is further increased by the presence of two single pole low pass filters (cut-off frequency of 34 Hz) in de a/c amplifier stages. A motor speed of 11 rps (corresponding to

a chopping frequency of 22Hz) was found to be optimal because the response of the analyser becomes virtually independent of motor speed fluctuations.

Figure 7. Influence of the chopper rotation speed on the sensor signal level.



5) Detector analyser sensitivity to ambient temperature. Ambient temperature sensitivity of the analyser was tested in the range 25-35 °C by changing the temperature of the air in a vessel in which the sensor was immersed. A gas mixture free of SF_6 was purged through the sensor. The air temperature in the housing of the sensor was measured. The signal amplitude was recorded as a measure of the sensor responsiveness (at tp1 (mVrms)). After a thermal equilibrium was reached (a state of constant temperature in the measurement head of the sensor) the head of the sensor was purged through a few times for a few seconds with a 2% SF_6 containing gas mixture from a gas cylinder. The zero point of the sensor varies during those transitional periods where the thermal equilibrium has not yet been reached. After a thermal equilibrium has been reached at 25 or 35 °C, the zero levels are almost equal and constant. The influence of the temperature on the zero level was determined to be less than 0.01 %SF_6/°C. The influence of the ambient temperature on the measurement accuracy was determined using measured output differences at 0% and 2% SF_6, and was calculated as 0.3 %/°C in the 0-2% SF_6 range. We conclude that, at a constant temperature, and after setting of a thermal equilibrium of the measurement sensor, no influence remains of the surrounding temperature on the position of the zero level and on the measurement accuracy. In practice, with SF_6 washout periods of 5

minutes, the remaining zero drift caused by the surrounding temperature are small, and its influence is easy to eliminate off-line by using suitable offset corrections.

6) Analyser sensitivity to air flow. Gas flowing through the transducer will exchange heat with the cuvette. After connecting the sensor in the breathing circuit, the temperature of the transducer head will usually decrease, which can theoretically influence the sensitivity of the sensor. We needed to study this effect because the transducer is calibrated with a low flow of 0.6 L/min from the gas-mixing pump whereas the measurements are performed at much higher lung ventilation flow rates. The effect was quantified by conducting an experiment in which the sensor output was measured while the cuvette was alternately purged with low and high air flow levels of 0.6 L/min and 18 L/min, respectively. The temperature of the gas flow was about 25 °C.

The air temperature in the sensor encasing was recorded simultaneously (using a small bead NTC thermistor, Fenwall Electronics, American Power Devices, MA, USA, measurement accuracy: ± 0.2°C). The sensor output was taken from test point tp1. The measured sensor voltage repeatedly reached a temperature equilibrium within 5-10 minutes after changing the gas flow through the cuvette from a low to a high level or vice versa. At high gas flow rates, the sensor signal decreased 12.4 mVrms compared to that at low flow rates, which corresponded with a flow-induced zero signal shift of -0.016 % SF_6. The measurement results show that the temperature in the sensor encasing decreased with 2 °C at high flow rates. The resulting influence on the measurement accuracy we consider to be equal to that which occurs if the ambient temperature decreases by 2 °C. This will amount to -0.6% full scale concluding from section 5. This is the estimate of the relative error in the concentration measurement which occurs if calibration is performed at a low flow levels and measurement is assumed at high flow levels. The observed flow-induced zero drift has multiple causes. It is highly probable that the flow-induced cooling of the sensor encasing will also decrease the temperature of the pyrodetector.

Given the fact that the pyrodetector is temperature sensitive, this may be a first explanation of the occurrence of the zero drift during changes in gas flow through the sensor. Results from a similar experiment, in which the temperature of the heat source (PT100 element) was obtained from a resistance measurement and making use of the temperature resistance of the PT100, showed that this temperature decreased with 1.6 °C after increasing the flow to 20 L/min. Since change of the temperature of the heat source

will probably lead to a change in the quantity of IR radiation, this may provide a second explanation for the occurrence of zero drift. We conclude that at least two factors influence the zero drift in variations of flow: the temperature of 1) the pyrodetector and 2) the heat source.

7) Analyser sensitivity to orientation and movement. In the steady state, the analyser did not show any signs of sensitivity to any particular orientation. We determined that fast changes in spatial position and/or orientation of the transducer head reduced the number of revolutions per minute (rpm) of the chopper. The reduction in motor speed lasted for 1 to 2 minutes. In order to minimise this effect, the motor voltage was artificially increased during this period by means of an active motor feedback loop.

The most probable cause of the reduction in rpm is a temporary increase of the motor axis resistance which is caused by a sudden change in position of the rotating motor axis. After 1 to 2 minutes the resistance of the motor axis has returned to normal, just as the motor output voltage. The explanation for the change in motor speed during this period can be found in the limited circulating amplification of the loop of control, which causes a relatively large load-dependent error of control (a proportional offset) of the number of revolutions. A higher level of amplification of the loop will result in a smaller error. However, the current setting of the control loop is satisfactory because the occurring changes in rpm are minimal and do not influence the output signal of the sensor (see figure 7). The electronics were designed to inhibit the effect of fluctuations of the chopper speed on the output signal. Moreover, if the transducer position is fixed using a stand or a bracket, these disturbances are avoided. Therefore, the sensitivity of the transducer to movement can be neglected in practical use.

Discussion

We present a detailed description of an analyser to measure SF_6 gas to conduct washout experiments for the determination of the end-expiratory lung volume by using a method similar to the one previously described by Jonmarker et al.(7). The design of the SF_6 analyser differs from the Jonmarker concept in terms of a different construction of the SF_6 measurement transducer, which includes the use of a 22 Hz filter. The current analyser has a compact design and is easy to use. Tests of the SF_6 sensor show that changes in temperature, changes in gas flow or changes in chopper speed do not introduce large

errors in the output signal. The test margins were estimated from clinically expected measurement settings.

Calibration of the SF_6 sensor was done by using a gas mixing pump to provide a range of SF_6 concentrations to construct a full calibration curve. However, because of the stability of the sensor it can be expected from this study that the SF_6 sensor can be calibrated by means of single checks at 1% SF_6 using a (premixed) gas mixture in a gas cylinder. This procedure enables easy calibration of the sensor at the bedside. Computerised zeroing of the recorded signal can treat unexpected signal drift of the sensor occurring during measurements with the analyser. Future improvement of the analyser may include a change in the design of the inline measurement sensor in terms of further reduction of the size of the measurement transducer, filtering of the analyser output signal and increased stability of the electronics. An alternative light source may be used such as a 10.6 μm laser. Further studies have to determine if redesign of the in-circuit transducer may render it more compact and disturbance resistant.

The sensor complies with the demands stated in the introduction in terms of measurement accuracy, response time to changes in SF_6 concentration and compact size. Application of the sensor in SF_6 washout tests to determine EELV in mechanically ventilated critically patients has been successfully commenced in our clinic (unpublished observations). Although we have developed this sensor to conduct washout tests in mechanically ventilated patients, the use of this sensor is not necessarily restricted to this group. In any study where inline breathing circuit measurement of SF_6 gas is desired, it may be profitable to evaluate the use of the described sensor.

Acknowledgements

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CHAPTER 4

A setup to measure the end-expiratory lung volume in mechanically ventilated patients

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Submitted for publication.

Abstract

Objective: A setup is presented which has been designed to determine the end-expiratory lung volume in mechanically ventilated patients.

Design: Prospective in-vitro study, and a case report to demonstrate monitoring of the end-expiratory lung volume in a mechanically ventilated patient

Setting: Research laboratory of a surgical intensive care unit.

Interventions: The end-expiratory volume of a lung model was measured during different ventilator settings using the multiple breath sulphur hexafluoride washout with the described setup. The frequency, tidal volume, peak inspiratory pressure and PEEP level were varied by making adjustments to an artificial respirator which was used to ventilate the lung model. No interventions were made during measurements conducted in the study patient.

Measurements and results: The end-expiratory volume of the dummy lung was determined by using a helium spirometer to be 2.9 ± 0.03 L (mean ± SD) with a repeatability of 104 mL, and the experimental setup of 3.0 ± 0.03 L (mean ± SD) with a repeatability of 131 mL. Determinations in a paralysed mechanically ventilated patient without voluntary breathing attempts showed a end-expiratory lung volume of 1.1 ± 0.04 L.

Conclusion: This setup can be used to determine the end-expiratory lung volume in mechanically ventilated patients.

Introduction

The end-expiratory lung volume (EELV, also referred to as functional residual capacity) is an important measure in lung function evaluation, because it equals the volume of air that participates in pulmonary gas exchange. This parameter is measured to monitor restrictive lung diseases and to assess the degree of hyperinflation in chronic obstructive lung disease(1). EELV measurements are routinely performed in lung function laboratories, but the availability to measure lung volume in mechanically ventilated patients is limited. This is caused by the fact that the setups used in lung function laboratories are often not suited for routine use in the intensive care setting, either because of their size (as in the case of body plethysmographs or mass spectrometers) or because of the limitation of the type of technique used to measure the EELV (for example, the application of the helium dilution technique necessitates a closed breathing circuit which is not generally used in the intensive care unit). Moreover, co-operation of mechanically ventilated patients in aid of the EELV measurement can often not be expected, which is an important consideration in designing a setup for this purpose. Another consideration in the routine measurement of EELV in this patient group is the variation of tidal volume and breathing flow during the period of mechanical ventilation. Measurements of EELV in these patients must be resistant to changes in breathing patterns or ventilator settings. The measurement of EELV during mechanical ventilation has been shown to provide important information in the study of development and treatment of lung failure(2-13). However, the lack of reliable (and commercially available) measurement systems has delayed the further evaluation of the potential role of EELV-monitoring in the treatment of lung failure.

We have developed an experimental setup for non-invasive determination of EELV in mechanically ventilated patients based on the multiple breath inert gas washout technique(8, 14, 15). With this technique, the lungs are equilibrated with a low fraction of non-toxic non-soluble tracer gas. After the tracer gas has been equilibrated within the lungs, the injection of tracer gas is terminated. The volume of tracer gas exhaled is considered to equal, or at least to parallel the EELV. The method of EELV determination used in this study employs sulphur hexafluoride (SF_6) as a tracer gas. The setup described in this study consists of an SF_6 analyser, a flow proportional gas injection system, a measurement system and is designed compactly and is user-friendly in its use. Our present design and test strategies differ from designs and studies previously described in the

literature. In this study, we describe aspects of design, validation, reliability of the measurement method and repeatability and accuracy of the obtained EELV measurements.

Materials and methods

The setup consists of an Evita 4 type ventilator (Drägerwerk Aktiengesellschaft, Lübeck, Germany), a tracer gas injection system and a measurement system. Figures 1 and 2 display drawings of the setup.

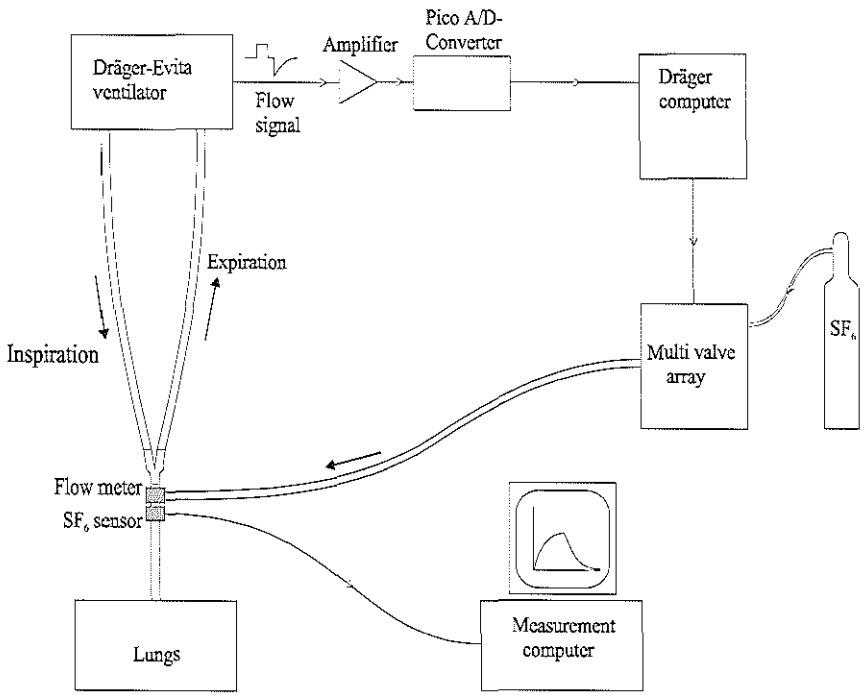

Figure 1. A schematical drawing of the measurement setup. The breathing circuit consists of the tubing of a Dräger-Evita ventilator and the lungs of the patient or lung model. In the breathing circuit the ambient flow is measured by a flow meter and the SF_6 gas is detected by a SF_6 sensor. After the EELV measurement is initiated, the multi-valve array lets through a flow of SF_6 gas. The number of valves which opens in the multi-valve array is determined by the Dräger computer and depends on the magnitude of the flow signal. The analog flow signal is converted into a digital signal by the Pico A/D converter. The signals of the flow and SF_6 gas in the breathing circuit are stored and analysed in the measurement computer.

Measurement system: The measurement system consists of a heated pneumotachograph (Fleisch No 1, Bilthoven, The Netherlands), an SF_6-gas analyser (Central Instrumentation Department, Erasmus University Rotterdam, The Netherlands) and a personal computer(IBM-compatible 586, 166 MHz processor). The flow meter measures the tidal flow in the breathing circuit, which is used to calculate the tidal volume.

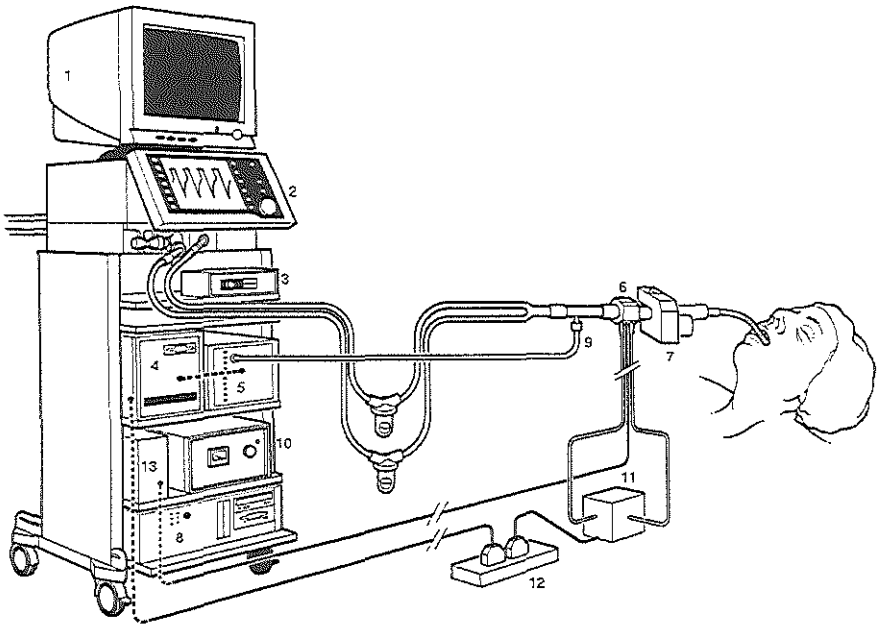

Figure 2. Drawing of the measurement setup (see also figure 1) integrated with an Evita 4 ventilator. The equipment rack is concealed in a steel encasing in such a way that the setup equipment does not interfere with procedures at the bedside during treatment of the patients. All tubing used is flexible and the electronic cables used have been tested for safety for patients and personnel, and safety during power overload.
(1. Monitor of the measurement computer 2. Display of the Evita 4 ventilator 3. Monitor switch 4. Injection computer 5. Multi-valve array 6. Flow meter 7. SF_6 transducer 8. Computer for data acquisition and analysis 9. Injection port for the tracer gas 10. SF_6 analyser 11. Pressure transducer 12. A/D converter 13. Flow meter heating unit)

For the tracer gas injection method a multi-array solenoid valve system is used (Babylog® 8000 ventilator, Drägerwerk AG Lübeck, Germany, figure 1 and 2). The analog signals of the flow meter in the breathing circuit and of the measurement system of the tracer gas

concentration are converted using an analog-digital converter (DAS-1720AO board, Keithley Instruments, Taunton, MA, USA). These signals (12 bit, ± 5V sample range) were sampled by the computer at a rate of 100 Hz, and then analysed using custom-made software developed under Testpoint™ (Capital Equipment Corporation, Billerica, MA, USA). The software first converts the output signal of the SF_6 analyser to gas fractions using a best fit of its non-linear calibration curve (figure 3). The calibration curve was obtained by presenting gas mixtures consisting of medical air and SF_6 in incremental steps of 0.02% SF_6 in a range of 0 to 2% to the SF_6 analyser. These mixtures were obtained by using a gas mixing pump (Gould/Godart b.v. Bilthoven, The Netherlands).

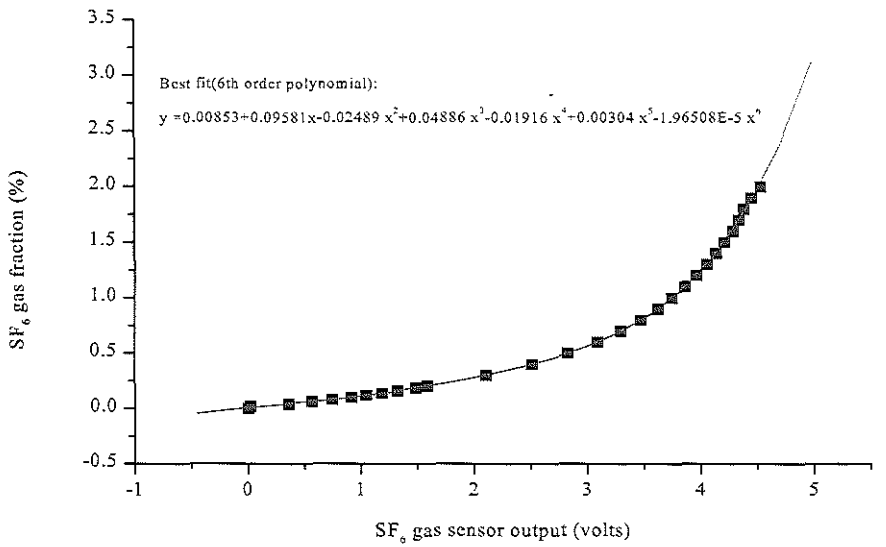

Figure 3. Example calibration curve of the SF_6 analyser. The function obtained after a 6th order polynomial curve fitting procedure performed on the calibration data of the analyser is presented in the graph.

The tracer gas injection system consists of a SF_6 tank and a flow-proportional gas injector (figure 1 and 2). The tracer gas is delivered to the injector at an inlet pressure of 2-6 bar. A ventilator especially suited for neonatal and paediatric patients (Babylog®8000, Drägerwerk Aktiengesellschaft, Lübeck, Germany) was modified to inject tracer gas

proportional to the inspiratory flow in the breathing circuit. The valve array of the ventilator consists of 20 valves of which 10 valves were electronically and digitally operated by a small sized auxiliary computer (386 SX, 20 MHz processor) using a custom-made software package (using Turbo Pascal). Each valve has a different orifice diameter which ranges from 40 to 820 μm. The system was configured to increase the number of open valves, and thereby the flow of tracer gas into the breathing circuit, with increasing *inspiratory* flow rate. The injection of the tracer gas was initiated and terminated manually or automatically via the main measurement computer. The measurement setup was integrated with an Evita 4 ventilator and was fitted according to the ISO/IEC 601 guidelines for safety of medical equipment.

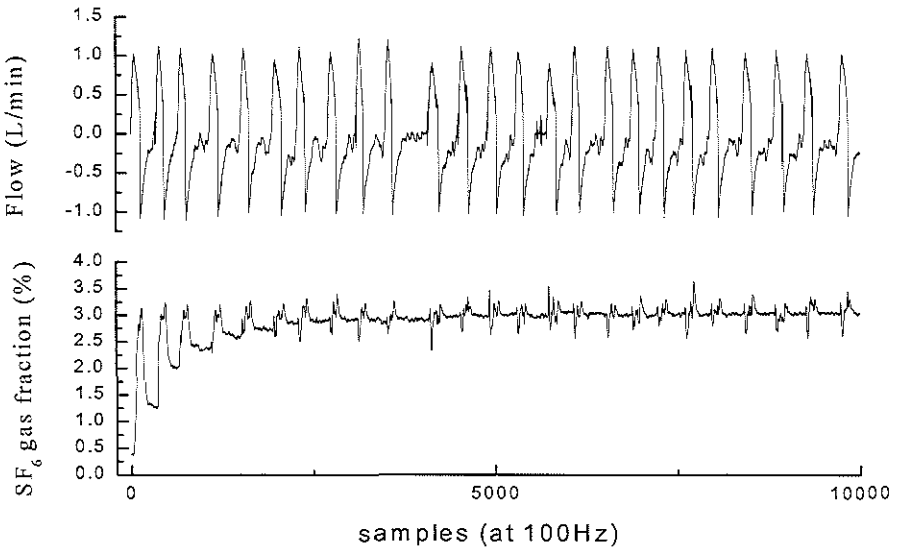

Figure 4. Recording of the breathing flow rate and the SF_6 gas concentration during wash-in of SF_6 gas into the lungs of a patient.

Signal treatment and analysis: The EELV at time point t_1 is calculated using:

$$EELV_{t_1} = \frac{\sum \int_{t_1}^{t_1'} \dot{V}(t)F(t)dt}{F_0 - F_{t_1}}$$

F : is the tracer gas fraction at different points in time; $F(t)$ is the decay of the tracer gas fraction over the entire washout period. F_0 is the tracer gas concentration in the lungs at the start of the washout, and F_{t_1} is the tracer gas fraction at t_1. $\dot{V}(t)$ is the respiration flow during the washout(7, 8, 16). The output signal of the SF_6 analyser drifted during washout measurements (fig 5) which was found to contribute significantly to the error of the EELV calculations. To eliminate electronic disturbance, the signal of the analyser was corrected for signal drift using an off-line correction method. The output signal of the SF_6-analyser was stored on disk, and subsequently imported as ASCII-file in a spreadsheet programme. For each washout, the deviation of each inspiration from the zero line was measured. Using a baseline correction function the irregularities of the SF_6 signal were subtracted to achieve a stable zero signal throughout the measurement period (figure 5). After a drift corrected SF_6 signal was obtained, the signal was fed into the calculation programme. The data acquisition computer was configured to calculate the coefficient of variation (CV= (standard deviation/mean)*100%) of the F_0 and $F(t)$ values *online* during the end of the washin period and the washout period. If the CV of these values exceeded 5% during data acquisition, the measurement was considered to contain an unacceptable level of signal disturbance and therefore discarded.

