Measurement of lung volume and an index of ventilation inhomogeneity during mechanical ventilation

Illustratie omslag: Th. Jordans, Molenweg 37, Groede.
Typeset by the author with Computer Modern fonts.
Printed by IGC printing, Dordrecht.

Measurement of lung volume and an index of ventilation inhomogeneity during mechanical ventilation

(Meting van het longvolume en een index voor ventilatie inhomogeniteit tijdens mechanische beademing)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam op gezag van de Rector Magnificus Prof.Dr P.C.W. Akkermans M.Lit.
en volgens besluit van het college van decanen.
De openbare verdediging zal plaatsvinden op woensdag 13 april 1994 om 13.45 uur

door
Paulus Eugene Marie Huygen
Geboren te Maastricht

Promotiecommissie

Promotor:	Prof. Dr H.A. Bruining
Co-promotor:	Dr Ir C. Ince
Overige leden:	Prof. Dr S.C.M. Luijendijk
	Dr J.M. Bogaard
	Prof. Dr B. Lachmann

Part of the research for this thesis has been supported by the Netherlands Asthma Foundation and part has been supported by the Ministery of Economic Affairs of the Netherlands (STIPT project) in cooperation with Mijnhardt BV, Bunnik, the Netherlands.

Opgedragen aan
Onno,
Tamar,
Tiemke

Contents

Chapter 1

Introduction

In the intensive Care Unit there is a striking difference between the state of the art of haemodynamic monitoring and that of pulmonary function monitoring. The haemodynamic status of Intensive Care patients is continuously monitored by devices producing signals of beat-to-beat electro-cardiograms and blood pressures, using sophisticated, fully developed devices, that can be delivered from stock and handled with ease by people without special technical background. The resulting signals are available in real-time, and the interpretation of the signal is based on physiologic models. On the other hand, pulmonary monitoring is usually limited to a few blood gas measurements per day, occasional chest X-ray and occasional inspection of airway pressures. These simple data are not sufficient to describe properties of the lung and the gas transport, and indicate deterioration of the lung function only at a very late stage, when the chances for complications have already been increased. It also means that in mechanically ventilated patients the clinician takes the control of the ventilation over from the patient without having direct information on the gas exchange process in the lung. Instead the clinician has to rely on secondary information like blood gas pressure. In most cases these techniques give adequate information. However, e.g. in patients suffering the Adult Respiratory Distress Syndrome the clinician tries to maintain the lung volume at a desired level by application of a positive airway pressure (PEEP, Positive End-Expiratory Pressure), but is not able to measure the lung volume that he wants to control.

This thesis reports on the development and validation of a multiple breath indicator gas wash-out system to measure the lung volume and ventilation inhomogeneity during mechanical ventilation. In a multiple breath indicator gas wash-out test the subject inspires from a gas-mixture containing a certain fraction of an inert, poorly soluble, indicator gas, until it is homogeneously distributed over the lung. Then the

indicator gas is withdrawn from the inspiratory gas-mixture and subsequently the flow and the indicator gas-fraction are measured at the mouthpiece during a few minutes. The quotient of the amount (or *partial volume*) of indicator gas that was present in the lung before the start of the wash-out and the indicator gas-fraction at that moment is equal to the lung volume. The variability of the rate of the decay of the expiratory indicator gas-fraction during the wash-out and breath-by-breath curves of the indicator gas-fraction as a function of expired volume give information on the efficiency of the ventilation. Information on gas-transport by diffusion can be obtained by comparison of the wash-out of gases with different diffusion coefficient, and information of distribution of ventilation-perfusion inhomogeneities can be obtained by comparison of the indicator gas-fraction signal with the signal of the carbon-dioxide fraction. The techniques mentioned are described in this thesis.

The most important parameters for monitoring lung function during mechanical ventilation are the end-expiratory lung volume and the dead space. The end-expiratory lung volume is of vital importance because post-operative pulmonary complications like pneumonia and atelectasis are generally caused by the post-operative reduction of the lung volume and because Adult Respiratory Distress Syndrome (ARDS) goes with massive collapse of alveoli, that can be (partly) reversed by application of positive end-expiratory pressure (PEEP) ventilation. The end-expiratory lung volume is an excellent quantity to titrate the amount of PEEP in ARDS because 1) it is stronger correlated to PEEP than total respiratory compliance or blood gas values are [28]; 2) it is non-invasive and 3) it can be semi-continuously monitored. Since the lung volume is also influenced by the volume of blood in the circulation, lung volume monitoring can be used to detect hypovolemia or hypervolemia.

Besides the lung volume, analysis of an indicator gas wash-out test can provide information on the fraction of the lung volume in which the gas has no contact with pulmonary blood (anatomical dead space or Bohr dead space fraction) and on existing ventilation inhomogeneity. This information can serve to detect the existence of lung illnesses like chronic obstructive pulmonary disease, and to monitor exacerbations and treatment of acute bronchial constrictions.

Although we developed the wash-out techniques with the aim to monitor mechanical ventilation, the multiple breath technique is also useful for fundamental research of gas transport in the lung. Lung diseases like chronic obstructive pulmonary disease, emphysema, fibrosis or lungcancer go with morphological and functional changes of the lung (for instance due to changes of the elasticity of the lung tissue or con-

striction of the airways). For the assessment of these changes and of the impairment of the gas-exchange process several lung-function tests are available. These tests are often aimed at measurement of lung volumes (e.g. the gas-volume in the lung at the end of a normal expiration or the maximum volume of air that can be inspired or expired) and at estimation of the increase of resistance to air-flow, e.g. measurement of the maximum volume of air that can be inspired or expired within one second. Most of the conventional lung-function tests require that the patient performs certain exercises like deep inspiration or expiration. This has several disadvantages: 1) not all patients are capable or willing to perform such exercises (this is especially true for young children and unconscious subjects); 2) the results of the tests depend on the collaboration and motivation of the patient and the skills of the laboratory assistant conducting the test; 3) the tests can not be performed during mechanical ventilation, when it is especially important to have insight into the ventilation process in order to optimize it; 4) the required test maneuvers may induce alterations in the gas transport characteristics which are not representative for the basic functioning of the respiratory system during normal breathing. Furthermore, evidence exists, that lung diseases have a rudimentary phase during which the most peripheral parts of the lungs are involved, but not the larger airways (small airways disease). This phase goes without complaints of the patients. The disorders of the small airways can not be measured by the usual lung function techniques.

Outline of the forthcoming chapters

Chapter 2 describes the development and validation of a device to generate the inspiratory gas-mixture for the wash-out test, that is suitable to be connected to the gas inlet of a Siemens Servo 900 series mechanical ventilator for use in daily clinical practice. This device mixes one out of two indicator gases in the inspiratory gas. When the wash-out starts, the second indicator gas is mixed in the inspiratory gas, so that the oxygen is not diluted, and the wash-in of the second gas can be analysed together with the wash-out of the first gas.

Chapter 3 describes a software package that records and analyses indicator gas wash-out tests. The described software runs on PDP11 computers, but after this manuscript was published a new version was made

that runs on the MS-DOS operating system. During a wash-out test it records the inspiratory and expiratory flow and the gas-fractions of one or more indicator gases, oxygen and carbon dioxide. Afterwards it combines several analysis techniques with the aim to provide a deeper insight into the nature of existing ventilation inhomogeneity than the individual techniques alone can provide. The program provides information concerning the end-expiratory lung-volume, distribution of ventilation and perfusion in the lung, the rôle of diffusion in the ventilation process and the metabolic oxygen uptake and CO_2 release and presents the results of the analysis in the form of tables and graphs.