Validation tests: In order to test the accuracy of the EELV measurement setup, the volume of a two-compartment dummy lung was repeatedly determined (Demonstrations Thorax, Drägerwerk, Lübeck, Germany). The EELV of the dummy lung was also measured using a helium dilution technique for reference. To assess the measurement error of the EELV determination the repeatability was calculated. Repeatability of the measurement results (r) is defined as: $r = t\sqrt{2}s$ where s represents the standard deviation of a population m of repeat determinations under repeatability conditions, and t is taken from the two-sided t-table with $(m-1)$ degrees of freedom at p=0.05 (17).

The EELV measurement was repeated three times at zero PEEP, and performed using two different helium spirometers. To assess if systematic differences exist between the EELV of the dummy lung in different ventilator modes, measurements of EELV were obtained using the experimental setup during mechanical ventilation of dummy lung in different ventilator settings. The dummy lung was ventilated in both volume controlled (Intermittent Positive Pressure Ventilation (IPPV)) and pressure controlled ventilator

modes (Biphasic Positive Airway Pressure (BIPAP)). The breathing frequency during the dummy lung experiments was either 10 or 18 breaths per minute. Finally, to demonstrate the in vivo accuracy of the EELV measurement, measurements were repeated at fifteen minute intervals in a mechanically ventilated fully immobilised and sedated patient, while no adjustments whatsoever were made on the ventilator. To perform these measurements, a waiver was obtained from the ethical committee of our institution and permission of the patient's next of kin was obtained according to the principles established for human studies of Helsinki.

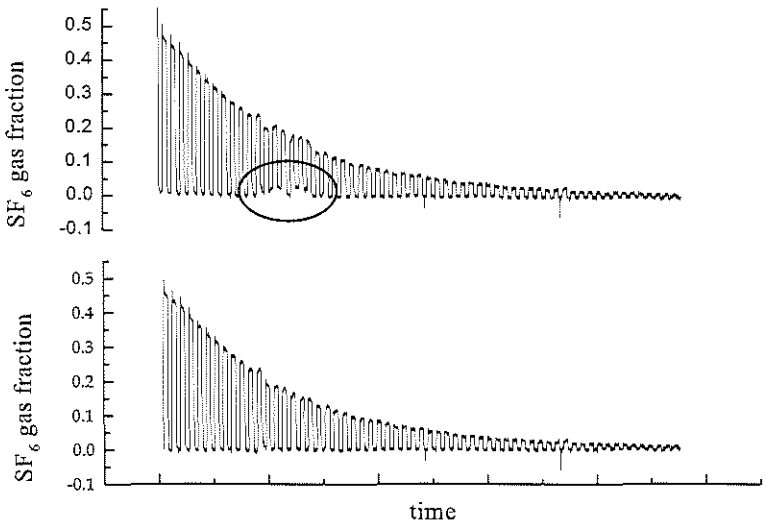

Figure 5. The area in the ellipse indicates the area where spontaneous drift of the SF_6 sensor signal occurred. The bottom graph displays the same washout curve after mathematical correction of the signal.

Results

Measurement system: Figure 1 shows the measurement setup and figure 2 shows the setup with its components integrated with a ventilator. The calibration curve of the SF_6 analyser is shown in figure 3. Figure 4 shows that the shape of the inspiratory flow curve is somewhat superimposed on the washin curve. This effect is caused by opening and/or closing artefacts of the valves of the injection system of SF_6. These gas flow artefacts can

potentially disturb proper determination of the concentration of SF_6 in the lungs at the start of the washout (F_0). This is because during the signal analysis in the EELV calculation algorithm (see methods section) any disturbance in the input F_0 value will directly affect the calculation of EELV values. The method section describes the procedure we used to eliminate artefacts of the SF_6 concentration signal off-line (See figure 5).

Validation tests: The helium dilution method was applied using a spirometer (Masterscreen FRC, Jaeger, Würzberg, Germany) measured the EELV of the dummy lung as 2.9 ± 0.03 L (mean ± SD). The repeatability of the helium dilution method using the Masterscreen spirometer was documented by the manufacturer to be 104 mL: Table 1 displays the mean of 10 EELV determinations in the dummy lung using the experimental setup in five different ventilator settings. The ventilator settings were changed in terms of I:E (inspiration : expiration) ratio, respiration frequency, inspiratory peak pressure and inspiratory time. The results of these 50 separate EELV measurements in the dummy lung show that during EELV measurements with a fixed level of (zero) PEEP the range in EELV was 3.0-2.9 L with a range in SD of 0.03-0.07 L.

The repeatability of the measurement method (at the 5% level of significance) calculated from the dummy lung measurements ranged between 85 and 241 mL, and the CV ranged between 1-2% in 10 repeated EELV measurements in 5 different ventilator settings. Figure 4 shows a washin of SF_6 gas and the flow in the breathing circuit during mechanical ventilation. Figure 6 demonstrates the variability of the EELV measurement when using this setup in a fully sedated patient during an unchanged ventilator setting.

MODE	RR	Pmax	PEEP	I:E	Tinsp (s)	TV (L)	mean EELV (L)	sd EELV(L)
BIPAP	10	30	0	1:2.5	1.7	1.2	3.04	0.06
BIPAP	18	30	0	1:1	1.7	1.2	3.04	0.07
SIMV	18	42	0	1:1	1.7	1.2	3.08	0.05
BIPAP	18	20	0	1:1	1.7	1.2	2.90	0.03
BIPAP	10	30	0	1:1	3.0	1.3	2.96	0.03

Table 1. Results of EELV measurements in a dummy lung obtained in different ventilator settings. RR= respiratory rate, Pmax= inspiratory peak pressure, I:E= inspiratory/expiratory ratio, Tinsp= inspiratory time, TV=tidal volume

During washout the concentration of SF_6 in the expired air gradually decreases. It can therefore be expected that, due to noise on the SF_6 signal below a certain SF_6

concentration level the inclusion of further breath cycles in the calculation of EELV will deteriorate the accuracy of the EELV measurement. Table 2 shows the breath by breath increment in EELV during 12 SF_6 washout tests. To study the influence of the error of the signal of the SF_6 transducer on the EELV measurement, the cumulative EELV was calculated breath by breath during 12 measurements in a dummy lung with a fixed setting of the ventilator. Table 2 displays the increase in EELV and the increase in CV.

The data of table 2 shows that the EELV does not increase significantly after a certain (equilibrium) value of SF_6 gas volume has been reached. As the amount of SF_6 declines, the effect of noise on the signal, and therefore the effect on the absolute value of the EELV increases. To remedy this, cut-off points were chosen for the SF_6 signal beyond where no further EELV calculation was made. We chose to exclude the part of the washout signal when the SF_6 analyser output signal was reduced to less than 0.050 V, because there the signal to noise ratio of the SF_6 analyser signal starts to increase. The repeatability of the experimental EELV measurement was 131 mL, and the CV was 4%.

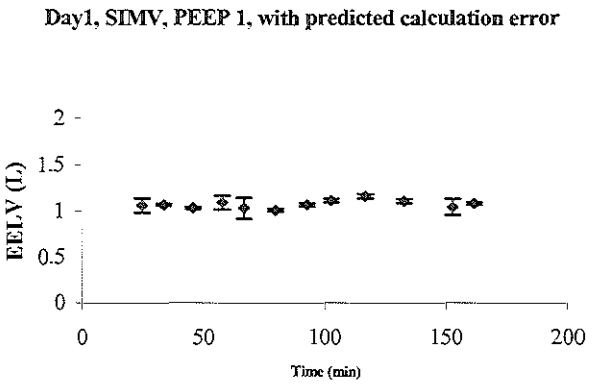

Figure 6. The result of repeated measurements in a paralysed mechanically ventilated patient with a fixed ventilator setting.

Figure 6 demonstrates the results of the determination of the EELV at 15-minute intervals in a mechanically ventilated and sedated patient. During the measurements the patient did not display any voluntary breathing attempt, no adjustments were made in the ventilator settings and no other manoeuvres were undertaken which are known to influence lung volume. In figure 6, at each interval the EELV represents the mean and standard deviation

of three measurements. The EELV of this patient during the measurement period was 1.1 ± 0.04 L.

Washout No:	1	2	3	4	5	6	7	8	9	10	11	12	sd (L)	mean (L)	CV
breath 1	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.01	0.8	1%
breath 2	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	0.02	1.4	1%
breath 3	1.8	1.8	1.8	1.8	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	0.03	1.8	1%
breath 4	2.1	2.1	2.1	2.1	2.2	2.1	2.1	2.1	2.1	2.1	2.1	2.1	0.02	2.1	1%
breath 5	2.4	2.3	2.3	2.3	2.4	2.4	2.4	2.3	2.3	2.4	2.3	2.3	0.03	2.3	1%
breath 6	2.6	2.5	2.5	2.5	2.6	2.5	2.6	2.5	2.5	2.5	2.5	2.5	0.04	2.5	2%
breath 7	2.7	2.6	2.7	2.6	2.7	2.6	2.6	2.6	2.6	2.6	2.6	2.7	0.03	2.6	1%
breath 8	2.8	2.7	2.8	2.7	2.8	2.8	2.8	2.7	2.7	2.7	2.7	2.7	0.04	2.7	2%
breath 9	2.9	2.8	2.8	2.8	2.9	2.8	2.8	2.8	2.8	2.8	2.8	2.8	0.05	2.8	2%
breath 10	2.9	2.8	2.9	2.8	2.9	2.8	2.9	2.9	2.9	2.9	2.9	2.8	0.04	2.9	1%
breath 11	3.0	2.9	2.9	2.9	3.0	2.9	2.9	2.9	2.9	2.9	2.9	2.9	0.04	2.9	1%
breath 12	3.1	2.9	3.0	2.9	3.0	3.0	3.0	2.9	2.9	2.9	2.9	3.0	0.06	3.0	2%
breath 13	3.0	3.0	3.0	2.9	3.0	3.0	3.0	2.9	3.1	3.0	3.0	3.0	0.06	3.0	2%
breath 14	3.1	3.1	3.1	3.1	3.1	2.9	3.1	3.0	3.0	2.9	3.0	2.9	0.09	3.0	3%
breath 15	3.2	3.1	3.1	3.0	3.1	3.0	3.0	3.2	3.0	3.0	3.0	2.9	0.08	3.1	3%
breath 16	3.2	3.3	3.0	3.0	3.1	3.2	2.9	3.0	3.1	3.1	3.1	3.2	0.10	3.1	3%
breath 17	3.1	3.0	3.1	3.1	3.1	3.2	3.1	3.1	3.1	3.0	3.2	3.0	0.07	3.1	2%
breath 18	3.2	3.1	3.0	3.0	3.2	2.9	3.1	3.2	3.1	3.1	3.0	3.1	0.10	3.1	3%
breath 19	3.3	3.1	3.2	3.0	3.2	3.0	3.2	3.0	3.1	3.2	3.2	3.1	0.08	3.1	2%
breath 20	3.1	3.1	3.1	3.2	3.1	3.0	3.2	3.1	3.2	3.1	3.1	3.0	0.06	3.1	2%
breath 21	3.2	3.2	3.1	3.1	3.1	3.1	3.2	3.0	3.4	3.1	3.2	3.1	0.09	3.1	3%
breath 22	3.3	3.1	3.2	3.3	3.2	3.0	3.2	3.1	3.1	3.1	3.2	3.1	0.10	3.2	3%
breath 23	3.3	3.1	3.2	3.1	3.2	3.2	3.4	3.1	3.2	3.2	3.1	3.2	0.08	3.2	3%
breath 24	3.4	3.2	3.3	3.2	3.3	3.2	3.2	3.3	3.2	3.3	3.2	3.2	0.06	3.2	2%
breath 25	3.2	3.4	3.2	3.2	3.3	3.2	3.3	3.2	3.2	3.2	3.2	3.4	0.07	3.3	2%

Table 2. Breath-by-breath cumulative EELV measurements in a mechanically ventilated dummy lung with a fixed ventilator setting

Discussion

We present a system to measure the EELV during mechanical ventilation. The method yields values of EELV after the washout has terminated and the calculation sequence has finished, which takes approximately three minutes. The system was evaluated in different ventilator settings, and was found to give reproducible results (See table 1 and 2). Furthermore, the determinations of EELV using the experimental technique compared well to the EELV determinations of the spirometer used in this study. The previously proposed accuracy requirements for standardised pulmonary function tests of 10% have been easily met with this setup(18). The repeatability of the described method of ± 131

mL should be clinically interpreted such that no changes in EELV can be confidently detected which are smaller than this value. This repeatability value is in the range of previous studies. Paloski et al. found a replication error in EELV measurement of 38-52 mL. Larsson and co-workers reported a range in CV of 0.6 to 6.6% while East et al. reported a reproducibility of the EELV washout technique of 188 ± 17 mL or 11.7 ± 0.7%. (6, 15, 19). Taking the repeatability of our technique into account, the results also compared well to the determinations of EELV using the helium dilution technique(9, 20-22). Drift of the signal of the SF_6 analyser occurred during the experiments, which is the main cause of error in the EELV calculation. The drift is most frequently seen when obtaining data from patients, which suggests a sensitivity of the SF_6 analyser to heated and humidified air. Humidified air was previously reported to show no effect on the signal, but the effects on the drift of the signal were not studied specifically(23). However, the effects of drift of the SF_6 sensor output can be removed from the signal using a mathematical baseline correction off-line which is described in the methods section. An alternative would be to reset the signal of the SF_6 analyser to zero during inspiration in the washout phase (8, 19). It is unclear to us if these systems provide better signal treatment or results than the measurement system discussed in the present study.

In this study, the assessment of the EELV measurement accuracy of the setup was done in a mechanically ventilated dummy lung and further demonstrated in a sedated mechanically ventilated patient. The determination of measurement accuracy of the setup in mechanically ventilated patients is cumbersome. This is because changes in body position, administration of pharmacological agents, administration of PEEP and other manoeuvres (common in the mechanically ventilated patient group) influence the magnitude of the EELV(21). Because prevention of these manoeuvres for the sake of our study purpose may not serve the benefit of the study patient, we limited our investigations to those intervals during the treatment of the patient where no therapeutical measures were undertaken. Furthermore, the recovery or deterioration of the underlying disease during the mechanically ventilated period may cause a change in EELV, which may hamper the determination of accuracy of the setup alone. To eliminate these effects as much as possible, we chose to obtain the data of repeatability of the EELV measurement in the study patient in a time period of approximately 3 hours by measurements which were obtained every 15 minutes.

The setup is used together with the Evita 4 ventilator (Dräger), but could be integrated easily with another type of ventilator. Despite the fact that development of this type of analyser started in 1985, it is not a commercially available product. Nevertheless, the need for a measurement system to measure the EELV in mechanically ventilated patients remains, because it enables assessment of the effects of different treatment modalities (such as PEEP application and titration, administration of drugs, endotracheal suctioning, change in body position) on the lung volume can be studied. We conclude that in this study, the described setup enabled performance of reproducible measurements of EELV.

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SECTION III:

EXPERIMENTAL STUDIES

CHAPTER 5

Non-invasive monitoring of non-shunted pulmonary capillary blood flow in the acute respiratory distress syndrome

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Abstract

Objective: Non-invasive monitoring of non-shunted pulmonary capillary blood flow, using the alveolar amplitude response technique (AART) in a porcine model of the acute respiratory distress syndrome (ARDS).

Design: Experimental animal study

Setting: University center for animal experiments

Interventions: In twelve mechanically ventilated pigs the non-shunted pulmonary capillary blood flow was varied by means of lung lavages and the application of positive end-expiratory pressure (PEEP).

Measurements and results: Non-shunted pulmonary capillary blood flow was determined by AART. Cardiac output (determined by the thermodilution method) corrected for venous admixture was used for comparison (r^2 varied between 0.58 and 0.94; $p < 0.01$). The trend in the development of non-shunted pulmonary capillary blood flow as measured with AART was in agreement with the trend detected by cardiac output corrected for venous admixture in 92% of all events.

Conclusions: We conclude that AART can be used to monitor changes in non-shunted pulmonary capillary blood flow in ARDS non-invasively and continuously.

Introduction

In patients suffering from the acute respiratory distress syndrome (ARDS), positive end-expiratory pressure (PEEP) is applied to increase the arterial oxygen tension (P_{a,O_2})(1, 2), and thereby the oxygen delivery. The improvement in oxygen delivery that is obtained by applying PEEP depends on the extra fraction of alveoli that is recruited on the one hand and the reduction of cardiac output on the other hand. It is difficult to find the optimum in oxygen delivery in practice because measurements of cardiac output and arterial blood gases cannot be carried out continuously. Monitoring of oxygen delivery can therefore only be done by repeated measurements, which is labor-intensive and time consuming. Also, not all patients to whom PEEP is administered are given a pulmonary artery catheter by which measurements of cardiac output can be made.

Several methods have been proposed to find the optimum level of PEEP. Reduction of venous admixture(3, 4), optimization of oxygen delivery(5) and adjusting PEEP to the near-normal volume of functional residual capacity(6) have all been proposed as methods for the titration of PEEP. The optimum level of PEEP has been defined as the level at which an intrapulmonary shunt lower than 15% is reached at an inspiratory oxygen fraction (F_{i,O_2}) of 0.5(3, 4). Titration of PEEP to the level of maximum lung compliance has also been done, and the optimum in lung compliance was found to correspond with the maximum in oxygen delivery(5). The appropriate level of PEEP in ARDS has also been suggested to lie beyond the lower inflection point of the static inspiratory pressure-volume curve(7, 8). The static inspiratory pressure-volume curve is constructed by inflating the lungs of the patient, often using a syringe with a large volume, and measuring the pressure at different inspiratory volumes. The inflection point of the pressure volume curve is seen where a significant increase in volume occurs, which is also referred to as opening pressure. Instituting PEEP above the opening pressure indicated at the inflection point not only improves the ventilation-perfusion relationship in the lung, but also prevents lung injury by repetitive opening-closing of alveoli.

The problem with the methods mentioned so far is that they either do not directly measure the oxygen delivery and/or necessitate invasive measurements. Because these

measurements are mostly done intermittently, the titration of PEEP cannot be carried out on-line. In addition, these techniques often necessitate the use of intravascular catheters, which harbor a risk of infection, especially in the critically ill.

A solution to these problems would be a monitoring technique that can measure the oxygen supply continuously, and non-invasively. Therefore, we evaluated the efficacy of the alveolar amplitude response technique (AART)(9) in determining the optimum level of oxygen delivery, and by optimum level of PEEP. With AART it is possible to measure the blood flow through ventilated alveoli(10), which is directly influenced by PEEP. This measurement can be done continuously, and non-invasively. In AART a soluble and inert tracer gas is administered into the breathing circuit of the patient. Its concentration is varied sinusoidally in time and the tracer gas concentrations in the inspired and expired air are measured. The sinusoid period is chosen such, that after passage of the blood through the various body compartments, the sinusoidal variations in tracer gas concentration have dampened out in the venous return; i.e. the tracer gas concentration in the venous return is constant. Because of this only the amplitudes and the phase difference of the time dependent parts of the tracer gas concentration in inspired and expired air are needed to obtain a measure of the pulmonary capillary blood flow(9, 10)(see the appendix). Other techniques using soluble gas to measure pulmonary capillary blood flow include rebreathing techniques and single exhalation analysis. Rebreathing techniques using soluble gases have been shown to be comparable to thermodilution cardiac output(11, 12). Single exhalation analysis also proved to be a valuable tool to determine pulmonary capillary blood flow in spontaneously breathing and awake humans(13, 14). Compared to AART, these techniques have important drawbacks for continuous monitoring. Firstly, to apply the single exhalation analysis in uncooperating, mechanically ventilated individuals, breath holding has to be mimicked using a inspiratory hold maneuver. The use of this maneuver disrupts the breathing pattern, which may not be desirable in critically ill patients, and also renders the technique unfit for continuous application. Secondly, rebreathing techniques necessitate the use of a rebreathing bag, or a closed circuit. In open-circuited respirators, the use of rebreathing techniques will necessitate switching to a closed circuit to perform the measurement. Contrary to AART, the necessity of these maneuvers in rebreathing techniques renders these techniques intermittent.

Many authors have applied AART (also referred to as the sinewave technique) (10, 15-17), and advanced the underlying theory(18-20). Zwart et al. applied this technique in animals, with halothane as the tracer gas, and compared the non-shunted pulmonary capillary blood flow as determined by the AART with the flow in the aorta(9) determined by the use of an electromagnetic flow probe. The technique was verified for animals in rest by means of the Fick method for oxygen, corrected for venous admixture during hyper- and hypovolemia(10). These early results indicated the monitoring potential of the technique, for the study of the influence of PEEP on intrapulmonary shunting(9). The results of the application of AART in healthy volunteers(15, 16) during exercise further established AART as a method for the monitoring of non-shunted pulmonary capillary blood flow. More recently, AART-resembling techniques employing nitrous oxide, argon and even oxygen have been developed for the measurement of non-shunted pulmonary blood flow and/or the alveolar volume(17, 18, 20, 21). The technique has been applied in human and animal studies over the last 20 years, but no results of the application of AART in disease models have been published. However, this measurement may prove to be important in the optimal application of mechanical ventilation and pharmacological agents that influence pulmonary blood flow. We therefore conducted a study designed to determine whether AART can be used to continuously monitor the non-shunted pulmonary capillary blood flow in diseased lungs, and during the administration of PEEP.