Chapter 4 analyses the effect of several error sources on the accuracy of multiple breath wash-out tests, using different analysis techniques. The analysed error sources include noise in the flow or gas-fraction signal, misestimation or variation of the delay of the gas-fraction measurement, limitation of the dynamic response of the gas-fraction measuring device, metabolic gas-exchange and solubility of the indicator gas. The analysis was applied on the set-up that has been described in the previous chapters. The critical source of error, the one that has to be dealt with primarily when the system is to be made more accurate, turns out to be the delay of the gas-fraction measurement.

Chapter 5 introduces a new technique to calculate the lung volume and a new index of ventilation inhomogeneity, the *Volumes regression index S*. The accuracy and reproducibility is shown by measurements on healthy subjects and on post-operative, mechanically ventilated patients. In the patients the volumes regression index was correlated with the pre-operatively determined Forced Expiratory Volume in one second (FEV_1) and compared with two conventional ventilation inhomogeneity indices obtained from the same wash-out tests, the Becklake index and the moment ratio index. The volumes regression index correlated better to FEV_1 than the other indices did.

Chapter 6 analyses the shape of the curve that is the basis of the volumes regression index, the *volumes estimations curve*. This shape is determined by the nature of the ventilation inhomogeneity involved. The shape is calculated for a few mathematical models of ventilation inhomogeneity. The influence of lung disease on the volumes estimations curve is determined by examination of the volumes estimation curves of wash-out tests on healthy subjects and on patients suffering from Chronic Obstructive Pulmonary disease e.g. pulmonary emphysema.

Chapter 7 is an epilogue that deals with the opportunities that the described wash-out technique gives to optimize mechanical ventilation, and in which further improvements are suggested to incorporate the technique into an automatical, unattended monitoring device, that interferes as little as possible with the patient care.

Chapter 2

Design and validation of an indicator gas injector for multiple gas wash-out tests in mechanically ventilated patients[1]

P.E.M. Huygen, B.W.A. Feenstra, W.P.J. Holland, C. Ince, H. Stam and H.A. Bruining

Abstract

A device to produce a step-wise indicator gas-fraction variation to initiate a wash-out test in mechanically ventilated patients is described. The device, which can be used in conjunction with the commonly used Siemens-Elema series 900 ventilators, is based on simple, off-the-shelf technology. It features the simultaneous use of two indicator gases (so that the influence of diffusion processes in the gas exchange to the patient can be measured) and maintains a nearly constant inspiratory oxygen fraction during a wash-out procedure. With this indicator-gas-injector, the transition time of the indicator gas-fraction at the beginning of the wash-out proved to be short enough to detect ventilation inhomogeneity by visual inspection of the wash-out curves. End-expiratory lung volume measurements using this device are presented on a test lung with known volume, on healthy volunteers and on critically ill patients.

Introduction

During artificial ventilation, the end-expiratory lung volume EEV can be determined by either closed circuit indicator gas dilution [93] or open-circuit indicator gas wash-out tests. The latter method is advantageous because information about the inhomogeneity of the ventilation can be obtained from variations in the decay rate of the (mean- or end) expiratory indicator gas fraction [95]. Most described implementations of wash-out tests during mechanical ventilation are based on nitrogen clearance. Although this method can be simply implemented [52], it has several disadvantages: it causes large variations in the oxygen fraction, and

1. *Crit Care Med* **18***(1990):754–759*

short transition times of the indicator gas-fractions are hard to achieve [12, 72]. An elegant, but technically difficult approach is to wash in an indicator gas by injection of the gas near the mouth of the patient during inspiration [27, 56]. The disadvantage of this method, however, is that it is difficult to maintain a constant inspiratory indicator gas fraction since a flow-proportional amount of gas must be continuously injected.

In this study, we describe a device with which to perform open-circuit wash-out tests via a commonly used ventilator (Servo 900 series, Siemens-Elema, Solna, Sweden). (The instrument makes wash-in tests possible too. In this study we use the term "wash-out" to include "wash-in" because analysis of the two tests is the same provided that the final inspiratory indicator gas-fraction is subtracted from the (varying) indicator gas-fraction signal during the test). Our device was devised to meet the following specifications: a) the transitions of the indicator gas fractions should be fast enough to facilitate detection of ventilation inhomogeneity by visual inspection of the wash-out curves (breath-by-breath semi-logarithmic plot of the mean- or end expiratory indicator gas fraction); b) the inspiratory oxygen fraction must remain constant so that the metabolic gas curves can be analyzed during the measurement, and oxygen variations, harmful to the patient (and influencing EEV), are avoided; c) the method must be easy to perform at the bedside in the intensive care ward and should not interfere with patient care and treatment; d) the EEV of the patient must not be influenced by the measurement (e.g. by end-expiratory pressure variation, tidal volume variation or temporary disconnection of the ventilator from the patient); e) the device should be able to perform a simultaneous wash-out process of two gases with different diffusion coefficients [95, 23, 17] and, f) it must be possible to perform the measurements under computer control.

Design of the instrument

To meet the above specifications, we developed a simple indicator gas injector, able to inject small amounts (1-2% by volume) of indicator gases into the oxygen/air mixture fed into a Siemens series 900 ventilator. The injector provides the ventilator of a constant flow of suitable gas-mixture that flushes the bellows of the ventilator during expirations (figure 2.1). Although this flushing process minimizes the transition time of the indicator gas fraction at the beginning of the wash-out, a small effect caused by the venting of the tubing between the ventilator and the patient remains during the first inspirations; this effect is small enough to allow for a visual diagnosis of the wash-out curve (as is shown in the results section). Using this injector, single or dual-gas wash-out/wash-in tests

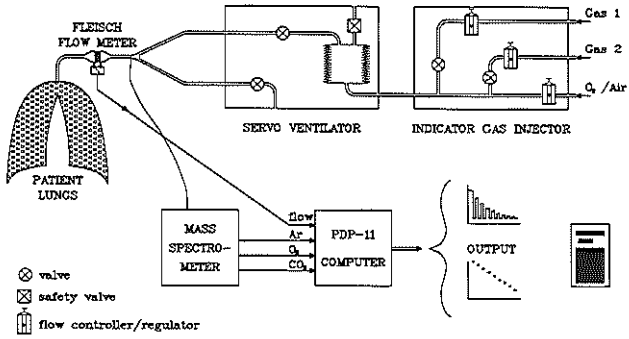

FIGURE 2.1: Measurement of EEV using the indicator gas injector. The indicator gas injector produces a constant gas flow which flushes the bellows of the ventilator during expirations. To generate variations of the indicator gas-fraction a built-in microprocessor controls valves to start or stop abruptly the injection of indicator gases in the oxygen/air mixture. The indicator gas-fraction and the respiratory flow are measured between the patient and the ventilator. Using these data EEV is calculated by a PDP-11 computer using the algorithm described in the appendix.

can be performed. In the latter case, the wash-in of one gas is combined with the wash-out of the other gas (dual-gas mode). An additional advantage of this method is, that the inspiratory oxygen fraction is not affected by the gas injection.