Materials and methods

Theory: Derivation of an expression for the non-shunted capillary blood flow, in terms of variables that are obtained by AART, is based on the Riley-Cournand model (see(6, 7, 16)) and the appendix). This model includes a dead space compartment that is continuously ventilated but lacks blood flow ($\dot{V}_D$), a shunt compartment having blood flow but no ventilation ($\dot{Q}_S$), and a single homogeneous alveolar compartment having both blood flow and continuous ventilation ($\dot{V}_A$). The basic concept of the model is a combination of ideal mixing boxes placed in parallel and series as is commonly used in modeling studies of the uptake of gaseous agents by the body(22, 23). Non-pulsatile ventilation and lung perfusion are assumed and the volumes of inspired and expired gas are taken to be equal. One of the basic assumptions in the AART model is that if a physiologically inert and soluble gas is inhaled, its end-expiratory partial pressure in the

pulmonary capillary blood equals that in the lungs(9, 10). In AART, the difference between the inspiratory and expiratory gas concentration sinusoids is described by means of the amplitude ratio and the phase difference. These two variables are used to calculate the blood flow through the ventilated compartment of the lung. This calculation furthermore requires as input the alveolar ventilation ($\dot{V}_A$) and the blood gas partition coefficient (λ) of the tracer gas used.

Both the end-inspiratory and end-expiratory fractions of the tracer gas form sinusoidally varying time series (see figure 1). The period (T), amplitude ratio (A_I/A_A) and the phase difference (α) of the sinusoids were calculated using a least-squares curve fitting technique in a spreadsheet (Quattro Pro, Borland International, Scotts Valley, CA, USA) with a personal computer (Pentium, American Megatrends, USA). Finally, the values for T, A_A/A_I, and α were entered in the expression:

$$\dot{Q}_{AART} = \frac{\dot{V}_A}{\lambda}\left(\frac{A_I}{A_A}\cos\alpha - 1\right) \qquad \text{Equation 1}$$

The alternative calculation of non-shunted pulmonary capillary blood flow, based on measurement of thermodilution cardiac output and venous admixture was done using:

$$\dot{Q}_{Td\,ya} = \dot{Q}_{Td}\left(1 - \frac{\dot{Q}_S}{\dot{Q}_T}\right) \qquad \text{Equation 2}$$

The derivations to obtain these equations are presented in the appendix.

Measurement protocol. This study was approved by the animal care committee of the Erasmus University Rotterdam and conforms to the guiding principles in the care and use of animals of The American Physiological Society.

Preparation. Twelve healthy female Yorkshire pigs, ranging in weight from 23 to 35 kg were IPPV ventilated with a respirator (Siemens 900), under pentobarbital anesthesia. The internal carotid artery was cannulated to acquire arterial blood samples. A pulmonary artery catheter was introduced in the internal jugular vein. The external jugular vein was cannulated to obtain mixed venous blood samples.

Indicator gas delivery system. Following Zwarts original approach(9, 10) we used halothane as the indicator gas. A gas-mixture containing halothane was produced as follows: A mass flow controller (inlet pressure 3-4 bar) (Hi-tec, Bronkhorst, Ruurlo, The Netherlands), controlled by a wave generator (Wavetek model 185, San Diego, CA, USA), produced a sinusoidally modulated flow of an oxygen-air mixture. This flow was led

through a halothane kettle and then mixed with a carrier gas. This carrier gas consisted of an oxygen-air mixture, which was regulated by a flow controller at a rate of 1 L/s. The mixture of tracer gas and carrier gas was fed into the low-pressure entrance of the ventilator. This resulted in an inspiratory halothane fraction between 0.1 and 0.9% depending on the tidal volumes used. The flow controllers of the oxygen-air mixture were adjusted until a sinusoidally varying inspiratory fraction of halothane between 0.1 and 0.9% was obtained.

Measurements: In- and expiratory flow measurements were made with a Fleisch pneumotachograph (Godart-Statham, Bilthoven, The Netherlands) which was calibrated with a 1 L syringe. The pressure difference over the flow meter was measured using a differential pressure transducer (Hewlett Packard model 270, HP International, California, USA) and a signal conditioner (Hewlett-Packard model 8805B carrier amplifier, HP International, California, USA). Cardiac output was measured by means of the thermodilution method. The cardiac output measurement system included a pressurized pistol which emptied a 10 mL saline filled syringe automatically at 0, 33% and 66% of the breath cycle (Central Instrumentation Department, Erasmus University Rotterdam, The Netherlands) according to the method suggested by Jansen(24, 25). Analysis of the temperature time curve was made with a cardiac output monitor (Datex, AS/3, Helsinki, Finland). For gas fraction measurements a mass spectrometer was used (QP 9000 or MGA 3000, Case Instruments, Kent, UK). The signals of the flow meter, and mass spectrometer (CO_2 gas fraction and halothane) were simultaneously registered by a pen recorder (Gould TA 2000, Gould Measurement Systems, Ilford, Essex, UK). The mass spectrometer was calibrated using a premixed gas mixture (BOC medical gases, Guildford, Surrey, UK) containing nitrogen, oxygen, carbon dioxide and halothane in proportions similar to those used in experimental conditions. To measure the mean expiratory CO_2 fraction, the expiratory air was mixed in a mixing chamber with a volume of 2 L (Respiratory flow unit, Centronic Medical, UK) which was connected to the expiratory outlet of the ventilator, and then sampled via a separate capillary by the mass spectrometer. The signals of the mass spectrometer were sampled with a frequency of 100 Hz, converted using an analog-digital converter, and stored on a computer disk. Blood samples were drawn into heparinized, plastic syringes. A blood gas analyzer (ABL 500, Radiometer, Copenhagen, Denmark) was used to measure blood gases, pH, and the hemoglobin concentration. The

oxygen saturation of the blood was measured with a second blood gas analyzer (OSM3, Radiometer, Copenhagen, Denmark).

After the surgical procedure, the animals were allowed to stabilize for one hour. Fluid status was maintained through continuous infusion of saline. The breathing frequency was adjusted until an arterial CO_2 between 34 and 45 torr [4.5 - 6 kPa] was obtained. To avoid hypothermia, the animals were placed on an electrically heated mat, which was kept at a temperature of 39.0 ± 0.5 °C.

Surfactant depletion was used to model ARDS. After baseline measurements were done, lung lavage was instituted with 35 mL/kg saline, according to the model described by Lachmann(26). For each experiment, two lung lavages were done. After the lavages varying levels of PEEP were applied in incremental and decremental steps between 0 and 20 cmH_2O [0-20 hPa]. After adjusting the ventilator, the animals were allowed to stabilize for 20 minutes before measurements were done. Except for the level of PEEP, no further adjustments whatsoever were made in the ventilator settings. Periods of hypotension subsequent to lung lavage were treated with increased infusion of saline and colloids.

Animals were killed after the experiments using a high dose of pentobarbital, or died during the experiment. The inspiratory partial pressure of halothane ranged between 0.1% and 0.5% for all experiments. In all experiments a sinusoid period between 1.5 and 3.0 minutes was used. Throughout each individual experiment, the forcing frequency of the gas sinusoid was kept constant.

Analysis: For each experiment, the correlation coefficient between $\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$ was calculated. The capability of AART to predict trends in the development of non-shunted pulmonary capillary blood flow was investigated by determining the number of instances in which the direction of changes in $\dot{Q}_{AART}$ corresponded with changes in $\dot{Q}_{Td,Va}$. Similarly, the capability of $\dot{Q}_{AART}$ to predict trends in the development of oxygen delivery was studied. This was done by calculation of the difference between the first measurement of an experiment (x_1) and subsequent measurements (x_i) using AART ($x_1 - x_i$, i=2,3,...n (n= final measurement of the experiment)) and the thermodilution cardiac output corrected for venous admixture; and the oxygen delivery ($y_1 - y_i$).

Results

Four out of twelve pigs died before sufficient post lavage measurements could be made. Data obtained from the remaining eight pigs covered a broad range of cardiac output and venous admixture values. In these experiments, a total of 131 data pairs ($\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$) were collected. A typical tracing as recorded during an AART experiment is shown in figure 1.

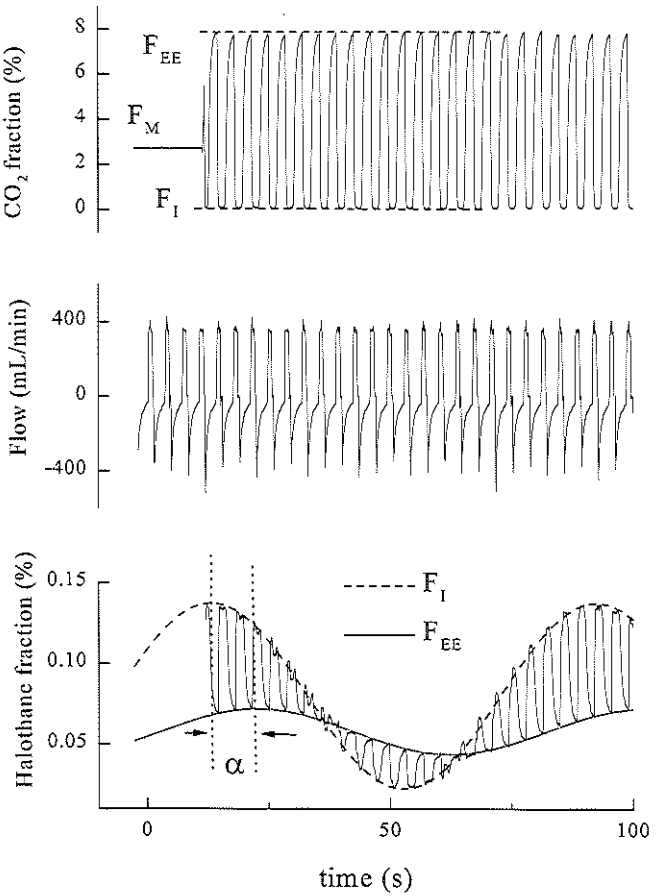

Figure 1. A tracing of the flow signal, CO_2 fraction, and halothane fraction recorded during an AART experiment. The phase shift (α) between the inspiratory halothane fraction (F_I) and end-expiratory fraction (F_{EE}). In the tracing of the CO_2 signal, the mean (F_M), inspiratory (F_I) and end expiratory (F_{EE}) CO_2 fraction are indicated.

Data of the ventilator settings that were used are given in table 1.

Pig	Weight(kg)	V_T[1](mL)	f[2](min^{-1})	F_iO_2[3]	PEEP[4](cm H_2O)
a	32	487±19	12	0.89	0-16
b	26	421±17	14	0.6	0-20
c	25	411±16	16	0.39	0-16
d	26	536±17	14	0.59	0-16
e	25	444±19	16	0.75	0-20
f	27	686±13	12	0.33	0-20
g	26	464±13	12	0.97	0-20
h	35	867±10	18	0.63	0-20

Table 1. The ventilator settings used (in IPPV mode) during the experiments. The letters a-h indicate each experiment, and correspond with the letters in figure 3.

Pigs f and h were from a different Yorkshire breed, which may be the reason for the larger tidal volume needed to achieve a physiological P_{a,CO_2}. Before lung lavage the P_{a,O_2} of the animals was in the range from 350-172 torr [47-23 kPa]. This decreased to 85-49 torr [11-7 kPa] after lung lavage. Prior to lung lavage the non-shunted pulmonary capillary blood flow as determined by AART ranged between 2.41-7.64 L/min, and after lung lavage between 0.39-6.03 L/min. Venous admixture ranged between 2-24% to 3-89% before and after lung lavage respectively.

Table 2 shows the ranges of PEEP-induced variation (before and after lung lavage) in venous admixture, non-shunted pulmonary capillary blood flow and thermodilution cardiac output. As displayed in table 2, the response of these variables to lung lavage varied considerably between experiments.

[1] tidal volume
[2] respiration frequency
[3] inspiratory oxygen fraction
[4] positive end-expiratory pressure

Table 2. This table presents ranges of PEEP-induced variation in venous admixture, effective perfusion (determined by the AART and the thermodilution cardiac output corrected for venous admixture) and thermodilution cardiac output before and after lavage, for each experiment, and n is the number of measurements made.

Ranges of PEEP-induced variation in pulmonary blood flow and venous admixture **before** lung lavage

Pig	n[5]	$\dot{Q}_S / \dot{Q}_T$ [6](%)	$\dot{Q}_{AART}$ [7] (L/min)	$\dot{Q}_{Td,Va}$ [8](L/min)	$\dot{Q}_T$ [9](L/min)
a	4	21-24	3.61-4.57	3.85-4.51	4.20-4.70
b	4	13-16	2.64-3.10	3.54-3.68	4.24-4.30
c	4	9-20	3.60-3.80	2.55-3.11	2.80-3.50
d	4	3-5	3.21-3.33	4.83-5.81	1.81-3.19
e	4	19-24	2.41-2.68	2.77-3.05	3.62-3.80
f	6	2-6	4.09-4.65	2.76-3.49	2.83-3.69
g	4	17-25	3.65-3.69	3.62-4.22	4.72-5.08
h	8	2-5	5.21-7.64	2.85-6.03	5.22-6.27

Ranges of PEEP-induced variation in pulmonary blood flow and venous admixture **after** lung lavage

Pig	n	$\dot{Q}_S / \dot{Q}_T$ (%)	$\dot{Q}_{AART}$ (L/min)	$\dot{Q}_{Td,Va}$ (L/min)	$\dot{Q}_T$ (L/min)
a	10	17-77	0.84-2.99	1.36-3.32	3.10-6.30
b	14	36-79	0.93-2.10	1.33-2.46	3.60-7.00
c	10	5-48	1.07-2.42	0.62-1.79	1.03-2.94
d	9	9-71	1.10-2.08	1.81-3.19	2.93-6.53
e	14	14-89	0.60-3.31	0.72-3.33	2.62-6.32
f	8	5-34	0.39-3.92	1.49-3.49	2.13-3.64
g	12	19-77	2.06-5.54	1.54-3.59	2.92-7.44
h	7	3-41	4.72-6.03	3.02-4.35	4.72-6.03

In figure 2 the effect of lung lavages and PEEP on the oxygen delivery, venous admixture, cardiac output and the non-shunted pulmonary capillary blood flow (as calculated by the AART) are shown as observed during an experiment. The effects of lung lavage and PEEP on these variables during this experiment are discussed below.

Venous admixture: Venous admixture was low before lavage, therefore PEEP had little effect on this parameter in this period. The effect of PEEP on non-shunted blood flow was still measurable. After the first lavage the venous admixture rises to 15%, which is reduced to 5% by the administration of PEEP. After the second lung lavage the condition of the lung has seriously deteriorated to a venous admixture of 30%, about one hour after

[5] number of measurements
[6] venous admixture
[7] non-shunted pulmonary capillary blood flow as determined by AART
[8] non-shunted pulmonary capillary blood flow as determined by the thermodilution cardiac output corrected for venous admixture
[9] thermodilution cardiac output

lung lavage. Increase in PEEP level to 16 cmH_2O [16 hPa] again reduced the venous admixture to 15%.

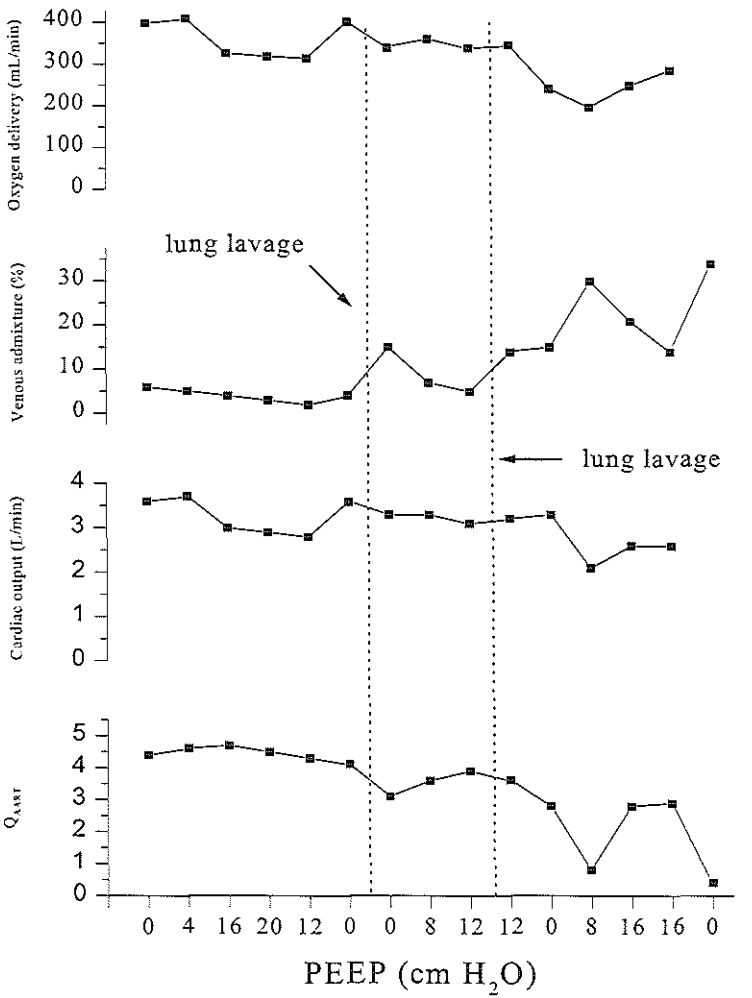

Figure 2. Changes in oxygen delivery, venous admixture, cardiac output and non-shunted pulmonary capillary blood flow (determined AART), at different PEEP levels during one experiment. The dotted lines mark the points of lung lavage.

Cardiac output: The cardiac output before lung lavage ranged between 3.6 and 2.7 L/min. PEEP administration of 16 to 20 cmH_2O [16 to 20 hPa] before lavage reduced the cardiac output to 3 L/min. In this experiment no significant effect of the lung lavage on cardiac output is seen. However, about one hour after the second lung lavage the condition of the pig seriously deteriorated and the cardiac output drops about 2 L/min.

Oxygen delivery: Prior to lung lavage, in the absence of significant venous admixture, oxygen delivery is seen to be linearly dependent on cardiac output. After the first lung lavage cardiac output is almost constant and because venous admixture is still low, no important change is seen in oxygen delivery. After the second lung lavage, the oxygen delivery decreases after the reduction of the PEEP level from 12 to 0 cmH_2O [12 to 0 hPa]. Non-shunted pulmonary blood flow (AART) Before the first lung lavage the application of PEEP has little effect on $\dot{Q}_{AART}$. This is in agreement with the low venous admixture, determined independently, but somewhat at odds with the decrease in cardiac output at high PEEP levels. The decrease of the $\dot{Q}_{AART}$ tracing after the first lavage is in agreement with that of venous admixture (increase) and cardiac output (little change). Also, after the second lung lavage the development of $\dot{Q}_{AART}$ is in agreement with what would be expected; venous admixture increases while cardiac output remains constant at first, leading to a decrease in non-shunted pulmonary capillary blood flow. Reducing PEEP levels from 12 cmH_2O to 0 cmH_2O[12 to 0 hPa] leads to deterioration, which worsens after increasing PEEP to 8 cmH_2O. This deterioration could only be counteracted by increasing PEEP to 16 cmH_2O[16 hPa]. A second cessation of the administration of PEEP resulted in death from hypoxia.

In figure 3 the $\dot{Q}_{Td,Va}$ is plotted against the $\dot{Q}_{AART}$ for all experiments. A least squares linear fit was made for each experiment. A linear relation was found between $\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$. Correlation coefficients ranged between 0.76 and 0.97 [r^2: 0.58- 0.94] and were significant for all experiments ($p < 0.01$). In theory, the slope of the best straight fitting lines in this graph should equal 1. The variation in the slope of the fitting lines from experiment to experiment, implies that a systematic error of some sort is present in these experiments. A number of sources of measurement artifacts that could have caused such a systematic error such as calibration errors, improper least squares fitting of the data and errors in the calculation procedures could be excluded (see also under discussion).

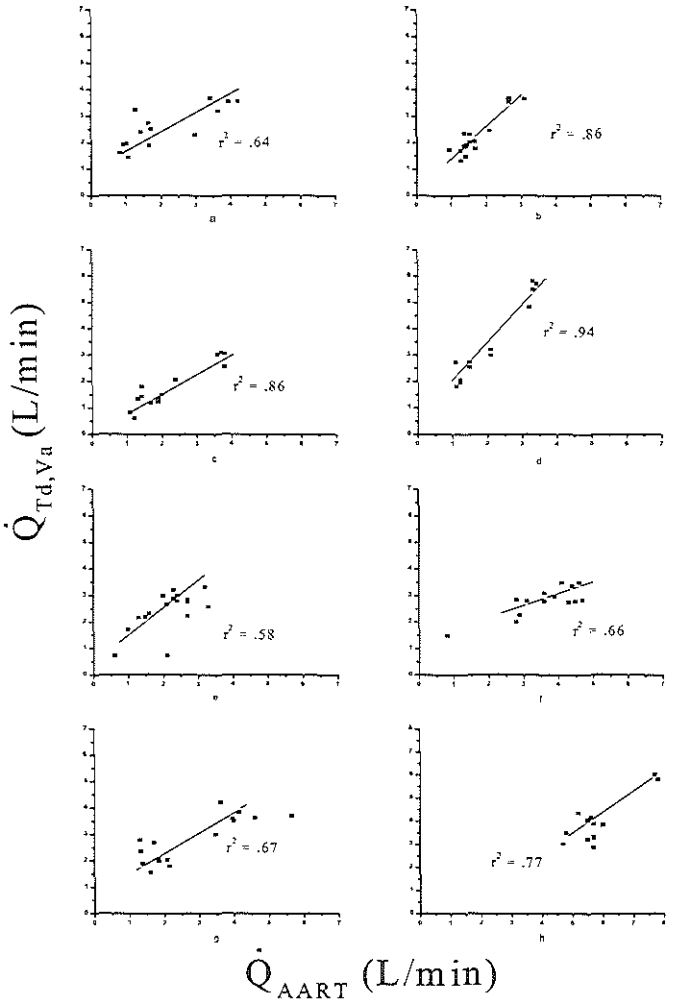

Figure 3. Non-shunted pulmonary capillary blood flow calculated by the AART and the shunt-corrected thermodilution cardiac output (r^2: 0.58- 0.94). The ventilator settings of experiments a-h are given in table 1.

Figure 4 shows how trends in the development of $\dot{Q}_{AART}$ corresponded to trends in the development of $\dot{Q}_{Td,Va}$ and oxygen delivery during the experiments.