The instrument supplies a constant flow of driving gas which enters the ventilator through the low pressure input, by-passing a primary pressure regulator. The main flow rate is maintained sufficiently high (up to 60 liters/min) to keep the pressure in the bellows at a prescribed safe working level. During expiration, excessive gas escapes by the safety valve of the ventilator, thereby flushing the bellows. The indicator gas injection starts or stops at the end of an inspiration. During the subsequent expiration the new gas-mixture replaces the old mixture in the bellows. Care should be taken in the choice of bellows, however, since some types provide inadequate flushing. We found the bellows introduced in 1988 by Siemens-Elema (with the same part number as the bellows manufactured previously) to be satisfactory in this respect.

In figures 2.2 and 2.3, the block diagram of the injector and the timing diagram of its control unit, respectively, are shown. The device provides a steady flow of gas obtained from a conventional oxygen/air mixer (961, Siemens-Elema, type not shown in figure 2.2). This flow is kept constant (independent of downstream pressure variations) by means of a flow controller/indicator (series 8900; 0-60 l/min, Brooks Veenendaal, the Netherlands). The flow controller requires a constant up-

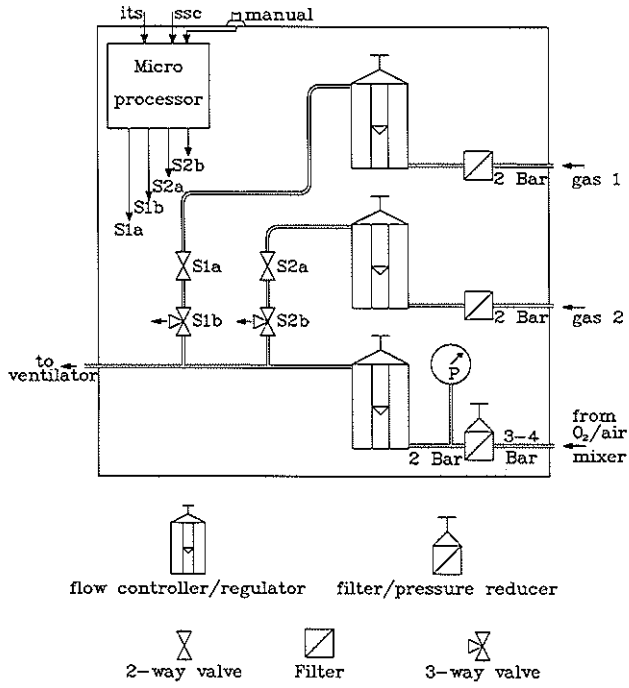

FIGURE 2.2: Block diagram of the indicator gas injector. The instrument supplies the ventilator with a constant flow of oxygen/air gas-mixture to which a constant flow of one of two indicator gases is added. The flows are kept constant by flow controller-regulators. The start of injection of an indicator gas, accomplished by the opening of valve S_{1a} or S_{2a}, is preceded by a brief venting of the output of the flow controller to air (by valves S_{1b} resp. S_{2b}) in order to release excessive pressure. The timing of the opening and closure of the valves is shown in figure 2.3. The micro-processor reads the inspiration timing signal (its) from the ventilator and the start-stop command signal (ssc) (or the manual switch), and controls the injection valves S_{1a}, S_{1b}, S_{2a} and S_{2b}.

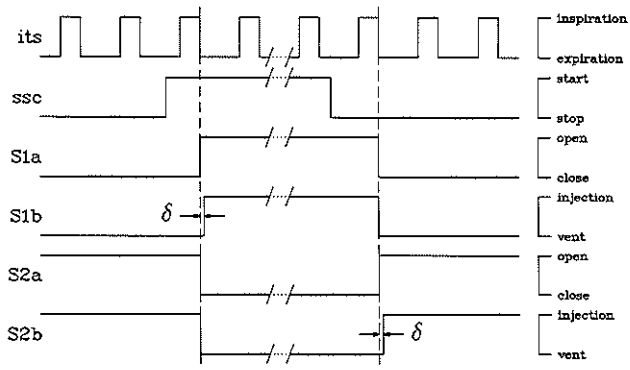

FIGURE 2.3: Timing diagram. Wash-in of gas 1 is initiated by (manual or computer-controlled) activation of the start-stop command line (ssc). At the end of the next inspiration (signalled by the inspiration timing signal (its), which is obtained from the ventilator) S_{1a} opens. During a time interval δ (0.2s) gas 1 vents to air (via S_{1b}) to stabilize the pressure. After this it is injected into the gas-mixture entering the ventilator. De-activation of ssc initiates termination of the injection. The (optional) second indicator gas, which washes in during the wash-out of gas 1, is controlled by S_{2a} and S_{2b}.

stream pressure which is accomplished by means of a pressure controller (B360 with filter, Watts, Redruth, UK)). The indicator gases are supplied from high pressure containers through double-stage pressure reduction valves (not shown), thus maintaining a constant, flow-independent pressure. Double-stage pressure reducers were chosen instead of single stage since the latter cause slow pressure and flow variations of up to 20%. The indicator-gas flows are kept constant by means of flow controller/indicators (0-1 l/min, Brooks) and can be injected into the mainstream through solenoid two-way- (B2 DB1026D, Honeywell Skinner New Britain, Conn.) and three-way (Minimatic ETO-3, Clippard, Cincinnati, OH) valves. The latter valves are needed to release excessive pressure at the start of the injection. Omitting them causes a bolus of pure indicator gas to enter the ventilator at the beginning of the wash-in process. The valves are controlled by an 8-bit micro-processor (8080, Intel, Santa Clara, CA). The operator selects either single or dual-gas mode operation by a switch. The operation of the device is explained by the timing diagram (figure 2.3). Our prototype, which has been set up spaciously, measures 46 × 36 × 26 cm, and can be placed underneath the ventilator.

Tests

To test the instrument, we performed single gas (argon) wash-out tests on: a) a dummy lung (demonstration thorax, Dräger, Lübeck, FRG) with a volume of 3.05±0.01 l (volume determined using a dilution technique); b) seven healthy volunteers who were artificially ventilated via a mouthpiece (with their noses closed by a nose-clip) and also underwent a standard helium dilution EEV measurement and c) 10 artificially ventilated patients. The set-up for the measurements is shown in figure 2.1. A mass spectrometer (Centronics, MGA 200, CASE, Biggin Hill, UK) measures the indicator gas-fractions as well as the fractions of the metabolic gases in the tube between the patient and the Y-shaped connector splitting the inspiratory gas from and the expiratory gas to the ventilator. The mass spectrometer obtains its sample gas at a rate of 100 ml/min via a 3 m capillary (exercise capillary, CASE), causing a delay of 330 ms, which is corrected for during the signal processing. The respiratory flow was measured with a flow transducer (Fleisch 2, 0 to 3 l/sec, SensorMedics, Bilthoven, The Netherlands) connected to a pressure transducer (MP 45-14-871 (0-2 mBar), Validyne, Northridge, CA). A computer (PDP-11, DEC, Maynard, MA) sampled the outputs of the mass spectrometer and the flow transducer with a frequency of 100 Hz and stored the obtained samples on disk for off-line analysis. From the obtained data the EEV was calculated using an algorithm based on the method of Zwart [95] and modified to account for the dead spaces in the tubing between the patient and the ventilator (see appendix). The algorithm was applied to a washout interval which lasted until 90% of the indicator gas was washed out from the lung.