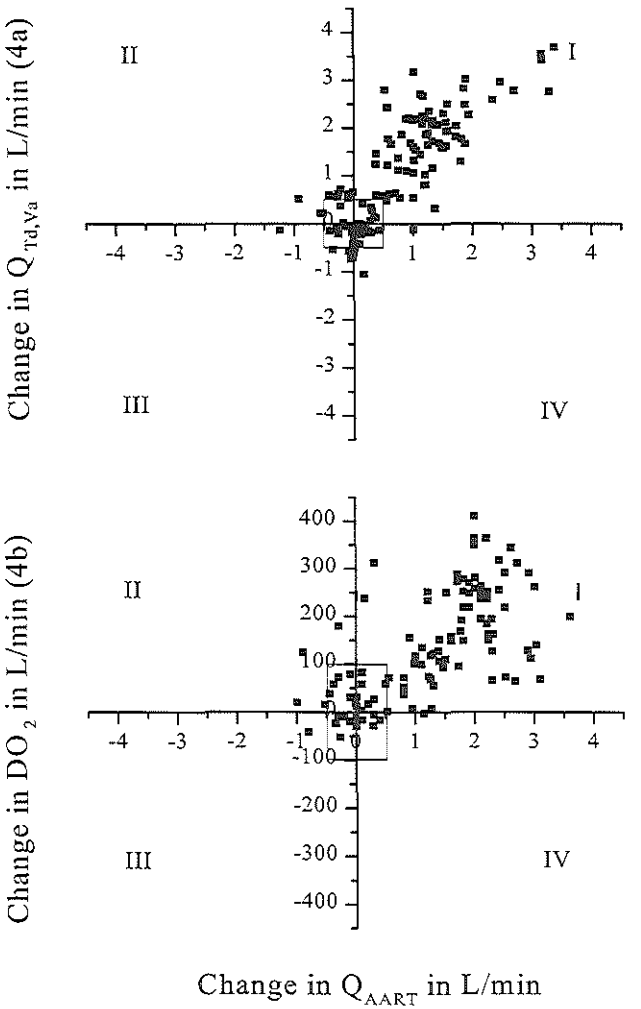

Figure 4. The direction of the change in non-shunted pulmonary capillary blood flow as indicated by the AART (X-axis) and the shunt-corrected thermodilution cardiac output (Y-axis) (figure 4a). The dotted square contains the changes in both $\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$ smaller than 0.5 L/min. Only changes larger than 0.5 L/min were considered as significant responses to variation in PEEP. Figure 4b indicates the direction of change in oxygen delivery ($\dot{D}O_2$) compared to the change in $\dot{Q}_{AART}$. The rectangle contains the changes where the is oxygen delivery smaller than 100 mL/min, and the change in $\dot{Q}_{AART}$ was smaller than 0.5 L/min. Data points in the quadrants II and IV indicate events where a change in the $\dot{Q}_{AART}$ was opposite in direction to the change in $\dot{Q}_{Td,Va}$.

All data pairs of the experiments have been included in this graph. The data points in quadrants I and III indicate occasions in which the direction of the change in $\dot{Q}_{AART}$ corresponded with the direction of change in $\dot{Q}_{Td,Va}$. We have defined a difference larger than 0.5 L/min in either $\dot{Q}_{Td,Va}$ or $\dot{Q}_{AART}$ between two data points as clinically significant changes in non-shunted pulmonary capillary blood flow. In this interval, 120 of 131 changes (92%) were indicated correctly by AART (figure 4a). From 131 changes, 11 clinically significant outliers (in quadrants II and IV) were found.

Therefore AART showed a similar trend compared to the thermodilution cardiac output corrected for venous admixture in 92% of all changes. Similarly, figure 4b indicates the change in $\dot{Q}_{AART}$ compared to the change in oxygen delivery. Here, a change in oxygen delivery larger than 100 mL/min and a change larger than 0.5 L/min in $\dot{Q}_{AART}$ was considered as clinically significant. From 131 changes, 126 changes were indicated by AART similar to the change in oxygen delivery. In 5 of 131 changes (4%) the trend in oxygen delivery was opposite in direction to the change in $\dot{Q}_{AART}$. Therefore, the trend between the oxygen delivery and $\dot{Q}_{AART}$ was similar in both variables in 96% of all changes.

Discussion

This study shows that AART can indicate changes in the development of non-shunted pulmonary capillary blood flow as well as the thermodilution cardiac output corrected for venous admixture in a porcine model of ARDS. A significant correlation was found between $\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$ in all experiments. Therefore, AART could be used for the monitoring of *changes* in non-shunted pulmonary capillary blood flow in this model of lung injury. The present study also suggests that PEEP can be optimized with the aid of AART in this disease model, because administration of PEEP will directly influence the change in non-shunted pulmonary capillary blood flow.

To our knowledge, this is the first study that describes the use of AART to measure the effect of different PEEP levels in a model of lung injury. The response of cardiac output, oxygen delivery and venous admixture to lung lavage and subsequent application of PEEP were recorded and compared. AART was shown to detect changes in non-shunted

pulmonary capillary blood flow, which also corresponded well with changes in oxygen delivery.

PEEP was shown to have a direct influence on the magnitude of $\dot{Q}_{AART}$. Measurement of non-shunted pulmonary capillary blood flow by AART may aid in optimizing the level of PEEP in diseases where an increase in intrapulmonary shunt fraction exists. Optimizing PEEP is beneficial, because accurate administration of PEEP will minimize the risk of barotrauma, cardiodepression and of other PEEP-related complications. Non-invasive indication of trends in non-shunted pulmonary capillary blood flow may therefore be a potential contribution to pulmonary monitoring.

The question remains why the quantitative relationship between AART and the thermodilution cardiac output corrected for venous admixture differed from experiment to experiment. The sources of the systematic error between different experiments may lay in AART, in the thermodilution method or in the calculation of venous admixture. With the present lack of a "gold standard" to compare AART with, these questions may be answered by future experiments in which a more precise method of determination of venous admixture is used. Further contributions to the accuracy may also be found in the correction for variation of the blood-gas partition coefficient (see below). Systematic experimental errors in $\dot{Q}_{AART}$ and $\dot{Q}_{Td,Va}$ were excluded. This implies that perhaps one or more of the assumptions of the AART theory, such as continuous ventilation and perfusion, and the absence of diffusion limitation, may be responsible for the quantitative difference between the $\dot{Q}_{AART}$ and the $\dot{Q}_{Td,Va}$ in the experiments. Accuracy may therefore be increased by further refinement of the theoretical lung model, as has been done by Gavaghan et al. who recently described a tidal model of ventilation for AART (27).

Another factor that is difficult to predict is the extent to which lung lavage will impair gas diffusion in the lungs of different animals. Further studies are needed to quantify the change in diffusion capacity in response to lung lavage, e.g. by measurement of the diffusion capacity of carbon monoxide(28). Before lung lavage, the healthy lungs of the animals are assumed to be matched in terms of ventilation and perfusion. Here, the time constant of change in the composition of the alveolar gas can be considered to be the same for all pigs and will equal the functional residual capacity divided by the alveolar ventilation. If, for example the lung volume is 3 liters and the alveolar ventilation is 6 L/min, the time constant will be 30 seconds(29). It is likely that the lung lavage creates a

variety of time constants for different areas of the lung because the collapsed unit will demonstrate a worsening in the mixing of alveolar gas. The change in mixing quality of alveolar gas after lung lavage will influence the end-expiratory fraction of halothane that we use as a measure of the alveolar tracer gas fraction.

The remainder of the gas exchanging alveoli can be divided in a "fast" and "slow" compartment. The fast compartment of the gas exchanging alveoli, which was not affected by the lung lavage, will continue to exchange the tracer gas without significant change. Poorly ventilated lung units however, will exchange the tracer gas differently compared to the unaffected lung part because they have a different (abnormal) time constant(29). It is likely that the slow compartment will differ in respect to size, and influence on the end-expiratory tracer gas fraction between the different pigs. The theoretical framework of the AART does not incorporate the possibility of ventilation-perfusion inhomogeneities at this moment. Methods need to be devised to quantify the ventilation to volume ratio in both normal and injured lungs to be able to enhance the accuracy of techniques which use soluble inert gases to measure pulmonary blood flow.

An alternative and more precise determination of the shunted pulmonary blood flow may be made by the measurement of sulfur hexafluoride (SF_6) retention(30). The gas is infused into the venous circulation, and the ratio between the arterial and venous concentration of the gas is considered as an estimate of the intrapulmonary shunt fraction. Another yet more complicated method is the multiple inert gas elimination technique(31), which is based on the infusion of six gases with different solubility in blood.

The value of the blood-gas partition coefficient (λ) was taken from the literature(32). The λ for halothane: 2.3, has been determined in human blood, at body temperature and ambient pressure. In our calculations, the partition coefficient of halothane was taken to be constant. No estimation of the variation of the blood gas partition coefficient during our experiments was made, and no correction factors could be obtained through the survey of the literature. Factors which are known to influence the blood gas partition coefficient significantly include hematocrit(33), osmolarity and temperature(32). In our experiments, all animals were fasted for 24 hours, in order to avoid the effects of the increase in lipid concentration of the blood caused by eating(34) which would increase the blood-gas partition coefficient of halothane. The body temperature was recorded for every measurement point of the experiments, but no influence of the temperature on the $\dot{Q}_{AART}$

was seen. Further studies are necessary to study variation of the blood gas partition coefficients during different physiologic states, as this may enhance the accuracy of the AART.

Nevertheless, the current results make clear that trends in significant changes in non-shunted pulmonary capillary blood flow are correctly monitored by AART. The possible applications of this technique range from the titration of PEEP to studying the changes in non-shunted pulmonary capillary blood flow as a response to pharmacological agents such as dopamine, surfactant or nitric oxide. This may significantly contribute to pulmonary monitoring during mechanical ventilation in future.

Conclusion: Comparison of AART with the shunt-corrected thermodilution cardiac output in a porcine ARDS model has shown that trends in non-shunted pulmonary capillary blood flow can be detected with this technique during mechanical ventilation.

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Appendix

In the three-compartment model the mass balance of the amount of inhaled inert gas and the amount which accumulates in the lung can be expressed as(10):

$$\frac{dP_A}{dt}V = \dot{V}_A(P_I - P_A) + \lambda\dot{Q}_{AART}(P_{\bar{v}} - P_A) \qquad \text{Equation 3}$$

The inspiratory tracer gas fraction is varied sinusoidally which results in a sinusoidal variation of P_A and $P_{\bar{v}}$ vary too. If the oscillation frequency is chosen high enough, the amplitude of the time dependent part of the venous concentration of tracer gas $P_{\bar{v}}$ will be negligible compared to the amplitude of the inspiratory and end-expiratory concentration(10). The expression for the time dependent part of the inspiratory tracer gas partial pressure P_I is:

$$P_I = A_I \sin(\omega t) \qquad \text{Equation 4}$$

Similarly, the time dependent part of the alveolar partial pressure PA is expressed as:

$$P_A = A_A \sin(\omega t - \alpha) \qquad \text{Equation 5}$$

The angular frequency (ω) must be chosen high enough to reduce the variations of $P_{\bar{v}}$ sufficiently. On the other hand, the ω must be low enough to enable significant tracer gas exchange between the blood and the alveolar gas within a single oscillation. By substitution of the sinusoidal functions P_I, P_A in equation 1, and assuming that the tracer gas concentration in the mixed venous blood ($P_{\bar{v}}$), that is returned to the lungs is constant in time the following expression is obtained(10):

$$\frac{A_A}{A_I} = \frac{\cos\alpha}{1 + \lambda \frac{\dot{Q}_{AART}}{\dot{V}_A}}$$ Equation 6

Solving for $\dot{Q}_{AART}$ yields:

$$\dot{Q}_{AART} = \frac{\dot{V}_A}{\lambda}\left(\frac{A_I}{A_A}\cos\alpha - 1\right)$$ Equation 7 (identical to equation 1)

A comprehensive evaluation of these equations has been provided in previous studies(9, 10).

Calculation of $\dot{V}_A$*:* Alveolar ventilation $\dot{V}_A$, needed in equation 7, was calculated from the measured total ventilation $\dot{V}_T$ using the Bohr equation (34); with dead space V_D and dead space ventilation $\dot{V}_D$:

$$\frac{\dot{V}_D}{\dot{V}_T} = \frac{V_D}{V_T} = \frac{P_{A,CO_2} - P_{M,CO_2}}{P_{A,CO_2}}$$ Equation 8

The type of dead space measured depends on the value used to express alveolar CO_2 concentration. When arterial CO_2 is substituted a value for physiological dead space is obtained. Introducing the end-expiratory CO_2 fraction in the Bohr equation results in a measure for airways dead space. To keep all AART measurements non-invasive, the end-expiratory CO_2 fraction was used to determine the alveolar ventilation.

Calculation of $\dot{Q}_{Td,Va}$ *:* Measured values of the thermodilution cardiac output were corrected for shunt to obtain an estimate of non-shunted pulmonary capillary blood flow $\dot{Q}_{Td,Va}$, using:

$$\dot{Q}_{Td,Va} = \dot{Q}_{Td}\left(1 - \frac{\dot{Q}_S}{\dot{Q}_T}\right)$$ Equation 9 (Identical to equation 2)

Venous admixture $\dot{Q}_S / \dot{Q}_T$ was calculated from the inspiratory oxygen concentration, the blood gas values and the cardiac output data as:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_{c,O_2} - C_{a,O_2}}{C_{c,O_2} - C_{\bar{v},O_2}} \qquad \text{Equation 10}$$

The oxygen content of the arterial and mixed venous blood was calculated using:

$$C_{a,\bar{v},O_2} = \frac{S_{a,\bar{v},O_2} \cdot 1.39 \cdot Hb}{100} + 0.0031 \cdot P_{a,\bar{v},O_2} \qquad \text{Equation 11}$$

and that of the end-capillary blood as:

$$C_{c,O_2} = \frac{S_{c,O_2} \cdot 1.39 \cdot Hb}{100} + 0.0031 \cdot P_{A,O_2} \qquad \text{Equation 12}$$

In this equation, the oxygen saturation of hemoglobin at the end-capillary level was considered to equal 100%.

Glossary

AART = alveolar amplitude response technique

$\dot{Q}_{Td}$ = total cardiac output, measured by the thermodilution method

$\dot{Q}_{AART}$ = non-shunted pulmonary capillary blood flow determined by the AART

$\dot{Q}_{Td,Va}$ = non-shunted pulmonary capillary blood flow determined by correcting thermodilution cardiac output for venous admixture

$\dot{V}_D$ = dead space ventilation

$\dot{V}_A$ = alveolar ventilation

$\dot{V}_T$ = total ventilation

V = total gas absorbing volume of the alveolar compartment (alveolar air + lung tissue + blood)

V_D = dead space

V_A = alveolar volume

V_T = tidal volume

P_{A,O_2} = alveolar oxygen tension

P_{a,O_2} = arterial oxygen tension

$P_{\bar{v},O_2}$ = mixed venous oxygen tension

P_{a,CO_2} = arterial carbon dioxide tension

P_{EE,CO_2} = end-expiratory carbon dioxide tension

$\dot{D}O_2$ = oxygen delivery

λ = blood-gas partition coefficient

α = phase shift between inspiratory and expiratory tracer gas fraction

A_I = inspiratory amplitude of tracer gas fraction

A_A = expiratory amplitude of tracer gas fraction

$2\pi/T$ = angular velocity

T = time period of sinusoid

f = respiratory frequency

S_{c,O_2} = end capillary blood oxyhemoglobin saturation

S_{a,O_2} = arterial oxyhemoglobin saturation

$S_{\bar{v},O_2}$ = mixed-venous oxyhemoglobin saturation

F_{i,O_2} = inspiratory oxygen fraction

F_{i,CO_2} = inspiratory carbon dioxide fraction

F_{m,CO_2} = mean expiratory carbon dioxide fraction

F_{EE,CO_2} = end expiratory carbon dioxide fraction

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CHAPTER 6

A novel method of evaluation of three heat-moisture exchangers in six different ventilator settings

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Abstract

Objective: The purpose of this study was to assess and compare the humidification, heating, and resistance properties of three commercially available heat-moisture exchangers (HMEs). To mimic clinical conditions, a previously validated, new, realistic experimental setup and measurement protocol was used.

Design: Prospective, comparative experimental study.

Setting: Surgical Intensive Care Unit, University Hospital Rotterdam.

Materials: An experimental setup consisting of a patient model, measurement systems, and ventilator and three different HME types.

Interventions: The air flow, pressure in the ventilation circuit, pressure difference over the HME, and partial water vapour pressure and temperature at each side of the HMEs were measured. Measurements were repeated every 30 min during the first 2 h and every hour up to 24 h for each HME at six different ventilator settings. The mean inspiratory and maximum expiratory resistance flow-weighted mean absolute humidity and temperature outputs, and humidification and heating efficiencies of HMEs were calculated.

Measurements and results: The Dar Hygroster had the highest humidity output, temperature output, humidification efficiency, and heating efficiency values throughout the study (32.8 ± 21. mg/l, 32.2 ± 0.8 °C, 86.3 ± 2.3%, and 0.9 ± 0.01%, respectively) in

comparison to the Humid-Vent Filter (25.3 ± 3.2 mg/l, 31.9 ± 0.8 °C, 72.2 ± 5.3%, 0.9 ± 0.02%, respectively) and the Pall Ultipor BB100 breathing circuit filter (23.4 ± 3 mg/l, 28.3 ± 0.7 °C, 68.8 ± 5.9%, 0.8 ± 0.02%, respectively). The inspiratory and expiratory resistance of the HMEs remained below clinically acceptable maximum values (2.60 ± 0.04 and 2.45 ± 0.05 cmH_2O/l per s, respectively).

Conclusion: The Dar Hygroster filter was found to have the highest humidity and temperature output of all three HMEs, the Humid-Vent filter had a satisfactory humidity output only at low tidal volume flow rate and minute volume settings, whereas the Pall Ultipore BB100 never achieved a sufficient humidity and temperature output.

Introduction

The upper airways heat and humidify inspiratory air and provide 65% of the humidity of inhaled air (1, 2). As a consequence, the inspiratory air reaching the lower airways is fully saturated with water vapour at body temperature. Bypassing the upper airways by endotracheal intubation or tracheostomy interferes with the normal process of humidification and warming. This effect is potentiated by the use of cold, dry medical gases during mechanical ventilation. Inadequate heating and moisturizing of inspiratory gas can produce severe airway damage and cause pulmonary function to deteriorate (3-10). Therefore, it is imperative that inspired gases are heated and humidified during mechanical ventilation. Either heated humidifiers (HH) or heat-moisture exchangers (HMEs) are used artificially to replace upper airway functions during mechanical ventilation. However, HHs have some disadvantages, such as condensation in the tubing sets, bacterial colonization of the condensed or reservoir water, over- and underhumidification, and overheating (11-15). On the other hand, HMEs, with their bacterial filtration properties in combination with their heat-humidity conserving functions, are good alternatives to HHs, although there is some doubt about their humidification capabilities and resistances to airflow (11, 16-19).

Several experimental studies have been done to test these properties of HMEs, where gravimetric humidity measurements and resistance measurements have been made outside the ventilation system by using a constant dry air flow (11, 16, 18, 20-28). Gravimetric humidity measurements are only reliable during long-term studies and give only an average value. The use of a constant dry air flow to measure resistance outside the

ventilation system may produce an underestimation. Furthermore, the expiratory resistance of the HME to characteristic decreasing air flow is as important as inspiratory resistance.

Because of the diverse techniques and methods used in studies performed so far, it is difficult to compare their results. The available standards for testing HMEs also have some shortcomings (11, 29-31). For these reasons the humidity and temperature outputs of three conventionally used HMEs in relation to their resistances were tested and compared with each other in this study using a new setup and method (29). We conducted an experimental study on three HMEs by using a new, more realistic experimental model where the test lung was able to produce stable heat and water vapour output at different ventilatory settings (29).

The aims of this study were to measure and compare the humidity and temperature outputs and humidification and heating efficiencies of the HMEs continuously in relation to their inspiratory and expiratory resistance over 24 h at different ventilator settings.

The optimal requirements for inspiratory air conditioning during mechanical ventilation are not well established. Recent data suggest that the lower humidity level of inspired air should be in the range of 24-27 mg/l and the upper level in the range of 32-35 mg/l (1, 2, 4, 7, 30-35). The temperature level should be between approximately 29 and 35 °C (1, 2, 30-35). Endotracheal tube occlusions related to insufficient HME humidity output have been reported (17, 36). The humidity output of HMEs in occlusion has been reported to occur between 10 and 28 mg/l (11, 20, 22, 27, 28, 37, 38). These results suggest that adequate inspiratory humidity ranges should be smaller, 28 mg/l being the lower limit. These ranges were used to interpret our results and to judge the efficacy of the different HMEs.

Materials and methods

The experimental setup. The experimental setup includes a patient model, measurement systems, and a ventilator, as shown in Figure 1. The patient model consists of a 1-litre training thorax (Übungs-thorax, M 13333, Dräger, Germany), a calibration bag with a capacity of 650 ml, a heated humidifier (Conchatherm 3, Kendall, London, UK), standard ventilator tubing, two one-way valves, connectors, and an incubator (Intensivpflege-Incubator 6500, Drägerwerk, Lübeck, Germany). The output of the patient model is

adjusted to produce a relative humidity of 100% at 34.5 ± 1.0 °C. The incubator is kept at 36.0 ± 1 °C to prevent condensation. A heated flowmeter (Fleisch No.2, Sensormedics, Bilthoven, The Netherlands), located between the training thorax and the HH, connected to a pneumotachograph (Type 17212, Godart-Statham, Bilthoven, The Netherlands) is used to measure the inspiratory and expiratory flow rate ($\dot{V}_I$ and $\dot{V}_E$). Two sampling ports are used to introduce the temperature probes, humidity sampling capillary, and pressure lines; one sampling port is located between the patient model and HME ("P" site), and the other is located between the HME and Y-piece of the ventilator tubing ("V" site). Temperature and partial water pressures at "P" and "V" sites are measured with two small bead NTC thermistors (Fenwal Electronics, American Power Devices, Mass., USA) and with a quadrupole mass spectrometer (MGA 3000, Case, Biggin Hill, UK). A differential pressure transducer (Hewlett-Packard model 270, HP International, Calif., USA) and a signal conditioner (Hewlett-Packard model 8805B carrier amplifier, HP International) are used to measure the pressure difference between the "P" and "V" site (ΔP_{HME}).