With the described set-up, we performed eight wash-in and eight wash-out experiments on the dummy lung, using a tidal volume of 1 liter and a ventilation rate of 10 l/min in the IPPV mode. The volunteers were also ventilated in IPPV mode, with ventilation rate and tidal volume set in a manner comfortable to the subjects (the range was between 8 and 13 l/min with frequencies between 9 and 12 breaths/minute). For each subject, 4 wash-in followed by wash-out tests were performed within one hour. The subjects were instructed to allow themselves to be ventilated as passively as possible. The inspiratory tidal volume is constant during IPPV; thus, variations of the expired tidal volume are equal to variations of the effective end-expiratory lung volume (EEV). To avoid momentary physiologic EEV variations, the data from tests in which the standard deviation of the expired tidal volumes was larger than 100 ml were discarded.

Measurements were also done on 12 intensive care patients, each

ventilated in IPPV mode. For each patient we performed (within one hour) four measurements, each one consisting of a wash-in followed by a wash-out test, and again we discarded the data from tests in which the standard deviation of the expiratory tidal volumes was larger than 100 ml.

Results

Wash-out curve

To illustrate that the device fulfills the design consideration that the transition of the indicator gas-fractions is fast enough to facilitate detection of ventilation inhomogeneity by visual inspection of the wash-out curve, figure 2.4 shows examples of the wash-out curves obtained from a ventilated post-operative patient without pulmonary problems and from a patient suffering from Chronic Obstructive Pulmonary Disease (COPD). The decay of the mean expiratory indicator gas-fraction of the patient without pulmonary problems has, after the first 4 expirations (needed to flush the ventilator tubes), a mono-exponential decay, indicating that the lungs are homogeneously ventilated. The decay curves produced with the dummy lung (not shown) indicated a similar mono-exponential decay. The decay of the indicator gas-fraction from the other patient is clearly not mono-exponential.

TABLE 2.1: Comparison of EEV, obtained from open-circuit argon wash-out tests (EEV_o) with that obtained from a closed helium dilution measurement (EEV_c) on healthy volunteers.

Subj.	sex	age yr.	length m	EEV_c l	EEV_o l	σ l	n	Diff. %
A	m	51	1.77	2.71	2.68	0.13	8	−2.2
B	m	42	1.72	3.37	3.14	0.32	8	−6.8
C	m	35	1.92	4.46	4.69	0.16	8	+5.2
D	f	30	1.75	2.61	2.33	0.08	8	−10.7
E	f	31	1.72	2.62	2.64	0.08	3	+0.8

(σ = standard deviation of EEV_o, n = number of open-circuit measurements performed and Diff. = $100\times(EEV_o\text{-}EEV_c)/EEV_c$)

EEV measurements

The mean and standard deviation of the EEV obtained from the 16 dummy lung measurements were 3.04±0.01 liters (to be compared to

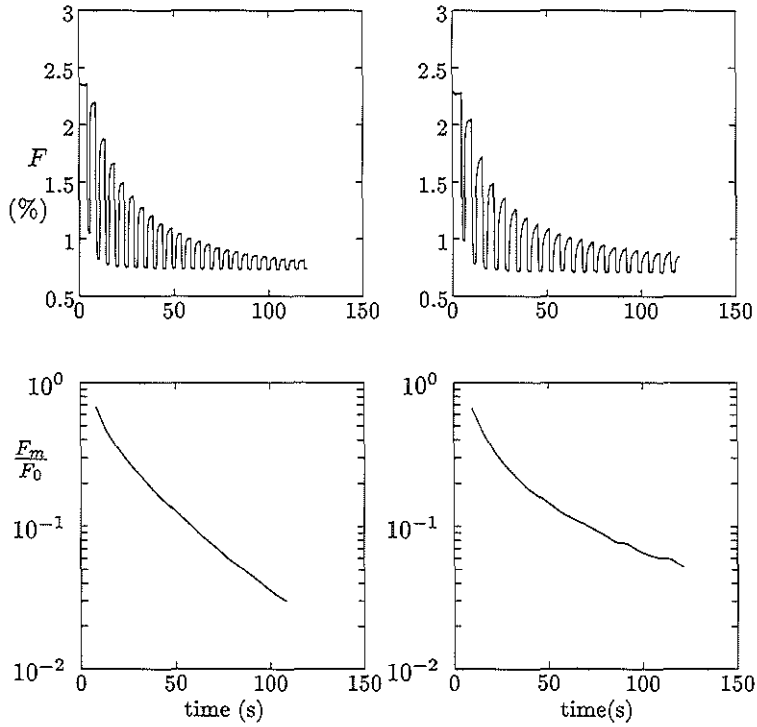

FIGURE 2.4: Comparison of the indicator gas-fraction curves (upper graphs) and wash-out curves (semilogarithmic graph of the mean expiratory indicator gas-fraction as a function of time; lower graphs) from measurements on a patient without pulmonary problems (left graphs) and a patient suffering from chronic obstructive pulmonary disease (right graphs) shows, after a transient period of 3-4 expirations, a mono-exponential decay in the patient without lung-problems, whereas the decay in the COPD patient is not mono-exponential. F_m, mean expiratory fraction; F_0, original indicator fraction.

TABLE 2.2: Results of EEV measurements in ICU patients

Subj.	sex	age yr.	clinical diagnosis	EEV l	σ l	n
1	m	14	Sepsis	0.89	0.03	8
2	m	19	Pulmonary contusion	1.35	0.03	8
3	m	64	Aortic Prosthesis (+COPD)	3.11	0.08	8
4	f	60	Cystectomy	0.73	0.02	8
5	m	59	Esophageal resection	1.40	0.08	8
6	m	67	Post thoracotomy	2.00	0.05	8
7	m	71	Respiratory insufficiency	1.18	0.05	8
8	m	81	Ruptured aneurysm	1.35	0.04	6
9	m	34	Multitrauma	2.32	0.07	8
10	f	74	Multiple rib fractures.	1.51	0.08	7

the actual volume of 3.05±0.01 liters). The results of the measurements on the healthy volunteers are listed in table 2.1. Two of the seven volunteers were unable to keep the standard deviation of the tidal volumes below 100 ml during any measurement, and were thus discarded from the trial. In the other five subjects the observed intra-individual standard deviations are within 10% (mean 5%). The mean of the ranges of the individual subjects was from 6% below to 8% above the mean value. In subject B, the largest range was measured, from 11% below to 18% above the mean value. The mean and standard deviations of the EEV differences, calculated from the wash-out tests and from the helium dilution tests equal -2.6±6.3%. The differences are not significant (by paired t-test). The results of the measurements on the patients are listed in table 2.2. The reproducibility was better than 6% (mean 3.5%).

Discussion

In this study, a device is described which can generate step-wise inspiratory indicator gas-fraction variations with which wash-out tests can be performed on ventilated patients. The device meets the specifications noted in the introduction. The wash-out curves of figure 2.4 show that the change of the indicator gas-fractions at the start of the wash-out is abrupt enough to allow interpretation of the wash-out curve by visual inspection. For a numerical assessment of the wash-out curve with a moment analysis the method of Felton et al. [35] can be used. The test measurements show that the amount of indicator gas which is inspired after the beginning of the wash-out process can be corrected for

to obtain accurate EEV measurements. The volume of the dummy lung is measured with a standard deviation of 0.3%. In the healthy volunteers, the differences between the EEV obtained by the wash-out and by the dilution method are not significant, and the observed intra-individual variations (mean range from -6% to +8% of the mean) are less than those found by Hruby and Butler [47], who found an average range in healthy subjects from 23% below to 27% above the mean. Since a generally accepted method for EEV determination does not yet exist for artificially ventilated patients, we could not compare our method with another. However, the validation on healthy volunteers, the agreement of the bed-side EEV measurements with the pathology of the patients and the fact that reproducible results were obtained with our technique provide confidence that the described method gives reliable bed-side EEV measurements.

Because the fraction of injected indicator gas is relatively small (<2%), the inspiratory oxygen fraction remains essentially constant during the tests. In dual-gas mode, where the injection of indicator gas 1 is alternated with the injection of indicator gas 2, inspiratory oxygen fraction variations can be completely avoided. The instrument does not interfere with patient care or treatment since it is not directly connected to the patient and has no influence on the control of the ventilation. When installed together with the ventilator on the same trolley, it occupies no extra floor space and does not need temporary disconnection of the ventilator from the pressurized driving gas mixture. The instrument is easy to operate and can be computer controlled.

With the described instrument, wash-out tests are performed routinely during intermittent positive pressure ventilation as well as positive end expiratory pressure ventilation. We are currently studying how to adapt the device to accommodate intermittent mandatory ventilation [8] as well. The instrument is used regularly in our intensive care ward. With the obtained signals, ventilation inhomogeneity, end-expiratory lung volume, Bohr dead space and metabolic rate are computed for bed-side assessment of the gas exchange status of ventilated patients. This is explained in the following chapters.

Compared to other described devices which perform wash-out tests during mechanical ventilation [93, 52, 12, 72, 27, 56] this apparatus is unique in its capacity to provide a dual gas mode. Furthermore it combines reliable, off-the-shelf technology with a reasonable short transition time of the indicator gas fractions and absence of oxygen fraction variations.

Appendix: Algorithm for EEV calculation

The algorithm is based on the relation between the dilution of the indicator gas in the lung and the net amount of indicator gas washed out [95], and can be applied to each wash-out breath cycle. It is assumed that the baseline level of the inspiratory indicator gas-fraction is subtracted from the (time-varying) indicator gas-fraction signal so that calculations of wash-in processes progress in the same way as wash-out processes. The following symbols are used:

EEV_j	EEV, estimated at the end of the j^{th} breath after the beginning of wash-out.
V_{TIj}	Inspired tidal volume of breath cycle j.
V_{TEj}	Expired tidal volume of breath cycle j.
F_0	Gas-fraction before the start of the wash-out process.
F_{Aj}	Mean alveolar indicator gas-fraction of breath cycle j.
F_{EEj}	End-expiratory indicator gas-fraction of breath cycle j.
F_{MEj}	Flow weighted mean expired indicator gas-fraction of breath cycle j.
F_{MIj}	Flow weighted mean inspired indicator gas-fraction of breath cycle j (caused by the dead spaces in the tubing of the ventilator).

At the end of each wash-out expiration k the EEV equals the quotient of the amount of net expired indicator gas and the alveolar indicator gas dilution caused by this removal process.

$$\text{EEV}_k = \frac{\sum_{j=1}^{k} V_{TEj} F_{MEj}}{F_0 - F_{Ak}} \tag{2.1}$$

Since the alveolar indicator gas-fraction is not measurable, it is approximated by the end-expiratory gas-fraction. At the end of the wash-out process both values have become small relative to F_0, and the influence of the difference of F_{EEk} to F_{Ak} on the EEV estimation becomes negligible:

$$\text{EEV}_k = \frac{\sum_{j=1}^{k} V_{TEj} F_{MEj}}{F_0 - F_{EEk}} \tag{2.2}$$

In order to account for the amount of indicator gas still present in the tubing at the beginning of the wash-out process, F_{MIj} is multiplied by the quotient of V_{TEj} and V_{TIj} (in order to account for the calibration difference between inspiratory and expiratory flow, assuming that the actual expired tidal volume is equal to the actual inspired tidal volume),

and then subtracted from the mean expiratory fraction:

$$\mathrm{EEV}_k = \frac{\sum_{j=1}^{k} V_{TEj}(F_{MEj} - F_{MIj} \times \frac{V_{TEj}}{V_{TIj}})}{F_0 - F_{EEk}} \tag{2.3}$$

Chapter 3

A Pulmonary Data Processing System for assessment of gas exchange properties by multiple gas wash-out.[1]

P.E.M. Huygen, B.W.A.Feenstra, E. Hoorn, J.R.C. Jansen and A. Zwart

Abstract

A data acquisition and processing system for the analysis of inert gas wash-out tests is described. The described system is in clinical use on spontaneous breathing patients as well as on mechanically ventilated Intensive Care patients. It combines several analysis techniques with an aim to provide a deeper insight into the nature of existing ventilation inhomogeneity than the individual techniques alone can provide. The signals measured are the respiratory flow, the fractions of one or two indicator gases washing out and the fractions of the metabolic gases oxygen and carbon dioxide. Analysis of these signals provides information concerning the end-expiratory lung-volume, distribution of ventilation and perfusion in the lung, the rôle of diffusion in the ventilation process and the metabolic oxygen uptake and CO_2 release. This article describes the algorithms used and the results that are presented.

Introduction

Lung diseases like chronic obstructive pulmonary disease, emphysema, fibrosis or lung cancer go with morphological and functional changes of the lung (for instance due to changes of the elasticity of the lung tissue or constriction of the airways). For the assessment of these changes and of the impairment of the gas-exchange process several lung-function tests are available. These tests are often aimed at measurement of lung volumes (e.g. the gas-volume in the lung at the end of a normal expiration (Functional Residual Capacity, FRC, or the maximum volume of air that

1. *Comp Meth Prog Biomed* **36**(1991):223–235

can be inspired or expired) and at estimation of the increase of resistance to air-flow, e.g. measurement of the maximum volume of air that can be inspired or expired within one second. Most of the conventional lung-function tests require that the patient performs certain exercises like deep inspiration or expiration. This has several disadvantages: 1) not all patients are capable or willing to perform such exercises (This is especially true for young children); 2) the results of the tests depend on the collaboration and motivation of the patient and the skills of the laboratory assistant conducting the test; 3) the tests can not be performed during mechanical ventilation, when it is especially important to have insight into the ventilation process in order to optimize it; 4) the tests provide insight into the abilities of the lung, but not into its performance during normal breathing.