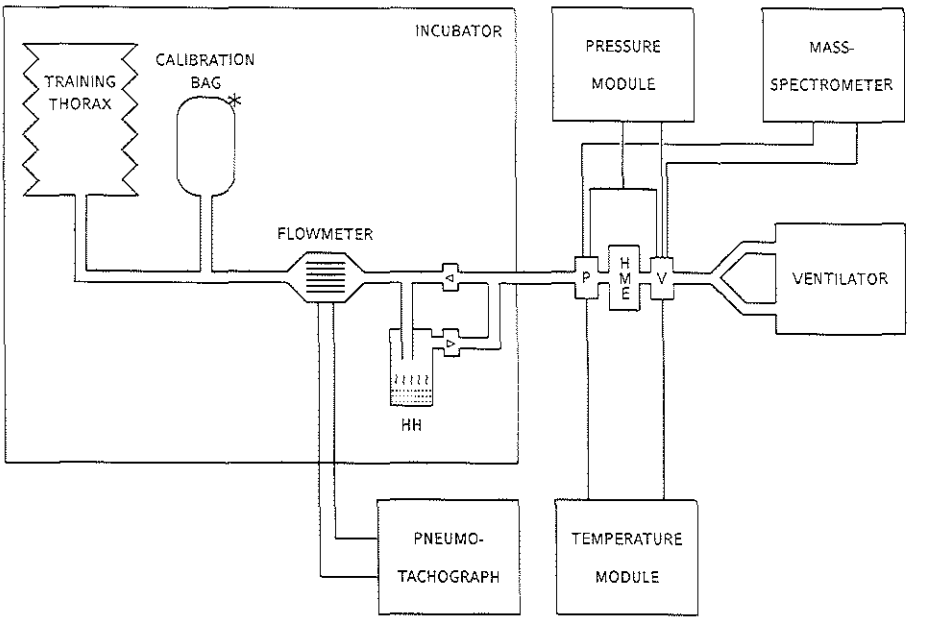

Figure 1. Experimental setup. ◄ denotes the direction of the flow on the one-way valve

The incubator and room temperatures (T_{inc}, T_{room}) are measured by two mercury thermometers with an accuracy of ±0.2 and ±0.1 °C, respectively. The technical details and calibration procedures of the measurement equipment have been described previously in more detail (29). A ventilator (Servo 900A, Siemens, Sweden) is used to ventilate the patient model in six different ventilator settings (Table 1). Central medical air with a dew point of .20°C (equal to 0.1 kPa or 0.85 mg/l humidity) is used to ventilate the patient model. Dar Hygroster (DHS) (Dar SpA Mirandola, Italy), Pall Ultipor BB100 breathing circuit filter (PUBB100) (Pall Biomedical, Fajardo, Puerto Rico) and Humid-Vent Filter (HVF) (Gibeck Respiration, Uppsala, Sweden) are compared in this study.

Measurement protocol. The patient model is ventilated for 2 h to stabilize the system without an HME before every measurement period. After HME is attached, the signals are saved on a PC every 30 min during the first 2 h and every hour up to 24 h. Besides these periodic recordings, the signals are plotted continuously.

Calculated parameters include (29): (1) mean inspiratory, mean expiratory, and maximum expiratory flow rates of five successive breaths ($\dot{V}_I$ mean, $\dot{V}_E$ mean, $\dot{V}_E$ max); (2) inspiratory and expiratory mean tidal volumes of five successive breaths; (3) mean respiration frequency; (4) flow-weighted mean inspiratory and mean expiratory partial water vapour pressures at the "P" and "V" sites of five successive breaths ($P_{H2O}(P)_{I,\,mean}$, $P_{H2O}(P)_{E,\,mean}$, $P_{H2O}(V)_{I,\,mean}$, $P_{H2O}(V)_{E,\,mean}$); (5) flow-weighted mean inspiratory and mean expiratory temperature values at the "P" and "V" site of five successive breaths ($T(P)_{I,\,mean}$, $T(P)_{E,\,mean}$, $T(V)_{I,\,mean}$, $T(V)_{E,\,mean}$); (6) mean inspiratory and mean expiratory absolute and relative humidity values at the "P" and "V" site of five successive breaths ($AH(P)_{I,\,mean}$, $AH(P)_{E,\,mean}$, $AH(V)_{I,\,mean}$, $AH(V)_{E,\,mean}$, $RH(P)_{I,\,mean}$, $RH(P)_{E,\,mean}$, $RH(V)_{I,\,mean}$, $RH(V)_{E,\,mean}$); (7) mean inspiratory and maximum expiratory resistance of the HME ($R(HME)_{I,\,mean}$, $R(HME)_{E,\,max}$); (8) humidification and heating efficiencies of the HME (H_{EFF}, T_{EFF}).

Statistical analysis. Results are expressed as mean ± SD over 24 h (n = 26). The results were statistically evaluated using two-way analysis of variance and correlation analysis. Correlation analysis was done separately for each HME and for each respiratory frequency to evaluate the effects of the different variables on the results. Differences are compared with the Student-Newman-Keuls procedure; $p < 0.05$ is considered significant.

Results

The ventilation parameters measured are shown in Table 1 together with their ventilator settings.

Ventilator Settings	Settings			Measured values				
	VT_E (ml)	f (/min)	I/E	VT_I (ml)	f (/min)	$\dot{V}_I$ (mL)	$\dot{V}_{E\ max}$ (ml)	$\dot{V}_{E\ mean}$ (ml)
1	600	10	½	639.6±9.4	10.1±0.03	508.6±18.3	780.7±10.2	160.6±6.1
2	800	10	½	834.4±6.2	10.1±0.02	633.8±2.8	906.7±14 + 1	221.6±2 +3
3	1000	10	½	1015.2±10.0	10.1±0.03	780.2±18.3	1001.4±29.3	256.9±10.9
4	600	15	½	597.1±12.3	15.1±0.04	686±4	787.9±7.2	238.1±2.4
5	800	15	½	766.9±5.2	15.2±0.1	875±8.6	904.8±14 + 9	306.3±2.9
6	1000	15	½	1038.0±11.0	15.2±0.04	1185.9±12 + 3	939.1±24 + 9	395.2±24+7

Table 1. Different settings and measured variables of the ventilator (VT_e mean expiratory tidal volume, f mean respiration frequency, I/E inspiratory/expiratory ratio, VT_i mean inspiratory tidal volume of five successive breaths, $\dot{V}_I$ inspiratory flow rate, $\dot{V}_{E\ max}$ maximum expiratory flow rate, $\dot{V}_{E\ mean}$ mean expiratory flow rate)

$T(P)_{E,\ mean}$ and $P_{H2O}(P)_{E,\ mean}$ of the test lung were 34.4 ± 1.3 °C and 5.1 ± 0.9 kPa, respectively, during the whole study (equal to an absolute humidity of 37.5 ± 2.3 mg/l or a relative humidity of 98.3 ± 4.2%). The room temperature was 25.7 ± 0.5 °C. The mean inspiratory fresh air temperature and humidity level were 25.3 ± 0.7 °C and 0.34 ± 0.05 kPa (equal to an absolute humidity of 2.46 ± 0.4 mg/l or a relative humidity of 10.5 ± 1.4%). Absolute humidity output, temperature output, humidification efficiency, and heating efficiencies of the HMEs in different ventilator settings with the inspiratory and expiratory resistances of the HMEs are shown in Table 2. The humidity output of the HMEs, although not stable, did not show a progressive increase during the 24-h measurement periods. Fluctuations in the humidity output were more remarkable with the HVF. The stabilization time of the humidity output was dependent on the HME used and the ventilator setting. The mean stabilization time was 1.5 h for PUBB100 and 2 h for HVF and DHS and in some ventilator settings was either reduced to 10 min or extended to 3±4 h. Temperature outputs of the PUBB100 were significantly lower than for the others at all ventilator settings. There was no significant difference between the temperature

outputs of the DHS and HVF at the first three ventilator settings; however, HVF temperature outputs were significantly lower than DHS outputs at ventilator settings 4, 5, and 6 (table 2). Temperature outputs of HMEs at different ventilator settings were more stable than their humidity outputs during the 24-h recording periods.

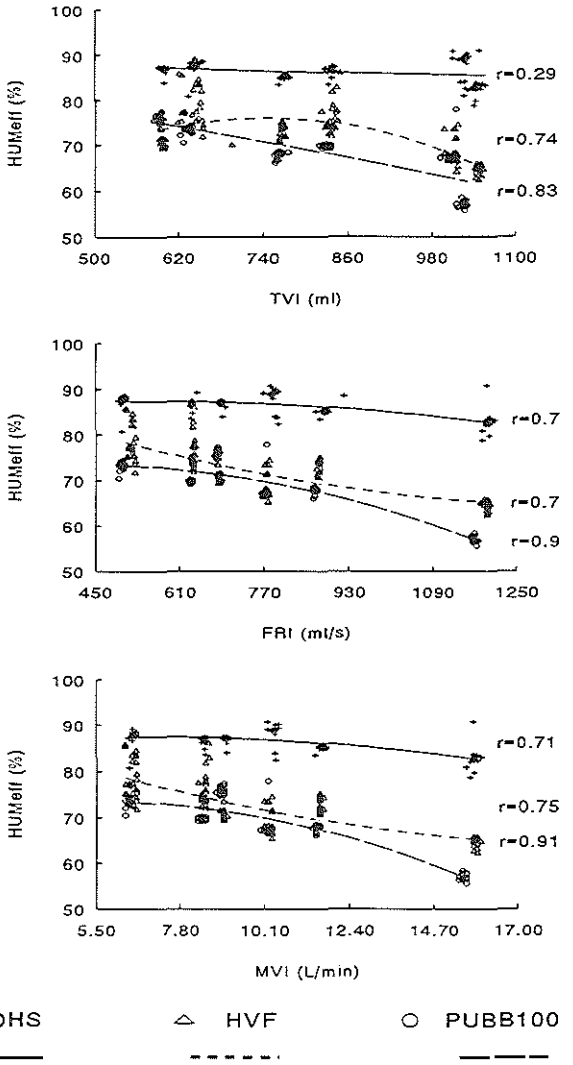

Figure 2. Correlation of humidification efficiencies of HMEs HUM_{eff} with tidal volume TVI, inspiratory flow rate FRI, and inspiratory minute volume MVI. Correlation coefficients (r) for each HME are shown next to the second-degree polynomial curve-fitting lines

Increasing tidal volume, inspiratory flow rate, and minute volumes decreased the humidification efficiencies of the HMEs to a different extent (figure 2 and table 2). Although these parameters had little influence on the DHS, the humidification efficiency of the DHS was significantly decreased by the combination of high tidal volume, inspiratory flow rate, and minute volumes. The effect of these variables on the humidification efficiency of the PUBB100 was more pronounced than for the HVF. The humidification efficiency of the PUBB100 decreased linearly with increasing tidal volume, flow rate, and minute volumes, while the slope of the regression line depended on the combination of these variables (figure 2).

The humidification efficiency of the HVF was decreased mainly by tidal volumes higher than 800 ml in addition to the effect of high flow rates. The PUBB100 had the lowest and the DHS the highest humidification efficiencies at each ventilator setting except 4, at which HVF was lowest (table 2). Humidification efficiency values did not show a progressive increase over 24 h. However, a stabilization time was needed for each HME at each ventilator setting. Mean stabilization periods were approximately 120, 60, and 50 min for DHS, HVF, and PUBB100, respectively, although it was difficult to establish an exact stabilization time for each because of fluctuations in humidification efficiencies over 24 h. Fluctuation was more prominent with the HVF than with the others. The heating efficiency of the DHS and PUBB100 inversely correlated with tidal volume, inspiratory flow rate, minute volume, and expiratory flow rate (figure 3).

Heating efficiency of DHS and PUBB100 was increased by increasing ventilation frequency, especially at high tidal volume settings. Similarly to the others, the heating efficiency of the HVF was affected minimally by ventilator variables except when combining a high tidal volume, inspiratory flow rate, and minute volume.

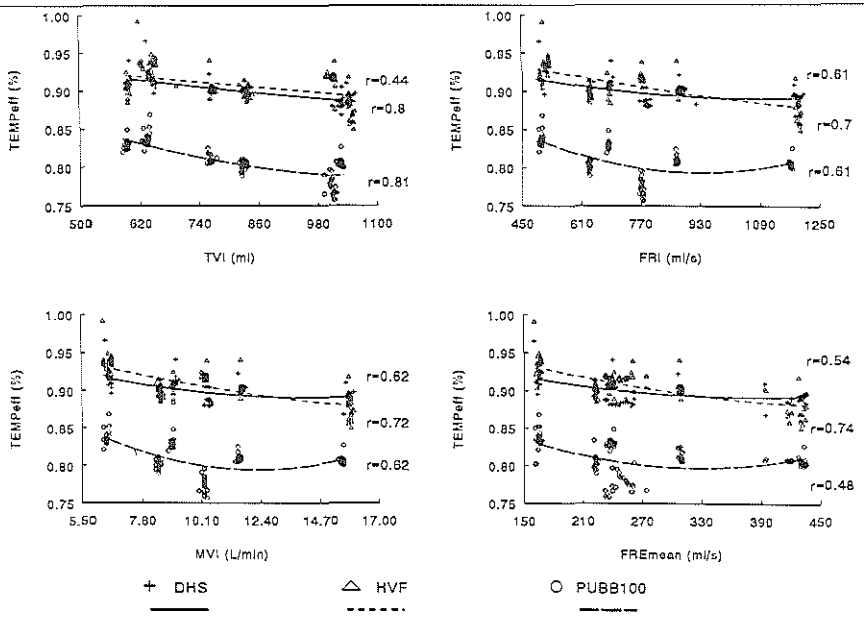

Figure 3. Correlation of $TEMP_{eff}$ with tidal volume TVI, inspiratory flow rate FRI, inspiratory minute volume MVI, and mean expiratory flow rate FREmean. Correlation coefficients(r) for each HME are shown next to the second-degree polynomial curve-fitting lines

The heating efficiency of the PUBB100 was significantly lower than in the other filters at every ventilator setting. There were no statistically significant differences between the heating efficiency of the HVF and the DHS at ventilator settings 2 and 5. The heating efficiency of the HVF at ventilator settings 1 and 3 was significantly higher than for the DHS, whereas it was significantly higher for the DHS than for the HVF at ventilator settings 4 and 6 (table 2). A stabilization time to achieve the optimal heating efficiency existed. During the stabilization period, which took 60±90 min, heating efficiency decreased, while humidification efficiency increased. This inverse relationship was more pronounced with the DHS. The inspiratory resistance mainly correlated to the inspiratory flow rate (figure 4).

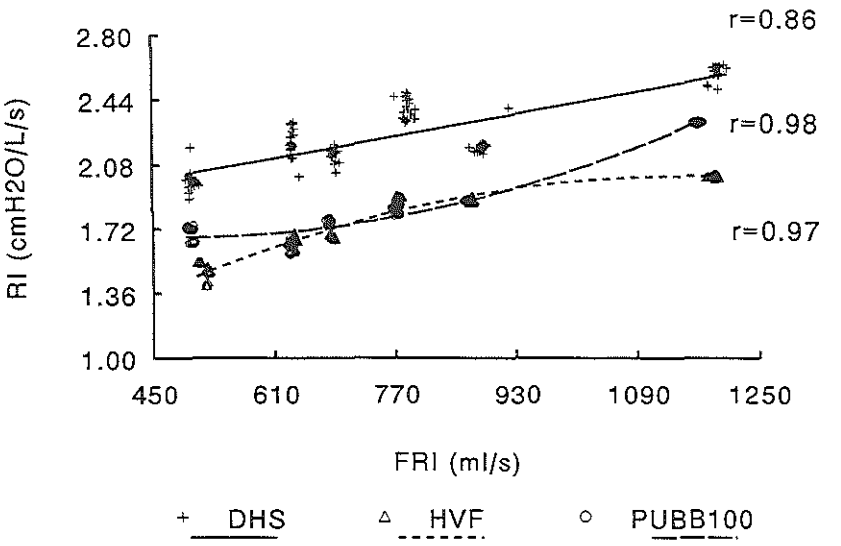

Figure 4. Correlation of inspiratory resistance RI with inspiratory flow rate FRI. Correlation coefficients(r) for each HME are shown next to the second-degree polynomial curve-fitting lines

We could not find any correlation between the inspiratory resistance and the humidification efficiency of the HMEs. However, there was an inverse correlation between the humidification efficiency and the resistance of the HVF (r = -0.75) and PUBB100 (r = -0.86). The inspiratory resistance of the DHS was higher at every setting than in the other HMEs. The expiratory resistance increased with increasing humidification efficiency and expiratory flow rates, which have an inverse relationship. The expiratory resistance of the DHS was the highest and of HVF the lowest at all settings (table 2). There was no significant change in the inspiratory and expiratory resistance over the 24-h recording periods with different HMEs at the different ventilator settings. However, some shortlived changes were observed during the recordings, being more frequent in the expiratory resistance than the inspiratory resistance. The expiratory flow pattern, temperature, and humidity output characteristics of the patient model used in this study, in addition to its mechanical properties, were comparable to those found in humans (1, 2, 32-34) and in agreement with the ISO standard (29-31). The technical properties of the measurement equipment complied with the ISO standard as previously described (29-31).

Table 2 Mean temperature and humidity output of the three HMEs at different ventilator settings, together with heating and humidifying efficiencies, and inspiratory and expiratory resistances ($AH(P)_{I,mean}$ mean inspiratory absolute humidity value at the "P" site of five successive breaths, $T(P)_{I,mean}$ flow-weighted mean inspiratory temperature at the "P" site of five successive breaths, HUM_{EFF}, $TEMP_{EFF}$ humidification and heating efficiencies of HME, $R(HME)_{I,mean}$, $R(HME)_{E,max}$, mean inspiratory resistance and mean maximum expiratory resistance of the HME)

Ventilator settings	HME	$AH(P)_{I,mean}$ (mg/l)	$T(P)_{I,mean}$ (°C)	HUM_{EFF} (%)	$TEMP_{EFF}$ (%)	$R(HME)_{I,mean}$ (cmH_2O/l per s)	$R(HME)_{E,max}$ (cmH_2O/l per s)
I	DHS	$32.0 \pm 2.1^{*,b}$	$31.3 \pm 0.3^{\S,b}$	$87.7 \pm 1.5^{*,j}$	$0.92 \pm 0.01^{*,a}$	$1.99 \pm 0.05^{*,a}$	$2.31 \pm 0.10^{*,p}$
	HV	$27.1 \pm 3.4^{*,d}$	$31.4 \pm 0.5^{\S,i}$	$78.9 \pm 4 + 2^{*,a}$	$0.94 \pm 0.01^{*,a}$	$1.48 \pm 0.04^{*,a}$	$1.84 \pm 0.03^{*,s}$
	PUBB100	$23.9 \pm 0.8^{*,a}$	$27.2 \pm 0.2^{*,a}$	$73.3 \pm 0.8^{*,a}$	$0.84 \pm 0.01^{*,a}$	$1.70 \pm 0.04^{*,a}$	$2.01 \pm 0.04^{*,a}$
II	DHS	$34.2 \pm 0.6^{*,c}$	$32.5 \pm 0.4^{\S,f}$	$86.5 \pm 0.9^{*,k}$	0.90 ± 0.01^{m}	$2.21 \pm 0.06^{*,a}$	$2.43 \pm 0.05^{*,r}$
	HV	$27.9 \pm 2.1^{*,d}$	$32.5 \pm 0.3^{\S,c}$	$75.9 \pm 3.3^{*,a}$	0.90 ± 0.01^{c}	$1.65 \pm 0.03^{*,a}$	$1.85 \pm 0.02^{*,s}$
	PUBB100	$25.7 \pm 0.3^{*,a}$	$28.8 \pm 0.2^{*,c}$	$69.7 \pm 0.3^{*,a}$	$0.80 \pm 0.01^{*,n}$	$1.63 \pm 0.03^{*,a}$	$1.90 \pm 0.05^{*,a}$
III	DHS	$32.7 \pm 2.0^{*,b}$	$31.5 \pm 0.9^{\S,b}$	$88.4 \pm 2.0^{*,b}$	$0.88 \pm 0.01^{*,a}$	$2.40 \pm 0.06^{*,a}$	$2.45 \pm 0.06^{*,r}$
	HV	23.2 ± 2.5^{a}	$31.5 \pm 1.1^{\S,i}$	68.6 ± 2.7^{a}	$0.92 \pm 0.01^{*,a}$	$1.89 \pm 0.01^{*,e}$	$1.91 \pm 0.01^{*,a}$
	PUBB100	22.5 ± 1.7^{e}	$27.8 \pm 0.3^{*,a}$	67.5 ± 2.2^{e}	$0.77 \pm 0.01^{*,a}$	$1.82 \pm 0.02^{*,a}$	$1.93 \pm 0.01^{*,a}$
IV	DHS	$33.9 \pm 1.2^{*,c}$	$32.8 \pm 0.8^{*,g}$	$86.9 \pm 0.7^{*,l}$	$0.91 \pm 0.01^{*,a}$	$2.14 \pm 0.03^{*,a}$	$2.16 \pm 0.03^{*,a}$
	HV	$24.9 \pm 1.3^{*,a}$	$32.1 \pm 0.4^{*,e}$	$70.8 \pm 0.9^{*,a}$	$0.91 \pm 0.01^{*,c}$	$1.68 \pm 0.01^{*,a}$	$1.68 \pm 0.01^{*,a}$
	PUBB100	$27.0 \pm 0.6^{*,a}$	$28.7 \pm 0.3^{*,e}$	$75.7 \pm 0.9^{*,a}$	$0.83 \pm 0.01^{*,a}$	$1.76 \pm 0.01^{*,a}$	$1.83 \pm 0.02^{*,a}$
V	DHS	$33.8 \pm 0.7^{*,c}$	$32.6 \pm 0.2^{*,f}$	$85.2 \pm 0.5^{*,a}$	0.90 ± 0.01^{m}	$2.18 \pm 0.02^{*,a}$	$2.09 \pm 0.05^{*,a}$
	HV	$27.1 \pm 1.1^{*,d}$	$32.4 \pm 0.3^{*,e}$	$73.3 \pm 1.4^{*,a}$	0.90 ± 0.01^{c}	1.89 ± 0.01^{e}	1.78 ± 0.01^{a}
	PUBB100	$22.5 \pm 1.1^{*,e}$	$28.9 \pm 0.1^{*,c}$	$67.8 \pm 0.7^{*,e}$	$0.81 \pm 0.01^{*,o}$	1.88 ± 0.00^{a}	1.77 ± 0.01^{a}
VI	DHS	$30.2 \pm 1.9^{*,a}$	$32.3 \pm 0.7^{*,h}$	$82.8 \pm 2.0^{*,a}$	$0.89 \pm 0.01^{*,a}$	$2.60 \pm 0.04^{*,a}$	$2.31 \pm 0.03^{*,p}$
	HV	$21.0 \pm 0.5^{*,a}$	$31.1 \pm 0.7^{*,i}$	$64.6 \pm 1.0^{*,a}$	$0.88 \pm 0.02^{*,a}$	$2.02 \pm 0.01^{*,a}$	$1.62 \pm 0.01^{*,a}$
	PUBB100	$17.8 \pm 0.4^{*,a}$	$28.6 \pm 0.2^{*,a}$	$57.1 \pm 0.7^{*,a}$	$0.81 \pm 0.01^{*,h}$	$2.32 \pm 0.00^{*,a}$	$1.95 \pm 0.04^{*,a}$

Letters show statistically significant differences between the HMEs at same ventilator setting. Symbols show statistically significant differences between different ventilator settings with the same HME. * significantly different from other HMEs in same ventilator setting; § significantly different from PUBB100 in same ventilator setting; [a] significantly different from other ventilator settings; [b] significantly different from ventilator settings 2, 4, 5, 6; [c] significantly different from ventilator settings 1, 3, 6; [d] significantly different from the ventilator settings 3, 4, 6; [e] significantly different from ventilator settings 1, 2, 4, 6; [f] significantly different from ventilator settings 1, 3; [g] significantly different from ventilator settings 1, 2, 3, 6; [h] significantly different from ventilator settings 1, 3, 4; [i] significantly different from ventilator settings 2, 4, 5; [j] significantly different from ventilator settings 2, 5, 6; [k] significantly different from ventilator settings 1, 3, 5, 6; [l] significantly different from ventilator settings 3, 5, 6; [m] significantly different from ventilator settings 1, 3, 4, 6; [n] significantly different from ventilator settings 1, 3, 4, 5; [o] significantly different from ventilator settings 1, 2, 3, 4; [p] significantly different from ventilator settings 2, 3, 4, 5; [r] significantly different from ventilator settings 1, 4, 5, 6; [s] significantly different from ventilator settings 3, 4, 5, 6

Discussion

In our study, the DHS was the only HME able to produce heat and humidity within the ranges suggested in the current literature, at every ventilator setting. The temperature and humidity outputs of the DHS at all ventilator settings were comparable to those of HHs tested in different studies (38). The humidity outputs of the HVF and PUBB100 were only within the recommended ranges at certain tidal volumes (600±800 ml), flow rates (520±870 and 500±680 ml/s), and minute volumes (6.5±11.6 and 6.4±8.9 l/min). The temperature output of the HVF was comparable to the DHS, while the PUBB100 was below 29 °C at every ventilator setting.

The PUBB100 achieved the required humidity output of 27 mg/l only at low minute volume, tidal volume, and flow rate setting in combination with insufficient temperature output.

The HVF had an adequate temperature output at each ventilator setting in combination with a relatively low humidity output. This resulted in a lower relative humidity output. Miyao et al. (39) have shown that relative humidity, rather than absolute humidity, is a dominant factor in cases of endotracheal tube and proximal tracheal occlusion. Therefore, the DHS is superior to the others because of a higher relative humidity output in addition to a higher absolute humidity output and high temperature output. Another concern about the HMEs is the stabilization time of the humidity and temperature outputs. Stabilization time was longer with more efficient filters and at the ventilator settings where HMEs produce high outputs. Even though this time is longer with more efficient filters, the initial output of these filters is still higher than the mean output of less efficient filters. Therefore, stabilization time seems not to be an important factor in clinical use. The inverse relationship during the stabilization period between humidity and temperature outputs possibly originates from the inadequate water reserve in the HME. Until the water reserve of the HME reaches an optimal level, less evaporation occurs during inspiration in comparison with the condensed water during a previous expiration. Therefore, during the next inspiration less energy is used for evaporation until the water reserve of the HME increases and excessive energy may be used to heat inspiratory air. As a result, after connection of the HME to the ventilation circuit, the temperature output of the HME may be higher than the patient's (model's) expiratory temperature for a short time. The water reserve of each HME is different and possibly higher with efficient filters, as can be

deduced from the results of studies which measure weight differences of the HMEs before and after use. Therefore, stabilization times depend on the ventilator setting and the type of HME. A progressive increase in the humidity output of the HMEs during 24 h has been found in some studies (20, 37, 40). Although the humidity output of the HMEs tested showed some fluctuations, a significant increase after the stabilization period was not found in this study.

The efficacy of HMEs depends on their resistance and humidity and temperature outputs. Differences between test methods and conditions may produce inevitable changes in the humidity and temperature output of the HMEs. Changes in the environmental temperature and temperature and humidity output of the patient model and the inspiratory fresh gas are circumstances which may produce differences in the temperature and humidity output. It is difficult to influence the variations in these parameters, or at least to prevent fluctuations in them in clinical and experimental studies. Even if the room temperature and patient model output are kept stable, the inspiratory fresh gas temperature and humidity levels will change according to the HME efficiency, as the ventilation circuit between the HME and Y-piece acts as an HME. As a result, the inspiratory fresh gas temperature and humidity level will be higher when a less efficient filter is tested. This will cause an overestimation of the temperature and humidity output of less efficient filters. Although the temperature and humidity of the patient model output and inspiratory fresh gas showed minimal changes throughout the study, the ventilator setting that gave the highest temperature or humidity output for any HME was different from the ventilator setting that displayed the highest humidity or temperature conserving efficiency for the HME.

Temperature and humidity outputs of HMEs have been reported to decrease with increasing tidal volume, inspiratory flow rate, and minute volumes (19, 22, 24, 25, 27). The same results have been found in this study. However, the influence of these variables on the temperature and humidity efficiencies of each HME was different. It may be essential to know the ranges of these variables in which adequate heat and humidity efficiencies are achieved for each HME. The DHS has been found to be a very efficient HME at every ventilator setting used in this study, but the humidification efficiency of the PUBB100 and HVF was only sufficient at certain ranges of the ventilation variables. While the heating efficiency of the HVF was always sufficient, that of the PUBB100 was inadequate in all ranges. Therefore, the HVF should only be used in the ranges in which

effective humidification efficiency is achieved, taking into consideration the importance of the relative humidity output in the upper airway secretions as mentioned above. Most of the efficiency formulas are based on gravimetric humidity measurements and involve the unfavorable aspects of the gravimetric method (16, 21, 22, 27, 28). The formulas calculating the efficiency of humidification during online measurements are relatively uncommon and inadequate. The use of flow-weighted mean temperature and humidity values offers a better method of describing HME efficiency. Several studies have been done to test resistances of HMEs; however, there are some shortcomings in their methodology, such as separation of HMEs from the actual breathing system, a maximum of four resistance measurements in a 24-h measurement period using dry air flow, and the use of constant air flow in the measurement of expiratory resistance (16, 18-28, 40). In this study, the shortcomings of these studies have been eliminated; the resistance measurements were done continuously in conditions closely resembling clinical conditions. The inspiratory and expiratory resistances of the HMEs tested in this study were always below the acceptable maximum resistance values established for inspiratory resistance of HMEs (21, 22, 30, 31, 35). Conti et al. (41) have shown in a clinical study that HMEs had no effect on the lung mechanics of mechanically ventilated patients. Therefore, the inspiratory and expiratory resistance of HMEs tested in this study are not a likely obstacle for their clinical use. However, caution should be exercised in patients with heavy and copious bronchial secretions for an unexpected increase in resistance. Contrary to other studies, no significant increase in inspiratory and expiratory resistance has been observed during the 24-h recording periods, but some short-lived increases, being more frequent with the more efficient HMEs, have been observed particularly in expiratory resistance (8, 21, 22). The progressive increases in resistance observed in some studies may be related to these short-lived changes, together with momentary and infrequent resistance measurements. Inspiratory and expiratory resistances were correlated with flow rates. A correlation between humidification efficiency and inspiratory resistance was not found. Contrary to other studies, an inverse relationship was found between the humidification efficiency and inspiratory resistance of the PUBB100 and HVF, showing the importance of the increasing flow rates on inspiratory resistance and humidification efficiencies. This finding is in agreement with the knowledge of the relationships between flow rate and humidification efficiency, and between flow rate and resistance (16, 18, 24,

25, 27). This relationship was not found significant for the DHS, possibly because of its narrower humidification efficiency range. In our opinion, the expiratory resistance is even more important than the inspiratory resistance because of its possible effects on lung mechanics and work of breathing. The expiratory resistance of the HME is related to the expiratory flow rate, which is mainly dependent on the mechanical time constant of the patient. In this study, we tried to imitate the expiratory flow profile of a mechanically ventilated patient in order to assess the influence of the HME on lung mechanics. Based on the finding of the present study conducted on three HMEs at six different ventilator settings, we conclude the following: (1) The Dar Hygroster is a reliable HME with a high humidity and temperature output which is comparable to HHs at all ventilator settings and can even be used when there is an increased risk of endotracheal tube occlusion during long-term mechanical ventilation. (2) The Pall Ultipor BB100 breathing circuit filter did not achieve the required humidity and temperature output at any ventilator setting. (3) The humidification efficiency of the Humid-Vent Filter was within acceptable ranges when low tidal volume, flow rate, and minute volume were used. The temperature efficiency can be compared with the Dar Hygroster and is much higher than the Pall Ultipor BB100 breathing circuit filter. This results in a decreased relative humidity in contrast to the others, but caution has to be exercised when used in patients with a high risk of endotracheal tube occlusion. (4) The inspiratory and expiratory resistances of the HMEs tested are within the clinically acceptable ranges. (5) Humidification and heating efficiency calculations are useful to compare results measured in different conditions. (6) Adequate heating and humidifying efficiency ranges have been defined.

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CHAPTER 7

Monitoring of the end-expiratory lung volume in mechanically ventilated patients

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Abstract

The objective of this study was to monitor the end-expiratory lung volume in mechanically ventilated patients. The study was conducted at a surgical intensive care unit of a university hospital. Fourteen patients requiring mechanical ventilation were included in the study. No interventions were made during the observation period. Measurements were made of end-expiratory lung volume, ventilatory parameters and arterial oxygen. Methods of analysis included Student's t-test, correlation analysis. Mean values of end-expiratory lung volume between survivors and non-survivors during admission to the intensive care unit were found to be significantly different (range of mean daily values of end expiratory lung volume: survivors 0.87-2.85 L; non-survivors 0.65-1.47 L; $p=0.05$). No difference was seen in the mean EELV of the patients with and without acute lung disease during the study period. No significant difference was found when mean PaO2/FiO2 ratio between the non-survivor and survivor group were compared (range of mean PaO2/FiO2 ratio: survivors 52.5-22.5; non-survivors 45.4-27.5, $p>0.05$). The main findings of this study are that mean EELV values were found to be significantly lower in survivors than in non-survivors.

Introduction

Over the last decades, much attention has been focused on the determination of the end-expiratory lung volume (EELV) or functional residual capacity in mechanically ventilated patients(1-12). The determination of EELV is of interest in many different lung diseases because it provides information on the intrapulmonary gas volume that participates in gas exchange. Physiologically, the EELV acts as an oxygen reservoir in the lung and therefore has an important role in blood oxygenation. Previous studies showed that in mechanically ventilated patients EELV measurement may be used to titrate positive-end expiratory pressure (PEEP) and that it enables monitoring of procedures and lung diseases which affect lung volume(10).

Techniques to determine EELV include body plethysmography, gas dilution methods such as the multiple breath nitrogen washout test and washout tests employing inert insoluble tracer gases and gas rebreathing techniques(11, 13-16). Of these techniques, few are suited for daily use in critically ill, mechanically ventilated patients. This is because application of these techniques either requires interruption of the breathing circuit (in rebreathing techniques), manipulation of the inspiratory oxygen fraction (in nitrogen washout techniques) or impractical large-sized measurement setups (when body plethysmography or mass spectrometry are used).

Recently, a setup was devised in our clinic to determine EELV during open-circuit mechanical ventilation which employs SF_6 gas washout and which bears some similarity to a previously described setup (8). With this method, low fractions of SF_6 (0.2%) are injected into the inspiratory port of the ventilator until an equilibrium has been reached within the lungs of the patient. Subsequently, the injection of SF_6 is terminated, and the patient will expel the SF_6 gas. Measurement of the concentration of SF_6 in the expired air during washout is combined with data from a flow meter, which enables the calculation of the total volume of expelled SF_6. This volume equals the EELV. The setup used in our study enables non-invasive measurement of EELV, without interruption of the breathing circuit or manipulation of the inspiratory oxygen fraction and does not require co-operation of the patient. We have conducted a study to evaluate the contribution of EELV-measurement to respiratory monitoring in mechanically ventilated patients.

Patients and methods

EELV determinations were conducted in 14 patients of the surgical intensive care unit of the University Hospital Rotterdam, The Netherlands. For this study, a waiver was obtained from the hospital's ethical committee. Patients were randomly selected to undergo EELV-monitoring. EELV monitoring was started within 48 hours after endotracheal intubation was commenced. Inclusion criteria for EELV monitoring were:

1) endotracheal intubation and mechanical ventilation

2) not likely to be extubated within 24 hours

3) presence of arterial catheter to obtain blood samples

Patients excluded from EELV monitoring:

1) patients expected to succumb within days or in whom treatment was withheld

2) patients in whom the weaning process was initiated

Physiologic data were obtained from the patient's chart and medical records. The EELV was determined by using a washout technique employing a non-toxic inert tracer gas, sulphur hexafluoride (SF_6)(8). The washout technique was employed by injecting a low fraction of pure SF_6 (0.2% of the total inspiratory gas flow) into the inspiratory tubing of the patient's ventilator. When the situation was reached that inspiratory and expiratory SF_6 concentrations were equal, i.e. when the concentration of SF_6 in the lungs equalled the concentration of SF_6 in the inspiratory gas mixture, the SF_6 wash-in was terminated. Thereafter SF_6 wash out was monitored.

The setup to determine EELV consisted of a mechanical ventilator (Evita 4, Drägerwerk Aktiengesellschaft, Lübeck, Germany), a tracer gas injection system and a measurement system. EELV determinations were performed twice daily in the study group for as long as the patients receive mechanical ventilation, with a maximum of two weeks. EELV determinations were initiated within the first 24 hours after admission to the intensive care. EELV determinations were terminated if the patient succumbed during the monitoring period, if the monitoring period exceeded a fortnight, or if weaning from the ventilator was initiated. Each EELV determination consisted of at least three SF_6 washouts of which the mean and standard deviation were calculated.

Measurement system: The measurement system consisted of a heated flow meter (type Fleisch No 1, Bilthoven, The Netherlands), an SF_6-gas analyser and a tracer gas injection system (Central Instrumentation Department, Erasmus University Rotterdam, The

Netherlands) and a personal computer (IBM-compatible 586, 166 MHz processor). The flow meter measures the tidal flow in the breathing circuit, which is used to calculate tidal volume. The sum of expired volumes of the tracer gas during washout is equal to the EELV. The setup determines the EELV during mechanically ventilation with a repeatability of ±130 mL and a coefficient of variation of 4%. The EELV values obtained in the study group were compared to reference values from the literature, which were obtained in supine positioned healthy individuals during spontaneous ventilation(17). Using the body height of the patients in the study group, the predicted healthy supine EELV was calculated. For men, the formula used was 5.85*height-7.05 and for women 1.39*height-0.424(17). At regular intervals, arterial blood gas values were measured using a blood gas analyser (ABL 500, Radiometer, Copenhagen, Denmark). The arterial oxygen levels were corrected for the inspiratory oxygen fraction by calculating the PaO2/FiO2 ratio.

Results

EELV measurements were performed in 14 patients. The analysis of the washout measurements to obtain the EELV values was carried out off-line. Ventilator modes used during the study were Synchronised Intermittent Mandatory Ventilation (SIMV), Assist Spontaneous Breathing (ASB) and Biphasic Positive Airway Pressure (BIPAP). If considered beneficial, PEEP was added. In the study group 13 patients underwent surgery prior to the monitoring period, 11 underwent upper abdominal surgery and two patients underwent extra-abdominal surgery. One patient did not undergo surgery but was admitted to the intensive care unit and endotracheally intubated because of respiratory failure due to pneumonia (Subject 12). Chronic lung disease (one patient suffered from chronic obstructive lung disease and another from sarcoidosis, both currently requiring therapy) was present in 2 subjects, and acute lung disease (fluid overload, acute respiratory distress syndrome) was present in 5 subjects.

Table 1 includes the demographics, diagnosis, performed surgery and lung condition of the study group. The predicted healthy supine EELV (EELVp) and outcome are also displayed in table 1.

Subject	Sex	Diagnosis	Operation	Pre-existing lung disease	Acute lung disease	Age (years)	EELVp (L)	Height (m)	Cause of death
1	m	Gastric carcinoma	Gastric resection	pulmonary sarcoidosis	ARDS	70	2.32	1.71	sepsis
2	m	Esofageal carcinoma	Esofageal resection	none	none	76	2.54	1.75	survived
3	m	Esofageal carcinoma	Esofageal resection	none	pneumonia	67	2.27	1.7	survived
4	m	Esofageal carcinoma	Esofageal resection	none	none	75	2.32	1.71	survived
5	m	Acute abdomen	Laparotomy	restrictive lung disease	none	60	2.98	1.83	MOF
6	m	Hepatic arteriodysplasia	Liver transplantation	none	fluid overload	17	2.43	1.73	Survived
7	m	Acute abdomen	Laparotomy	none	none	74	2.27	1.7	Survived
8	m	Klatskin tumor	Hemihepatectomy	none	none	69	2.81	1.8	Survived
9	m	Necrotizing fasciitis	Laparotomy and necrotectomy	none	none	69	2.54	1.75	cardiac arrest
10	f	Tongue carcinoma	Commando resection	none	none	65	1.84	1.63	Survived
11	f	Oesofago-gastric necrosis	Gastric resection	none	ARDS	41	1.79	1.59	MOF
12	f	Respiratory insufficiency	None	none	pneumonia	48	1.83	1.62	sepsis
13	f	Necrotizing fasciitis	Escharotomy right arm	none	none	55	1.90	1.67	survived
14	f	Colonic perforation	Subtotal colectomy	none	none	40	1.91	1.68	survived

Table 1. Demographics, diagnosis, surgery and lung conditions of the study group. (m=male, f=female, EELVp = predicted healthy EELV, MOF= multi organ failure)

There were 5 females and 9 males in the study group. Five patients died during the EELV monitoring period, all deaths occurring at the intensive care unit. In the group with lung disease 4 out of 6 patients died while in the group without lung disease death occurred in 1 out of 8 patients. Termination of the EELV monitoring was initiated in the case of planned extubation in the survivor group, or when the weaning process had been started. In the non-survivor group, all patients were monitored until death. All deaths in this study occurred during an uninterrupted period of endotracheal intubation during admission to the intensive care unit. Survival of the study patients was monitored until discharge from the intensive care unit.

The obtained EELV values of the study patients displayed a normal distribution which was determined using the Kolmogorov-Smirnov test. Statistical analysis was performed using Student's t test. Figure 1 shows the average daily EELV over the measurement period in survivors (figure 1a) and non-survivors (figure 1b), which was statistically significant (p=0.049, see also table 2).

Subject	Mean EELV (L)	SD EELV (L)	Mean PaO2/FiO2 ratio	SD PaO2/FiO2 ratio	Death during monitoring period
1	1.36	0.48	41.6	11.7	Yes
2	1.60	0.24	26.4	5.3	No
3	1.81	0.63	22.5	2.3	Yes
4	2.53	0.22	28.7	12.8	No
5	1.00	0.01	29.1	5.8	Yes
6	1.27	0.29	43.6	6.2	No
7	2.98	0.31	26.0	5.0	No
8	1.62	0.10	52.5	-	No
9	0.93	0.09	27.5	1.0	Yes
10	1.92	0.08	32.0	2.8	No
11	0.64	0.09	45.4	6.7	Yes
12	1.44	0.28	44.3	11.4	Yes
13	0.86	0.14	37.5	4.5	No
14	1.31	0.28	35.3	3.2	No

Table 2. Values of EELV and PaO2/FiO2 ratio in the study group

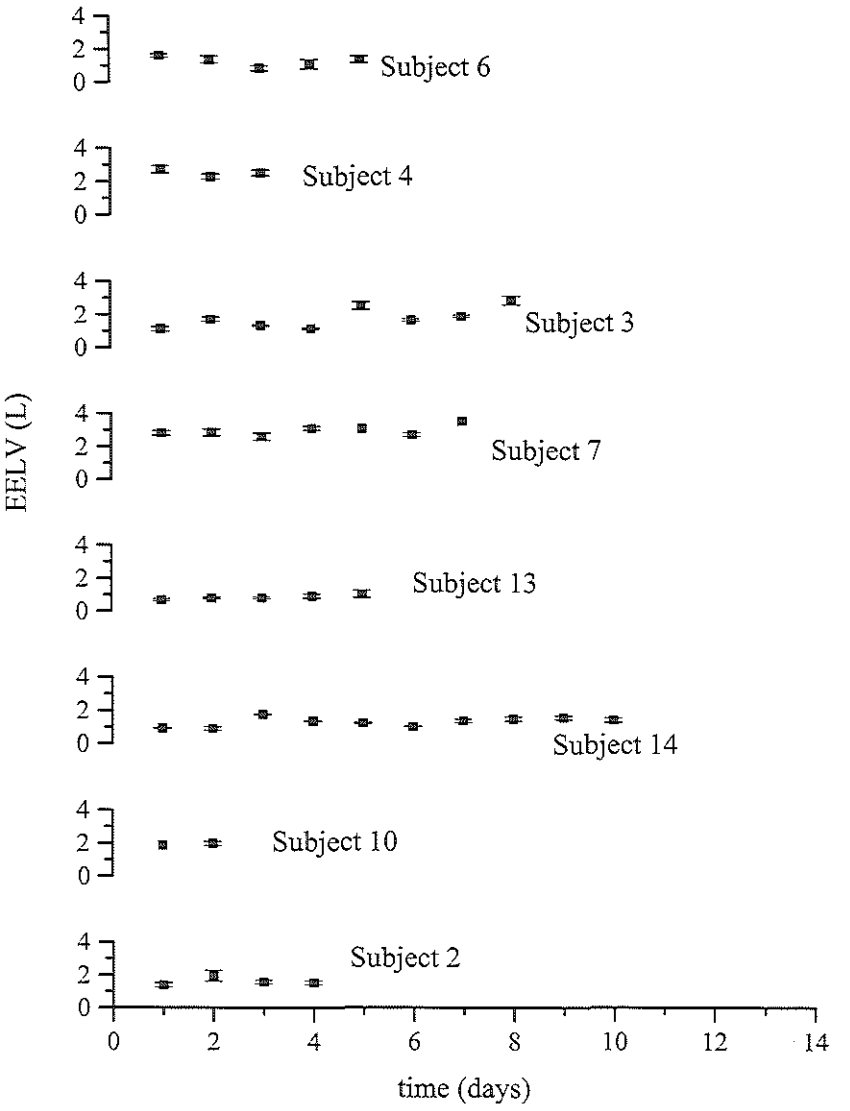

Figure 1. Mean daily EELV of survivors (figure 1a, left page) and non-survivors (figure 1b, right page). Data of one patient (Subject 8) was excluded from the graph because only one mean EELV value could be obtained before endotracheal extubation was successfully performed.