The multiple-breath indicator gas wash-out test can be performed without active collaboration of the patient, and can reveal detailed information about the ventilation process. In such a test the subject inspires from a gas-mixture in which the fractions of one or more poorly soluble, inert indicator gases change step-wise from a constant original value F_1 to a new (constant) value F_2. During the following breath-cycles, while the indicator gas-fractions in the lung are altering, the inspiratory and expiratory flow as well as the gas-fractions of the inspiratory and expiratory gas-mixture are measured continuously. Usually wash-out tests are employed to measure the end-expiratory volume of the lung or to obtain a crude index of the inhomogeneity of the distribution of the inspired gas into the lung [39, 36]. In some applications the decay of the indicator gas-fraction is decomposed as the sum of a discrete number [38, 46, 87] or a continuous distribution [41, 59, 62, 69] of mono-exponential curves representing regions with different ventilation-to-volume ratios. The software package described in this paper (PDPS, Pulmonary Data Processing System) however is aimed at providing a deeper insight into the ventilation process itself, the rôle that diffusion in the gas-phase plays in ventilation [32, 23] and distribution of the ventilation/perfusion ratio. Therefore it features multiple-gas wash-out (combining the wash-out of the gases helium and SF_6, of which the diffusion coefficients differ a factor seven), and measurement of the fractions of the metabolic gases oxygen and carbon dioxide.

Using the obtained signals, existing ventilation inhomogeneity can be characterized as the result of either (synchronous or asynchronous) emptying of parallel units with different specific ventilation ratios or diffusion-dependent inhomogeneity in the end of the bronchial tree (the acini) [32, 95, 65, 23]. Comparison of the fractions of the inert gases washing out with the fractions of the metabolic gases oxygen and car-

bon dioxide can reveal whether the inhomogeneity in the ventilation is compensated by the alveolar perfusion or not. Finally the metabolic rate can be calculated.

The advantage of PDPS is not the application of novel techniques, but the utilization of the possibility that the mass spectrometer provides to measure several gases in the inspired and expired air simultaneously. Multiple-breath wash-out and single-breath expirograms and dead space analysis have been used by Fowler [37], and extended by Tsunoda [88] and Lewis [62], whereas the gas-exchange ratio analysis has been exploited by Serra [84] and Rahn [79]. Due to our combinatory approach typical ventilation patterns, characteristic for lung diseases like obstructive pulmonary disease, emphysema or cystic fibrosis can be recognized. These individual methods alone are insufficient to make this discrimination.

This paper describes the operation of the program, the algorithms used in the analysis of the measured signals and the form in which the results are presented.

Computational methods and theory

Measurement set-up

We performed wash-out tests with the configuration shown in figure 3.1. In order to record respiratory flow and gas fractions the subject breathes via a mouth piece through a tubing system containing 1) a Fleisch nr. 2 flow meter (SensorMedics, Bilthoven, the Netherlands) measuring inspiratory and expiratory flow; 2) the tip of a sample capillary connected to an Airspec MGA3000 quadrupole mass spectrometer (Chest Scientific Instruments LTD, Biggin Hill, UK); 3) a two-way valve separating inspiratory and expiratory gas flow and 4) a (manually controlled) three-way valve to provide inspiration gas either from room air or from a Douglas-bag containing a mixture of 21% oxygen and small fractions (±2%) of helium and SF_6 in nitrogen. The mass spectrometer samples the oxygen, carbon dioxide and inert indicator gas fractions in the inspired and expired gas mixture with a sample frequency of 50 Hz. The outputs of the flow meter and the mass spectrometer are connected to the A/D converter of a PDP-11 computer. First the subject breathes air. In order to start a wash-in test the laboratory assistant commands the computer to start data sampling (with a frequency of 50 Hz) and to store the samples on disk. One breath cycle later the laboratory assistant connects during expiration the inspiratory tube to the Douglas-bag using the switch. During the successive breath-cycles the difference between the inspired

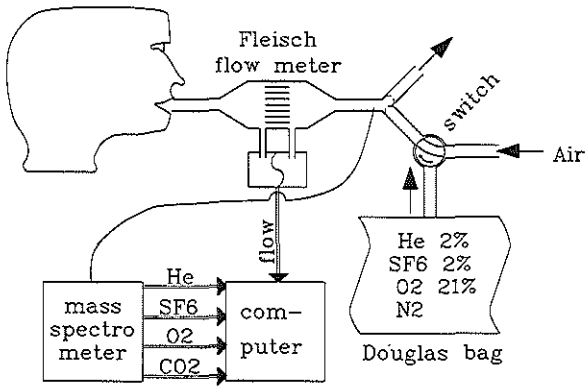

FIGURE 3.1: Measurement set-up. Tubing system containing a Fleisch flow meter, a capillary to an Airspec MGA3000 mass spectrometer, one-way valves and a gas switch selecting gas 1 (room air) or gas 2 (from Douglas bag). The outputs of the flow meter and the mass spectrometer are connected to ADC channels of the computer.

and expired indicator gas fraction decreases. When the difference between these gas fractions has become negligible, a wash-out test can be initialized by switching the inspiratory gas back to air. The duration of the wash-out is dependent on the patient. For lung-healthy subjects a duration of 2 minutes is sufficient, but for patients with severe COPD or emphysema much more time is needed (up to 4 minutes) to wash more than 90% of the indicator gas out of the lung. Data sampling stops automatically after a pre-set maximum time interval has elapsed or by a single-key command issued by the laboratory assistant.

Pattern recognition and analysis of the data

After recording the wash-out test PDPS performs an off-line analysis of the obtained signals. In this analysis it discerns expirations and inspirations, finds the inspiratory indicator gas-fraction before and after the beginning of the wash-out, searches for the first wash-out inspiration and calculates characterizing parameters for each expiration. The characterizing parameters are for expiration number i: the time it starts (t_{bi}), the time it ends (t_{ei}), tidal volume (V_{Ti}), and for each of the metabolic and the inert indicator gases the end expiratory fraction F_{Ei} and the flow weighted mean expiratory fraction F_{Mi}. Both F_{Ei} and F_{Mi} are calculated relative to F_I, the inspiratory fraction of the gas in question. For example the flow weighted mean expiratory fraction is conventionally

defined as $\frac{1}{V_{T,i}} \int_{t_{b,i}}^{t_{e,i}} F(t)\dot{V}(t)\,dt$, but we have chosen to define it as

$$F_{M,i} = \frac{1}{V_{T,i}} \int_{t_{b,i}}^{t_{e,i}} (F(t) - F_{I,i})\dot{V}(t)\,dt \tag{3.1}$$

($F(t)$ = gas fraction and $\dot{V}(t)$= flow). In this way the algorithms and procedures to analyse a wash-out test are identical to those to handle a wash-in process (in which the inspiratory indicator gas-fraction rises step-wise). The only difference between wash-in and wash-out is a change in sign. For convenience we further speak about wash-out although we actually mean washout/wash-in. Furthermore we will assume in the following of this article that $F_I = 0$.

Presentation of results

Expirogram

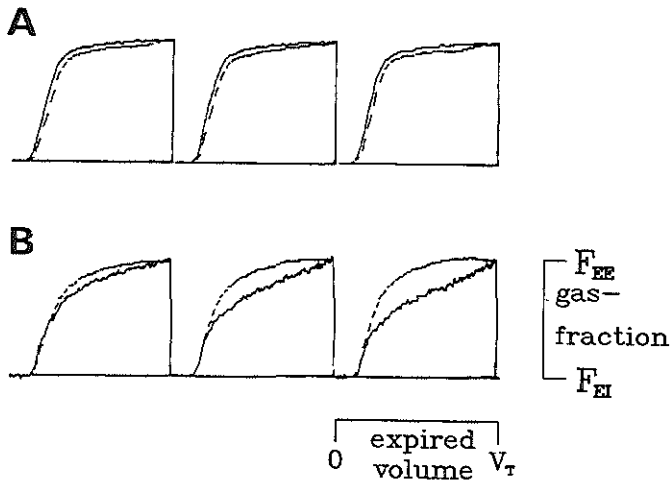

FIGURE 3.2: The first 3 expirograms of CO_2 (dotted line) and He of a subject with normal lungs (A) and of a subject with sequentially emptying, unequally ventilated parts in his lungs (B). The expirogram is a single-breath graph of the expired fraction of a gas, scaled between the inspiratory and the end-expiratory indicator gas-fraction, as a function of expired volume, in this figure scaled between zero and the tidal volume. The enhanced dilution of the early emptying parts of subject B shows up as an increasing difference between the courses of the indicator gas-fraction and the CO_2 gas fraction.

An expirogram is a graph showing the fractions of one or more gases in the expiratory gas mixture against expired volume or against

time, during one expiration. In order to enable comparison of the expirograms of the two indicator gases (helium and SF_6) and carbon dioxide and of subsequent expirograms of the indicator gases during the wash-out process the gas-fractions are scaled between the inspiratory and the end-expiratory value of the same breath. In this way the decreasing fraction of the indicator gas caused by the wash-out is only visible as an apparent increasing noise level. Figure 3.2 shows an example of first three expirograms of helium and carbon dioxide after the beginning of the wash-out of a subject with normal lungs (A) and of a subject with unequally ventilated, asynchronous emptying parts in the lungs (B). In the healthy subject the gas-fractions rise steeply to an almost level "alveolar plateau" representing the gas from alveolar origin. The shape of the expirogram does not change in the course of the wash-out. In the recording B there is not a sharp transition form the rising part of the curve to the alveolar plateau, while in the indicator gases the alveolar "plateau" is very steep and steepens in the course of the wash-out, due to the fact that the regions with the highest ventilation rate empty early in the expiration and have a faster indicator gas dilution than the regions that empty later in the expiration. This phenomenon is easy to recognize by comparison of subsequent expirograms and comparison of the carbon dioxide and the helium expirogram of the same expiration.

Analysis of the shape of the expirogram

In order to obtain a single number quantification of the shape of the expirogram the fractional area of the frame in which it is drawn that is not occupied by the expirogram itself is calculated (shaded area in figure 3.3): If the x-axis is scaled between 0 and V_T, and the y-axis scaled between the end-inspiratory and the end-expiratory fraction, the area in the frame itself equals to $F_E \times V_T$ (F_I being equal to zero). The (unshaded) area under the expirogram equals to $\int_{t_b}^{t_e} F(t)\dot{V}(t)\,dt = F_M \times V_T$, where F_M represents the flow-weighted mean expiratory gas-fraction. Now we choose the single-number quantification of the expirogram to be the fraction D_b of the area of the frame that is not covered by the expirogram:

$$B = \frac{\textit{shaded area}}{\textit{total area in frame}} \tag{3.2}$$

$$= \frac{F_E - F_M}{F_E} \tag{3.3}$$

This number is in fact equal to the Bohr "dead space" fraction [45] as defined for the steady-state CO_2 wash-out. Bohr "dead space" is an

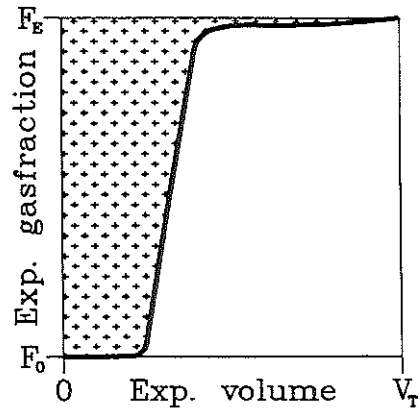

FIGURE 3.3: Shape analysis of the expirogram. The expirogram is drawn in a normalized frame (*abscissa*: expired volume scaled between 0 and tidal volume; *ordinate*: expiratory gas fraction scaled between inspiratory fraction and end-expiratory fraction). The fraction B of the area in this frame that is not covered by the expirogram (the quotient of the shaded area and the total area in the frame) serves as a single-number characteristic of the shape of the expirogram. In fact B is equal to the Bohr "dead space fraction".

approximation of the pulmonary dead space assuming 1) that a part V_D of the expired tidal volume (V_T) comes from the dead spaces containing inspiratory gas, and the rest comes from the alveolar spaces where the inspiratory gas is mixed with the gas present in the lung before the beginning of the inspiration, and 2) that the end-expiratory gas-mixture is representative for the mixture in the alveolar spaces. Then the amount of each of the gases expired during a single expiration equals:

$$F_M V_T = F_I V_D + F_E(V_T - V_D) \tag{3.4}$$

where F_M stands for mean expired gas-fraction and F_E for end-expiratory fraction. Hence the Bohr "dead space" fraction equals to:

$$\frac{V_D}{V_T} = \frac{F_E - F_M}{F_E} \tag{3.5}$$

$$= B \tag{3.6}$$

(F_I being equal to zero). The value of the Bohr "dead space" as an estimation of dead space, however, is questionable because the assumption that the end-expiratory gas fraction equals the mean alveolar fraction is generally not true. A systematic change of the breath-by-breath determined indicator gas Bohr "dead space" value in the course of the

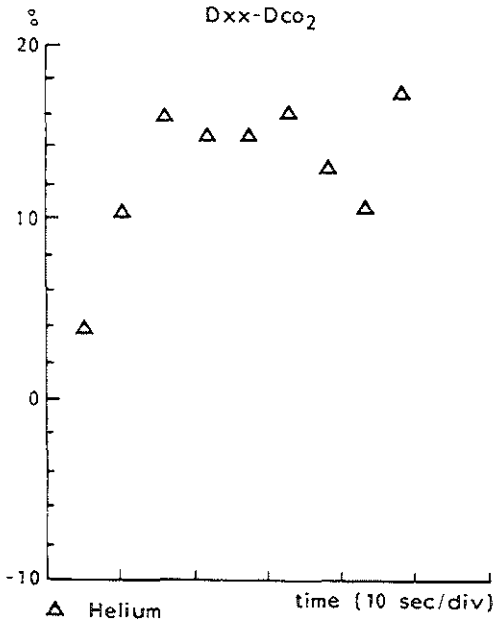

FIGURE 3.4: Breath-by breath values of the differences of the Bohr "dead space fraction" for He and the Bohr "dead space fraction" for CO_2. The inhomogeneity causes the "dead space" to rise in the course of the wash-out.