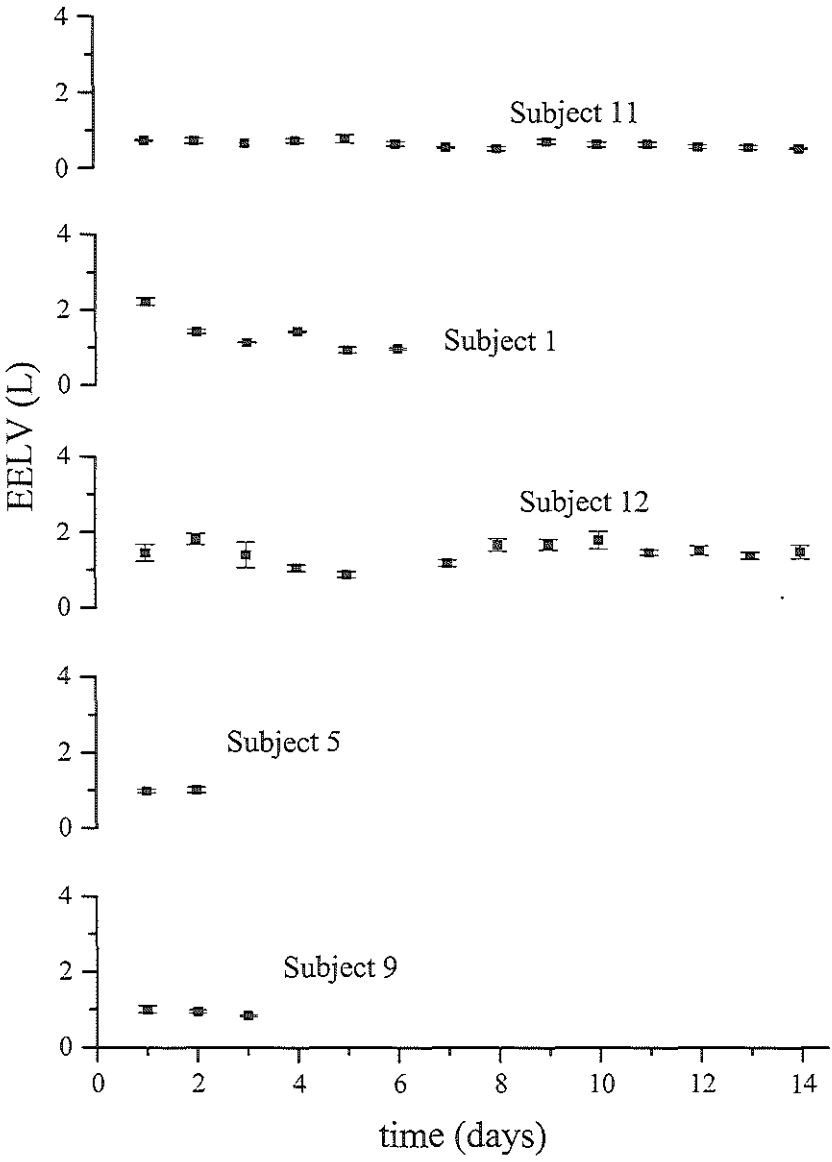

Figure 2 displays the mean ± sd EELV (L) in survivors and non-survivors over the entire measurement period. No significant differences were found in body height and weight, body surface area, age or predicted supine EELV between survivors and non-survivors. There was no statistically significant difference in EELV magnitude between males and

females. The ratio of EELV and EELVp did not differ significantly between survivors and non-survivors (p=0.06). Table 2 displays the mean EELV during the study period in the study patients. The difference in mean EELV in patients with and without lung disease was not statistically significant (p=0.25).

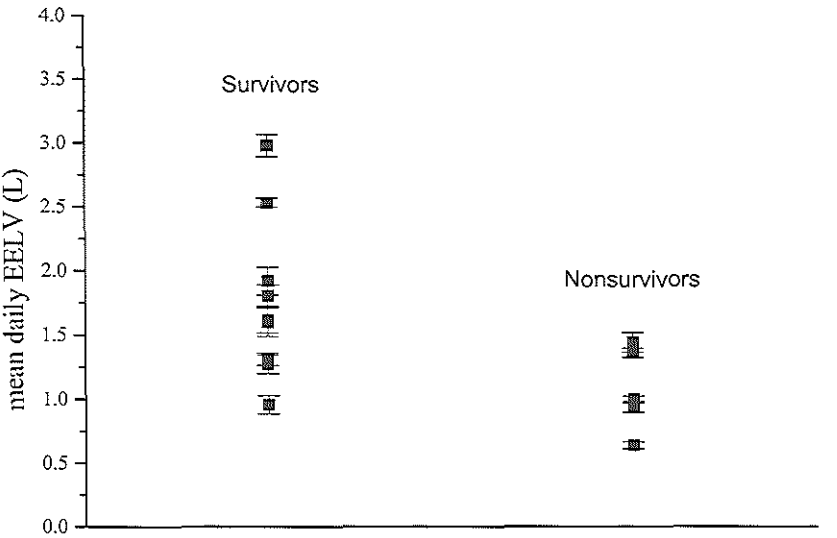

Figure 2. Mean EELV between survivors and non-survivors

The difference in the slope of the regression lines of the EELV of all study patients during the study period was calculated and studied separately for survivors and non-survivors. This was done to study the trend in EELV during the monitoring period. No statistically significant differences in slope were seen (p=0.11). There was no statistically significant difference in the duration of the monitoring period between survivors and non-survivors. Table 2 also indicates the PaO2/FiO2 ratio in the study group. The difference in PaO2/FiO2 ratio between survivors and non-survivors was found to be statistically insignificant (p=0.57, see also figure 3).

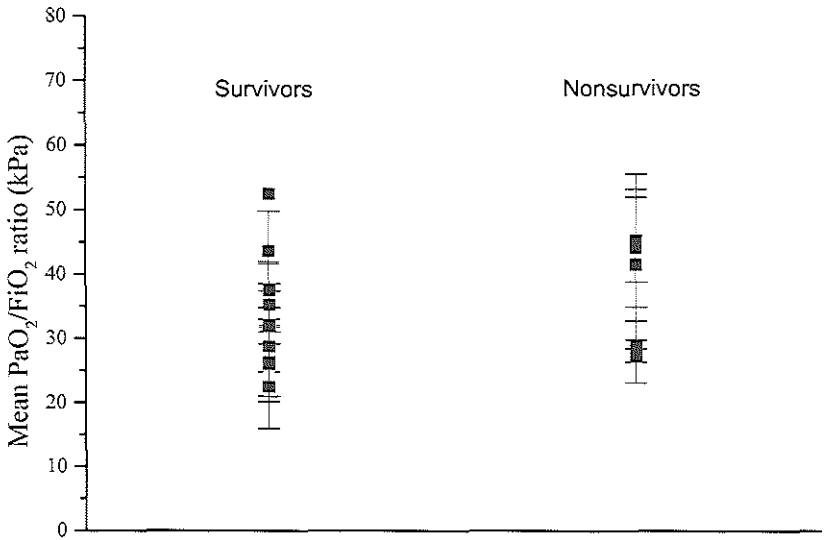

Figure 3. Mean PaO2/FiO2 ratio between survivors and non-survivors

A correlation coefficient of r^2=0.093 was seen between EELV/EELVp and PaO2/FiO2 ratio in the study group. In non-survivors the correlation coefficient was r^2=0.4272 and for survivors r^2=0.3282

Discussion

The results are presented of a study in which EELV was monitored in 14 mechanically ventilated patients. The calculation of EELV was performed using a multiple breath SF_6 gas washout technique(8). Mean daily EELV was found to be significantly lower in the non-survivor group. The ratio of EELV and EELVp did not differ significantly between survivors and non-survivors. Diagnosis of ARDS was documented in two patients of the study group, both of whom did not survive. The trend in EELV was not significantly different between survivors and non-survivors.

This may be due to the fact that the EELV varies considerably during the monitoring period, which is probably caused by treatment measures during the intubation period such as endotracheal suctioning, administration of pharmacological agents and the application

of PEEP. However, a reduction in the premortem EELV may be the cause of the statistical difference seen between the final EELV of the monitoring between survivors and non-survivors. The finding that the EELV during mechanical ventilation is lower in patients who succumb compared to those who survive can theoretically be expected in cases where restrictive lung disease such as the acute respiratory distress syndrome (ARDS) are present, which are known to be correlated with a high mortality rate(18). However, we are not aware of any experimental studies which suggest a lower EELV in non-survivors compared to survivors, although many authors have reported decreases of EELV in restrictive lung failure(18-20). Gattinoni et al. recently reported a study addressing intrapulmonary and extrapulmonary causes of ARDS. In that report a comparison was included of the EELV of patients with an intrapulmonary caused ARDS versus extrapulmonary ARDS and the magnitude of EELV was found to be similar for both groups of patients(21).

No correlation between the EELV and the PaO2/FiO2 ratio was found in this study, which may be attributable to the design of the study (See figure 3). The patients in our study did not experience any long-lived deterioration of their arterial oxygen tension during the mechanically ventilated period due to the fact that treatment was instituted to achieve a physiological arterial oxygen tension for mechanically ventilated patients. Furthermore, the arterial oxygen tension is known to depend not only on lung volume and the oxygen fraction of the inspiratory air, but also on cardiac output and the oxygen carrying capacity of the blood(22).

In this study, no attempts were made to measure the preoperative EELV, because this is not possible for all types of admissions to the ICU, e.g. in the case of trauma patients and other emergency admissions. The aim of this study was to determine whether routine monitoring of EELV may benefit pulmonary surveillance of mechanically ventilated patients. No difference was seen in predicted EELV (calculated using nomograms obtained in the literature) between the survivors and non-survivors. This finding is important because it excludes the possibility of a priori differences in EELV between survivor and non-survivor group, which could be expected because of the body height of the study subjects. An important feature of this study is that data were obtained without any study related interventions. The current patient group displays a wide range of (pulmonary) conditions. Thirteen patients of the patient group underwent surgery.

Thoracic or abdominal surgery influences the magnitude of EELV. After surgery in the abdominal or thoracic cavity, the vital capacity of the lung (and hence the EELV) is known to decrease. Induction of anaesthesia, and the use of anaesthetics themselves reduce the muscular tone of the rib cage. In the first days after surgery, the EELV slowly increases(23). This increase is caused by recovery from atelectasis, sputum retention, abdominal distension and pain which are common causes of pulmonary dysfunction after surgery. It has been suggested that monitoring of EELV may contribute to early detection of deviations from normal (postoperative) recovery patterns(21). A recent review addressed the question of relevance of the EELV measurement in the critically ill(24). In this review article a further discussion of Gattinoni's EELV measurement in extrapulmonary and intrapulmonary ARDS is discussed, and the difficulty of measurement of EELV in ARDS is stressed.

Previous studies have shown that many factors influence EELV, which include body height and position, sex and the presence of chronic pulmonary disease(22). During the EELV monitoring period in this study, patients were often physically active to an extent that their EELV may have changed drastically within a 10-minute measurement period. These physical activities which influence the position of the diaphragm include changes in body position, coughing and changes in breathing pattern. However, physical activity in spontaneously breathing mechanically ventilated patients is to be expected and minor changes in the body position of the study patients occurred. Therefore, the measurements of EELV were initiated only in conditions when the effects of body movements on EELV were thought to have subsided and measurements of EELV which were made during unexpected body movements were discarded. The single most important finding in this study is that a difference was seen between the EELV of survivors versus non-survivors. Future studies in larger patient groups are necessary to establish the contribution of EELV measurement for diagnosis and treatment of pulmonary conditions in mechanically ventilated patients.

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SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

Section I, Study of the literature concerning postoperative pulmonary complications

Chapter 1 "Risk factors for postoperative pulmonary complications". An overview of the literature concerning postoperative pulmonary complications (PPC) is presented. The aim of this study was to explore the literature to delineate the factors which lead to PPC. The chapter summarises pre-operative, intra-operative and postoperative factors which may cause PPC. The study indicates factors which are important considerations for postoperative mechanical ventilation. The study concludes that a generally accepted definition of PPC is lacking, which is supported by the fact that the incidence of PPC is reported to vary between 20 and 69% in studies conducted until now, which impairs the comparability of studies on PPC.

Section II, Development of devices and measurement techniques

Chapter 2 "A fast computer controlled proportional gas injection systems for lung function studies". This chapter describes the design of a gas injection device based on a mechanical ventilator for neonates (Babylog®, Dräger, Germany) which was changed by the manufacturer from a mechanical ventilator into a system in which the component valves can be controlled by custom-made software. The software for externally controlling these valves was designed and tested in our clinic to be used for flow proportional gas injection for wash-out tests. For this purpose, no instruments are available commercially to perform flow proportional gas injection into the inspired air. However, they are required for optimal performance of washout tests in mechanically ventilated patients.

Our studies focused on the use of this system in SF_6 washout tests. This chapter describes the components of the injection system and its control system. We aimed to design a compact user-friendly system to be used in the intensive care setting in mechanically ventilated patients. In the development of the system hardware problems included the electronic noise generated by the valves of the system. This noise tended to disturb the output gas flow of the tracer gas during the closing and opening of the valves. This problem was overcome by off-line computer analysis in which we selected the jitter-free

area of interest of the output signal of the signals of the gas analyser. Only these selected areas are subsequently presented to our analysis program for calculation.

Another hardware related problem was the limit of data transmission of the analog-digital converter which we used to convert the voltage output signal of the ventilator breathing flow transducer to a digital output signal. This caused a delay in response between the actual inspiratory phase and the injection of tracer gas. Similarly, this delay was corrected off-line. In conclusion, we expect that the use of A/D converters with a higher rate of A/D conversion and data transmission speed will reduce the effect of noise superimposition on the gas signal, thereby enhancing the possibilities of the injection system.

By definition, the injection of gas using real time flow signals will be initiated at a later time point than the flow signal itself, which will cause a delay between the initiation of the inspiratory signal of the breathing flow and the tracer gas signal. In our study, we have noted the effect of this delay and corrected this using off-line mathematical correction of the data. Other ways to synchronise the two signals are to decrease the delay in the electronic circuitry of the injection system to a minimum, and to shorten the path length between the valve array and the injection port in the breathing circuit. To achieve this, it may be that a redesign of the setup is necessary.

We conclude that the potential applications of such a flow proportional gas injection system are wide. The flow proportional gas injection system used in this study can achieve a stable concentration of indicator gas in the lungs of (mechanically ventilated) patients and of healthy study subjects regardless of the breathing pattern or ventilator setting. This may serve either diagnostic purposes (when inert gases are used) or therapeutic goals such as the administration of nitric oxide in the treatment of pulmonary hypertension.

Chapter 3 "Design and validation of an analyser to measure sulphur hexafluoride during respiration" This study presents the results of a 7-year period of development of an analyser to measure SF_6 to be used for lung function studies in mechanically ventilated patients. The study was initiated with the modification of a Siemens CO_2 analyser, as was previously described(1). In the development process, the prototype was constructed with other components and displayed different characteristics from the Jonmarker model. We deemed it necessary to present this analyser of which the component technology and characteristics are a departure from the previously described prototype.

Previously conducted EELV measurements in our clinic demonstrated the need for a small-sized SF_6 analyser because of the drawbacks encountered in the intensive care setting during measurements with a setup employing a large sized and noisy mass spectrometer for respiratory gas analysis(2, 3). To our findings, routine measurements in the intensive care setting can only be done effectively if a small-sized setup is used. However, despite the fact that small-sized mass spectrometers have now become commercially available, the need for sample capillaries of considerable length when employing mass spectrometers introduces an increase in response time between the signal of breathing flow and the gas signals obtained by mass spectrometry. The use of an inline SF_6 gas detector inherently reduces the problem of high response time of breathing gas signals.

The analyser was submitted to tests of pressure and temperature sensitivity, linearisation in the calculation of gas fractions, chopper motor speed and measurement of the response speed to abrupt changes in gas concentration. We conclude that the sensor is easy to use, and stable in terms of pressure and temperature sensitivity. A further increase in measurement stability can be obtained by rigidly positioning the SF_6 transducer such that it is resistant to vibrations.

The electronic drift of the signal of the analyser discussed in this chapter is the most important drawback of the system. To eliminate signal drift, several directions for improvements can be taken. A change in type of pyrodetector seemed appropriate to improve the signal drift, but previous searches into this detector type for the sake of signal stability did not yield a satisfying alternative. Other possibilities include improvement in the stabilisation circuitry of the analyser and elimination of disturbances of the signal by improvement of the design of the SF_6 transducer.

A different approach to deal with the electronic signal drift may be to present the signal of the SF_6 transducer to a computerised self-learning system. Techniques such as fuzzy logic or neural network-based systems may be used to identify the characteristics of the output signal of the transducer(4). After these characteristics have been defined, online mathematical correction of the disturbances of the signal of the SF_6 analyser are possible. Because of the limited possibilities of improvement of the hardware at this time, computer-based analysis of the signal to correct disturbances of the signal currently seems to be the best alternative.

Chapter 4 "A setup to measure the end-expiratory lung volume in mechanically ventilated patients" In this study the previously described flowproportional gas injection unit, the SF_6 analyser, a measurement computer and a mechanical ventilator were integrated into a setup to perform bedside measurements in mechanically ventilated patients. We chose to engineer the setup in such a way that measurements could be obtained in mechanically ventilated patients for an extended period of time. The setup was first tested by conducting EELV measurements in a dummy lung of which the EELV was previously measured using a helium dilution technique. Measurements in the dummy lung were also done in different ventilator settings, in which the effect of change in respiratory frequency, tidal volume, PEEP and inspiratory pressure was determined. Finally EELV measurements are demonstrated in a mechanically ventilated, paralysed patient during fixed ventilator settings in which the EELV was expected to be stable. The chapter further describes determination of measurement accuracy and repeatability of the EELV measurement. The results of the study are that measurements of EELV with the described setup can be expected to have a replication error of 131 mL, which is in the range of accuracy values reported in previous studies.

Because of the choice of components of the current setup, the size can be easily reduced to at least a third of its volume. The setup is currently integrated with the ventilator, but it is possible to physically separate the EELV measurement system. When separated, the measurement system can be used independently from the ventilator. This may be particularly of use when the setup is to be used to follow up larger patients groups or non-mechanically ventilated patients. We conclude that the set-up can be used to determine EELV with an accuracy range that is suited for conducting lung function studies in mechanically ventilated adults.

Section III Experimental studies

Chapter 5 "Non-invasive monitoring of non-shunted pulmonary capillary blood flow in the acute respiratory distress syndrome". This study presents the results of a pilot study to evaluate the alveolar amplitude response technique (AART) in ARDS. When the technique is used, halothane vapour with a pre-set sinusoidally varying fraction is purged in the inspiratory tubing of the breathing circuit. The attenuation of the inspiratory gas fraction is used as a measure for the pulmonary circulation of the alveoli which participate

in the pulmonary gas exchange(5). AART was selected for evaluation because of its potential to monitor "effective" lung perfusion non-invasively, without interruption of the breathing circuit.

The technique was applied in mechanically ventilated pigs. To study if the AART was able to detect the onset of alveolar collapse, the animals underwent surfactant depletion to mimic ARDS. The measurements of the non-shunted pulmonary capillary blood flow were done before and after surfactant depletion was initiated. During the experiments, PEEP was applied, to study if alveolar recruitment was signalled by the increase in non-shunted pulmonary capillary blood flow, as measured by AART. To compare the AART measurements of non-shunted pulmonary capillary blood flow, thermodilution cardiac output measurements and calculation of intrapulmonary shunt, were done simultaneously. The results of the study indicate that trends in non-shunted pulmonary capillary blood flow were similar in direction when both techniques were compared.

The results of the pilot study are encouraging, but future studies are necessary to determine what measures have to be taken to increase the agreement between the shunt-corrected cardiac output measurements obtained by thermodilution and AART. Advancement in the theory used on which the calculation method of the AART is based may increase the accuracy of the measurement of the non-shunted pulmonary capillary blood flow. Current analysis of the gas sinusoids in AART employs the three compartment model of Riley and Cournand, which may oversimplify the description of the lung in cases of COPD, or in general when ventilation inhomogeneity is present(6). Also, as the technique employs sinusoids, an attractive way to graphically present the signals of the gas sinusoids for calculation of monitoring purposes may be done by using a Lissajous figure.

Future studies should preferably be done with a different inert water-soluble gas than halothane because of the side effects of halothane. In our study, the toxicity of halothane was not a major concern, as the inspiratory concentration of halothane was kept below 1%. Nitrous oxide would be the ideal substitution if it would not have the same molecular weight as carbon dioxide (44 Dalton). This causes conflict in the measurement of the two gases when using a mass spectrometer. Correction methods to decipher this conflict at the 44 molecular weight are possible, but they are difficult and cumbersome to implement.

Other measurement techniques (non-mass spectrometry based) may be a contribution to facilitate the clinical use of nitrous oxide in the application of the AART.

Further research to evaluate the use of the AART in clinical studies has to be conducted in sepsis and other frequently encountered diseases in the ICU. To implement the AART in clinical studies, the efficacy of the flow proportional gas injector (See also chapter 2) in the administration of sinusoids of tracer gas has to be evaluated. If the flow proportional gas injector functions satisfactorily in this setting, the AART can be applied to measure the pulmonary perfusion of ventilated alveoli in spontaneous breathing.

Chapter 6 "A novel method of evaluation of three heat-moisture exchangers in six different ventilator settings". This chapters deals with the implementation of a new setup and measurement technique to measure humidity and heat exchange. The setup was evaluated in this study in a patient model which consisted of a dummy lung to investigate if differences exist between three commonly used heat-moisture exchangers (HMEs). The study comprised of 24-hour measurements of a single HME. Each HME type was evaluated in three different ventilator settings. The results of the study are that the Dar Hygroster has the highest heat and moisture output compared to the Gibeck Humid-vent and the Pall BB100 when compared in a patient model. The filters with the highest heat and humidity output have thereafter been used for conditioning the inspiratory gases in mechanically ventilated patients of our institution.

Chapter 7 "Monitoring of the end-expiratory lung volume in mechanically ventilated patients". The setup described in chapter 4 was used to measure EELV in patients of our SICU. Fourteen patients were included in the study if they were likely to be endotracheally intubated beyond a period of 24 hours. Daily EELV measurements were done in triplicate, at least two times a day during a period of two weeks, or until extubation. No study related interventions were made. The results of the study are that a significantly lower EELV was seen in non-survivors. Furthermore, a negative trend in EELV was observed in EELV in the non-survivors. To our knowledge, no earlier study reported similar data.

To strengthen the commonly held notion that the EELV, and monitoring of its trend may be an predictor of survival a change in study design may be necessary. The EELV should preferably be measured at least twice daily and when ventilator settings are changed, in

large patient groups of the intensive care ward. As discussed in chapter 4, a redesign of the current setup is recommended.

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SAMENVATTING (SUMMARY IN DUTCH)

Respiratoire complicaties na een operatie kunnen de opnameduur in het ziekenhuis verlengen en hebben soms dodelijke gevolgen. Kennis van de oorzaken en behandeling van deze complicaties is dan ook onontbeerlijk voor de klinische praktijk. **Hoofdstuk 1, Sectie I**, geeft een samenvatting van de huidige literatuur betreffende postoperatieve respiratoire complicaties. In deze literatuurstudie werd een verband gelegd tussen de risicofactoren voor het ontstaan van postoperatieve respiratoire complicaties en de perioperatieve fase. De studie laat zien dat er nog geen algemeen geaccepteerde definitie voor een postoperatieve respiratoire complicatie bestaat, hetgeen tot gevolg heeft dat de incidentiecijfers van postoperatieve pulmonale complicaties variëren tussen 20 en 74%.
Voor het bewaken van de respiratoire conditie bij postoperatief beademde patiënten zijn een aantal hulpmiddelen beschikbaar: hiertoe behoren bijvoorbeeld de bepaling van bloedgassen, thoraxfoto's en de meting van zuurstofsaturatie van het bloed. Nadelen van deze technieken zijn dat ze of alleen intermitterend gebruikt kunnen worden en/of maar een deel van de longfunctieparameters kunnen karakteriseren. Er is echter een achterstand in het niveau van de ontwikkeling van apparatuur en technieken waarmee aanvullende longfunctiekarakteristieken gemeten kunnen worden bij mechanisch beademde patiënten. In experimentele longfunctielaboratoria werd aangetoond dat het mogelijk is om de doorbloeding van het gasuitwisselende deel van de long te bepalen op een niet-invasieve wijze, hetgeen potentieel gebruikt zou kunnen worden als hulpmiddel om bijvoorbeeld de instellingen van de beademingapparatuur te optimaliseren. Een andere techniek, die sinds geruime tijd in longfunctielaboratoria wordt toegepast meet het eind-expiratoire longvolume (EELV). Deze parameter geeft een indruk van de grootte van het longvolume dat participeert in de gaswisseling. Deze parameter is gestoord bij restrictieve longaandoeningen en chronisch obstructief longlijden. Experimentele studies tonen aan dat meting van deze parameter derhalve bruikbaar kan zijn voor het signaleren van veranderingen in de conditie van de longen van mechanisch beademde patiënten. Het ontbreekt echter aan een geschikte methode voor toepassing van deze techniek bij deze patiëntengroep.
Om deze technieken toe te kunnen passen werden in deze studie meetopstellingen ontworpen, vervaardigd en in testsituaties geëvalueerd (**Sectie II**). Het doel van de studies

in dit proefschrift is het evalueren van methoden die gebruikt kunnen worden voor bewaking van intensive care patiënten na een operatie op het ontstaan van longfalen. De studies werden uitgevoerd in het Experimenteel Diercentrum en de chirurgische intensive care van het Academisch Ziekenhuis Rotterdam in de periode tussen 1993 en 1999.

Voor meting van het EELV selecteerden wij een non-invasieve, potentieel automatiseerbare meetmethode (zie Hoofdstuk 4). Bij de toepassing van deze techniek is een gasinjectiesysteem noodzakelijk. **Hoofdstuk 2, Sectie II**, beschrijft een digitaal gestuurd gasdoseersysteem dat in mede in onze kliniek werd ontwikkeld, en alhier in een EELV meetopstelling (Zie hoofdstuk 4) werd geïntegreerd. Voor experimentele longfunctiestudies, zoals uitgevoerd wordt in onze kliniek, is een dergelijke injector noodzakelijk. De ontwikkeling van dit injectiesysteem werd gestart omdat eerdere prototypen van gasinjectiesystemen uit in onze kliniek niet in staat waren om bij patiënten met een onvoorspelbaar en onregelmatig adempatroon een stabiele fractie indicatorgas te bereiken tijdens injectie. De literatuur beschrijft enkele prototypen van injectiesystemen die wel in staat zouden zijn om een stabiele indicatorgasfractie in long te bereiken bij patiënten met een onvoorspelbaar adempatroon, maar deze zijn niet (commercieel) verkrijgbaar. Het beschreven gasdoseersysteem bestaat uit een bank met mechanische kleppen van oplopende diameter. De gasdoseereenheid werd beschikbaar gesteld door de firma Dräger en bestaat uit een gemodificeerde mechanische ventilator welke oorspronkelijk bedoeld was voor beademing van neonaten (type Babylog). Het injectiesysteem laat de kleppen van de ventilator op geleide van de vorm en grootte van het signaal van de inademing openen of sluiten, waardoor een stabiele fractie van het indicatorgas in de long wordt verkregen. Het hoofdstuk beschrijft de componenten van het gasdoseersysteem, en het uiteindelijke systeemontwerp. Voorts worden de metingen besproken van de traagheid van het injectiesysteem, de frequentierespons en de uiteindelijke stabiliteit van de geïnjecteerde gasfractie. De resultaten van de studie laten zien dat het gasdoseersysteem goed bruikbaar is voor flowgestuurde injectie van indicatorgas in ademcircuits van kunstmatig beademde patiënten. De injector is gebruikt in de EELV meetopstelling welke wordt beschreven in hoofdstuk 4.

Hoofdstuk 3 beschrijft de ontwikkeling en testresultaten van een meetsysteem voor de bepaling van zwavelhexafluoride gas (SF_6) in ademcircuits. SF_6 wordt onder andere toegepast als indicatorgas bij uitwastests voor de bepaling van het EELV. De huidige

sensor werd verkregen door het meetspectrum van een infrarood CO_2 analysator te verschuiven naar het gebied waar SF_6 gedetecteerd kan worden. De sensor is bedoeld voor de bepaling van SF_6 gedurende uitwastests of mogelijk voor andere technieken waarbij detectie van SF_6 gas wenselijk is. De ontwikkeling van de beschreven SF_6 sensor werd gestart omdat eerder onderzoek uitwees dat bij de toepassing van uitwastests het gebruik van een meetinstrument met een hoge nauwkeurigheid en snelle responstijd wenselijk is. Omdat een dergelijke sensor ontwikkeld werd voor metingen bij mechanisch beademde patiënten op een intensive care afdeling is het tevens van belang dat het instrument klein van formaat is, en op generlei wijze interfereert met de behandeling van de patiënt of klinische meetapparatuur. De resultaten van de ontwikkeling van het meetinstrument laten zien dat het ontwerp aan de voornoemde eisen voldoet. Verder onderzoek is echter noodzakelijk om het meetinstrument minder storingsgevoelig te maken. Op grond van onze resultaten lijkt het mogelijk dat de beschreven SF_6 detector in de toekomst voor andere doelen kan worden ingezet.

Hoofdstuk 4 beschrijft de ontwikkeling en evaluatie van een meetopstelling om het EELV te bepalen. Hiertoe werd het gasdoseersysteem met de SF_6 detector geïntegreerd die in respectievelijk hoofdstuk 2 en 3 werden beschreven. De EELV meetopstelling werd getest door het EELV van een kunstlong (met een bekend EELV) herhaaldelijk te bepalen, tijdens verschillende beademingsinstellingen. Uit deze gegevens werd de meetfout herleid, en deze resultaten werden gebruikt om een algoritme te ontwikkelen waarmee tekortkomingen van de componenten van de meetopstelling (signaalstoring door injectieartefacten van het gasdoseersysteem, en signaalinstabiliteit van de SF_6 analysator) te detecteren, en waar nodig deze te elimineren of te herstellen. Het meetsysteem werd vergeleken met de resultaten van een EELV bepaling door een spirometer uit het longfunctielaboratorium van onze kliniek. Tenslotte werd het meetsysteem gedemonstreerd in een mechanisch beademde patiënt waarvan theoretisch geen fluctuatie in het EELV verwacht kon worden. Bij deze patiënt waren de beademingsinstellingen niet veranderd tijdens de EELV meetperiode en was er geen ademinitiatief aanwezig als gevolg van de toediening van sedativa en spierverslappers. De registratie van het EELV bij deze patiënt geeft een indruk van de nauwkeurigheid van de in-vivo EELV bepaling door de beschreven meetopstelling. Deze studie laat zien dat de meetopstelling in staat is het EELV op 131 mL nauwkeurig te meten met een variatiecoëfficiënt van 4%. Deze

gegevens suggereren dat de meetopstelling bruikbaar is voor bepaling van klinisch relevante veranderingen in het EELV van beademde patiënten.

Hoofdstuk 5, Sectie III beschrijft een meetopstelling voor toepassing van de alveolaire amplitude response techniek (AART). Eerdere studies toonden aan dat deze techniek gebruikt kan worden voor de non-invasieve bepaling van de bloedstroom langs geventileerde alveoli (longblaasjes). De meetopstelling zoals beschreven in het hoofdstuk werd geheel vervaardigd in onze kliniek. In deze studie werd gebruik gemaakt van een model waarin acuut longfalen werd geïnduceerd. Hiervoor werden biggen gebruikt die ter inductie van acuut longfalen surfactantdepletie ondergingen. De alveolaire bloeddoorstroming werd verder gevarieerd door manipulatie van het niveau van positieve eind-expiratoire druk (PEEP) dat de proefdieren tijdens kunstmatige beademing kregen. Metingen van de door de AART gemeten effectieve alveolaire bloeddoorstroming $\dot{Q}_{AART}$ werden vergeleken met een andere, gangbare (invasieve) techniek voor de bepaling van de effectieve alveolaire bloeddoorstroming $\dot{Q}_{Td,Va}$. De resultaten laten zien dat de $\dot{Q}_{AART}$ veranderingen in de bloedstroom van geventileerde alveoli signaleert. Verder onderzoek is noodzakelijk om te bepalen hoe de nauwkeurigheid en vergelijkbaarheid met andere meetmethoden voor de effectieve longperfusie kan worden verhoogd. Om de techniek voor toepassing in klinische situaties geschikt te maken is het noodzakelijk om de techniek te evalueren in andere klinisch belangrijke ziektemodellen (m.n. chronisch obstructief longlijden, sepsis).

Hoofdstuk 6 beschrijft de toepassing van een meetsysteem voor de bepaling van warmte en vochtuitwisseling bij 3 verschillende typen beademingsfilters. Bij mechanische beademing wordt veelal gebruik gemaakt van een endotracheale buis. Dit heeft tot gevolg dat de lucht die de patiënt ontvangt niet meer bevochtigd en verwarmd wordt door de bovenste luchtweg. Dit kan leiden tot uitdroging van longsecreties, hetgeen de normale huishouding van de luchtweg en longparenchym verstoort. Dit kan uiteindelijk leiden tot longschade als gevolg van onder andere longontsteking en collaberen van longdelen. Voor de bevochtiging van de uitademingslucht wordt in de klinische praktijk onder andere gebruik gemaakt van warmte- en vochtretinerende beademingsfilters, ook wel kunstneuzen genoemd (HMEs). Van deze HMEs zijn verschillende typen commercieel verkrijgbaar, waarvan de efficiëntie van warmte en vochtuitwisseling vaak onduidelijk is. Om de efficiëntie van 3 verschillende typen in onze kliniek gebruikte HMEs te

documenteren werd een experimentele opstelling gebruikt welke bestond uit een patiëntenmodel en een eerder beschreven meetopstelling voor de registratie van warmte- en vochtoutput. De output van de HMEs werd geregistreerd gedurende een 24-uurs periode en elk type werd gedurende 6 verschillende beademingsinstellingen geëvalueerd. De resultaten van het onderzoek laten zien dat er significante verschillen bestaan in bevochtigings- en warmteconserveringsefficiëntie tussen de onderzochte typen HMEs.

Hoofdstuk 7 beschrijft de resultaten van het in dit proefschrift beschreven meetsysteem (Hoofdstuk 4) voor de bepaling van het EELV in mechanisch beademde patiënten. In deze studie werd het EELV van patiënten dagelijks bepaald gedurende de periode dat zij endotracheaal geïntubeerd en beademd werden op de intensive care afdeling. Met de EELV meetperiode werd gestart binnen 24 uur na aanvang van mechanische beademing bij die patiënten waarvan verwacht werd dat zij niet binnen 48 uur ontwend zouden worden van de ventilator. Veertien patiënten werden geïncludeerd in deze studie. Er werden geen studiegerelateerde interventies verricht. Het normale EELV van elke patiënt werd geschat door middel van nomogrammen uit de literatuur. De resultaten van de studie laten zien dat het EELV van de overlevende patiënten significant groter is dan het EELV van de niet-overlevenden. In deze studie werd geen verschil gezien tussen het zuurstofgehalte in het arteriële bloed tussen deze beide groepen. Hoewel het aantal patiënten in deze studie klein is, mogen de resultaten dienen als een aanmoediging voor verder onderzoek. Door veranderingen aan te brengen in het ontwerp van het in hoofdstuk 4 beschreven meetsysteem (met name reductie van de omvang van de meetopstelling) zou het mogelijk zijn om het verloop van het EELV bij grotere patiëntenaantallen te vervolgen. Hierdoor wordt de mogelijkheid geschapen om het normale postoperatieve verloop van het EELV bij verschillende aandoeningen te karakteriseren en afwijkingen hiervan te signaleren.

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**In memoriam S. Kanhai (1993)*

CURRICULUM VITAE

The author was born on the 4th of February, 1970, in Paramaribo, Suriname. He received his primary school education in both Suriname and the Netherlands. His secondary school education was obtained from 1982 to 1989 in Rotterdam, The Netherlands. In 1989 he started his medical training at the Erasmus University in Rotterdam. In 1993 he finished his preclinical exams. During this preclinical period he worked as a research student at the Intensive Care Unit of the Department of General Surgery of the University Hospital Rotterdam where he studied the characteristics of different types of heat moisture exchangers using a patient model (Supervisor: Prof.dr. H.A. Bruining). The results of this study are presented in this thesis. After obtaining his medical qualification in 1996 he worked as a PhD student at the Intensive Care Unit of the Department of General Surgery of the University Hospital Rotterdam, during which periode he studied the development and application of non-invasive techniques to measure effective pulmonary perfusion and end-expiratory lung volume. The results of these studies are presented in this thesis. In 1997 he was hosted at the Nuffield Department of Anaesthetics, University of Oxford, United Kingdom to study the sinewave technique (Supervisor: Prof.dr. C.E.W. Hahn). Since 1999 he is a resident in Surgery at the Bronovo Hospital, The Hague (Supervisor: Dr. A.B.B. van Rijn). He will continue his training in Surgery at the Bronovo Hospital and at the Leiden University Medical Center (Supervisor: Prof.dr. O.T. Terpstra).

NOTES

Wij stonden nu alleen in de operatiekamer. Het personeel, ik, en Liedka: het meisje. In haar blootje zat ze op de tafel zonder geluid te huilen. Ze werd languit op de tafel neergelegd, vastgeklemd, haar keel werd schoongewassen, met jodium ingesmeerd, en ik pakte het mes; daarbij viel mij de gedachte in: 'Wat doe ik eigenlijk?' Het was heel stil in de operatiekamer. Ik nam het mes en bracht een verticale snee aan op het poezelige witte keeltje. Er kwam geen druppel bloed te voorschijn. Voor de tweede maal bracht ik met het mes een snee aan langs het witte strookje dat tussen de uiteengeweken huid te voorschijn was gekomen. Weer geen spatje bloed. Langzaam, terwijl ik mij bepaalde tekeningen uit anatomische atlassen voor de geest probeerde te halen, begon ik met de stompe sonde de dunne weefsellaagjes te scheiden. En tóén kwam onder de wond opeens donker bloed ergens vandaan gegutst en overspoelde in een oogwenk de hele wond en begon langs de hals te stromen. De verpleger begon het met tampons op te betten, maar het bloeden hield niet op. Indachtig alles wat ik op de universiteit gezien had, begon ik met pincetten de randen van de wond aan te drukken, maar zonder enig gevolg.

De kou sloeg mij om het lijf en mijn voorhoofd was door en door klam. Ik kreeg er bittere spijt van dat ik naar de faculteit voor geneeskunde was gegaan, dat ik in deze rimboe terecht was gekomen. In woedende wanhoop stak ik lukraak de pincet uit, ergens in de buurt van de wond klikten de spitsen op elkaar, en... onmiddellijk hield het bloeden op. De wond betten wij uit met plukken verbandgaas, en daar lag de wond dan schoon en volstrekt onbegrijpelijk vóór mij. Nergens was een luchtpijp te bekennen. Mijn wond vertoonde geen enkele gelijkenis met welke tekening dan ook. Er verstreken nog eens twee, drie minuten, waarin ik volkomen werktuiglijk en verdwaasd nu eens met het mes, dan weer met de sonde in de wond peuterde, op zoek naar de luchtpijp. En tegen het einde van de tweede minuut wanhoopte ik eraan dat ik haar ooit zou vinden. 'Dat is het einde,' ging het door mij heen, 'waarom heb ik dit gedaan? Ik had immers geen operatie hoeven voor te stellen, en Liedka zou dan kalmpjes bij mij op de ziekenzaal gestorven zijn, maar nu... nu zal ze sterven met een opengereten keel, en nooit, met niéts zal ik kunnen aantonen dat zij evengoed gestorven zou zijn, dat ik het voor haar tóch niet erger had kunnen maken...' Een van de vroedvrouwen wiste zonder een woord mijn voorhoofd af. 'Leg je mes maar neer, zeg maar: ik weet niet wat ik verder moet,' zo gingen mijn gedachten, en voor mijn geestesoog doemden de ogen van haar moeder op. Ik nam opnieuw het mes op en gaf gedachteloos een diepe, felle jaap in de hals van Liedka. De weefsellagen weken uiteen, en onverwachts lag daar de luchtpijp voor mij.

'De haken!' schoot ik hees uit.

De verpleger gaf ze aan. Ik priemde de ene haak aan de ene kant vast, een tweede aan de andere, en een ervan gaf ik over aan de verpleger. Nú zag ik nog maar één ding voor me: de grauwige kraakbeenringen van de strot. Het scherpe mes prikte ik in de strot en... ik verlamde van schrik. De strot kwam uit de wond omhoog, de verpleger—zo flitste het door mijn hoofd—had zijn verstand verloren: hij begon hem opeens naar buiten te rukken. Achter mijn rug slaakten de beide vroedvrouwen een stomverbaasd 'ah'. Ik keek op en zag opeens wat er aan de hand was: de verpleger viel blijkbaar in zwijm van de benauwde lucht en scheurde daarbij de luchtpijp stuk daar hij de haak niet losliet. 'Alles zit me tegen, dat is het lot,' dacht ik, 'nu hebben we Liedka vast en zeker om hals gebracht,' en in mijn gedachten voegde ik eraan toe: 'Rest mij alleen nog naar huis te gaan, en dan jaag ik me een kogel door de kop...' Op dat moment schoot de oudste vroedvrouw—kennelijk een heel ervaren kracht—bijna als een tijgerin op de verpleger af en griste hem de haak uit de hand, terwijl ze tegelijk met op elkaar geklemde tanden zei: 'Ga maar verder, dokter...'

De verpleger viel met een bons neer, stootte zich, maar wij keken niet naar hem om. Ik stak het mes in de strot, zette er verwolgens een zilveren buisje in. Het gleed vlot op zijn plaats, maar Liedka bleef roerloos liggen. Er kwam geen lucht in haar keel zoals dat zou moeten. Ik loosde een diepe zucht en bleef werkeloos toezien: méér kon ik niet doen. Ik voelde de neiging om iemand om vergiffenis te vragen, mij berouwvol te tonen over mijn lichtzinnigheid, over het feit dat ik mij ingeschreven had aan de medische faculteit. Er hing een loden stilte. Ik zag Liedka blauw wegtrekken. Ik wilde al alles erbij neergooien en in huilen uitbarsten, toen Liedka plotseling heftig sidderde, een golf van rotklonters in een straal door het buisje spoog, en de lucht fluitend in haar longen schoot; toen begon het meiske te ademen en zette het op een blèren. De verpleger krabbelde op dat ogenblik overeind, wierp, bleek en bezweet, suffig en vol ontzetting een blik op haar strot en begon mij te helpen bij het dichthechten van de keel.

Als door een droomsluier en door een waas van zweet dat mijn ogen had overtogen, zag ik de gelukkige gezichten van de vroedvrouwen, en een van hen zei tegen mij: 'Gò, die operatie hebt u er maar schitterend afgebracht, dokter.'

Michail Boelgakow, 'De stalen strot'. *Verhalen van een jonge arts.* (1924)
Amsterdam, De Arbeiderspers, 1974

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