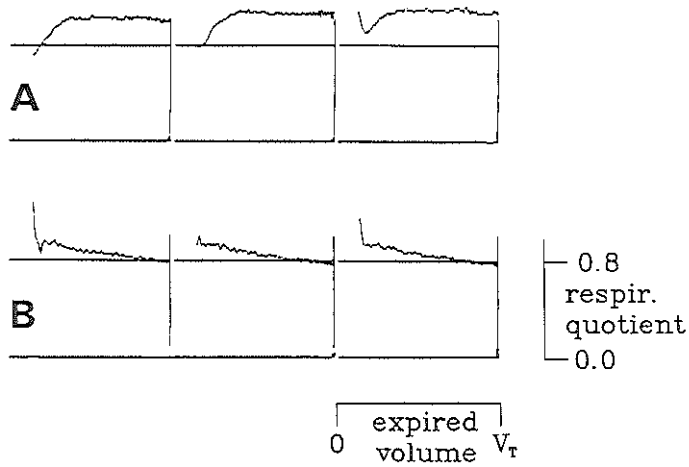

FIGURE 3.5: Gas exchange ratio graphs (ratio of $\Delta F_{CO_2}/\Delta F_{O_2}$) of the same expirograms as in figure 3.2. The decreasing gas-exchange ratios in B show that the ventilation inhomogeneity is not compensated by the perfusion.

wash-out is an indication of the existence of ventilation inhomogeneity due to sequential emptying of parallel compartments in the lung with different ventilation ratio. In order to show these systematic variations PDPS is able to produce graphs of the subsequent "dead spaces" for the carbon dioxide as well as for the indicator gases as a function of time. In order to reduce the influence of breath-by-breath variations of tidal volume (causing variations of the location of the diffusion front) PDPS plots a graph of the breath-by-breath differences between the Bohr "dead space" of the indicator gas and the Bohr "dead space" of carbon dioxide. Figure 3.4 shows such a graph for the same wash-out test as used for figure 3.2. This example shows clearly how in the course of the wash-out process, the Bohr "dead spaces" of the indicator gas increase relative to the steady-state "dead spaces" of carbon dioxide, reflecting the changes of the expirograms.

Gas exchange ratio and metabolic rate

The gas exchange ratio R is the quotient of the volume of carbon dioxide released into, and oxygen taken up per volume unit of expired gas. The program plots graphs of the gas exchange ratio of the expired gas as a function of expired volume. Variations in gas exchange ratio within one breath are caused by regional variations of the ventilation/perfusion ratio in the lung. In areas where ventilation is high compared to perfu-

sion much carbon dioxide is released compared to the amount of oxygen taken up. Figure 3.5 is an example of the breath-by-breath gas-exchange ratio plots. These plots are drawn from the same breath-cycles as in figure 3.2. The course of the gas exchange ratios in part (B) shows that the ventilation inhomogeneity shown by the expirograms is not compensated by the perfusion, but that the highly ventilated parts emptying early in the expiration have a higher ventilation/perfusion ratio than the parts emptying later in the expiration.

End Expiratory Volume of the lung.

The end expiratory volume EEV at the end of the last expiration before wash-out starts can be calculated using the well-known mass balance equation [34] stating that the partial volume in the lung occupied by the indicator gas before the wash-out, equals the sum of the partial volume of the indicator gas at the end of the n^{th} wash-out expiration and the net partial volume washed out during the previous n wash-out breath-cycles:

$$F_{A0} \times \text{EEV} = F_{An} \times \text{EEV} + \sum_{i=1}^{n} F_{Mi} V_{Ti} \tag{3.7}$$

$$\text{EEV} = \frac{\sum_{i=1}^{n} F_{Mi} V_{Ti}}{F_{A0} - F_{An}} \tag{3.8}$$

F_{A0} and F_{An} are the alveolar indicator gas fractions at respectively the end of the last expiration before wash-out and at the end of the n^{th} wash-out expiration. Generally $F_{A0} = F_1$, the inspiratory indicator gas-fraction before the beginning of the wash-out. Since there is no way to measure F_{An} it is approximated by the end expiratory fraction F_{En}. Thus the approximation of the EEV, calculated using the first n breath-cycles since the beginning of the wash-out is equal to:

$$\text{EEV}_n^* = \frac{\sum_{i=1}^{n} F_{Mi} V_{Ti}}{F_{E0} - F_{En}} \tag{3.9}$$

This approximation is not valid for the general case. At the end of the wash-out, when nearly all the indicator gas has disappeared, $F_{An} \approx 0$ and $F_{En} \approx 0$, and equation 3.9 provides a good estimation of the EEV. If e.g. the wash-out is continued until 98% of the indicator gas has been washed out, and at that moment $F_{An} = 2F_{En}$, then the difference between EEV_n^* and the actual EEV equals 2%. The accuracy can be improved by extrapolation of the curve obtained by plotting the breath-by-breath EEV_n^* estimations as a function of F_{En} [51].

We use the deviation of EEV_n^* and the actual EEV (obtained by extrapolation or a long prolongation of the wash-out) to reconstruct

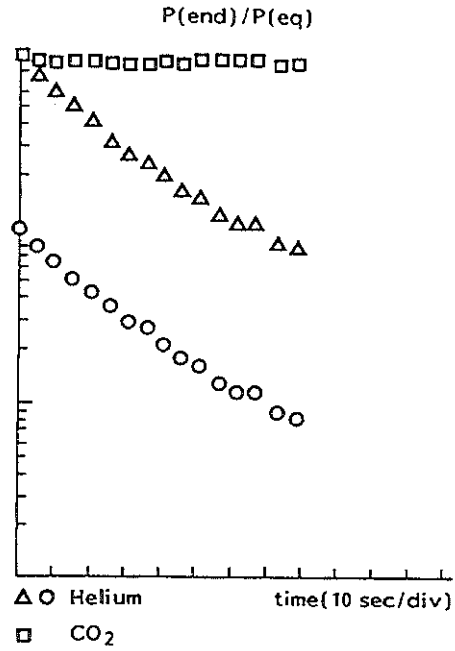

FIGURE 3.6: Wash-out graph of He and CO_2, showing the end-expiratory fraction of the indicator gas and CO_2 as a function of time. The quotient of the He and CO_2 values is displayed a decade lower (using circle symbols). In this way the effect of variations in tidal volume on the wash-out curve can be partly corrected.

the deviation between F'_{An} and F_{En} for lower values of n, where this deviation has a large influence on EEV*. The quotient of EEV^*_n and the true EEV is:

$$\frac{\text{EEV}^*_n}{\text{EEV}} = \frac{F_1 - F_{An}}{F_1 - F_{En}} \tag{3.10}$$

So deviations from unity of

$$\frac{F_{An}}{F_{En}} = \frac{\text{EEV}^*_n}{\text{EEV}} + (1 - \frac{\text{EEV}^*_n}{\text{EEV}})\frac{F_1}{F_{En}} \tag{3.11}$$

are due to regional variations of emptying or filling rate in parts of the lung. Therefore PDPS is able to produce graphs of F_A/F_E for the indicator gases as a function of time.

The wash-out curve

Indicator gas wash-out is described by a graph of normalized end-expiratory fraction F_{Ei}/F_{A0} or normalized mean expiratory fraction F_{Mi}/F_{A0}, as a function of time. The shape of the wash-out curve is influenced by variations in tidal volume. To indicate these variations and to reduce their influence on the wash-out curve, the mean and end-expiratory carbon dioxide fractions are displayed as a reference, and the quotient of the indicator gas fraction and the carbon dioxide fraction is displayed a decade lower. An example is shown in figure 3.6.

Program description

For computer architectural reasons the software system consists of a small main program performing command interpretation and a set of subprograms for specific tasks (recording, analysis and graphical output). The programs communicate by way of a chaining mechanism, and by files containing parameters or results of the preliminary analysis on data files. Command interpretation can be done in an interactive or in stand-alone (batch) mode. In the batch-mode a list of commands is executed on a series of data files. The command list can be stored in a file before the program starts, entered during program execution, or entered automatically by executing the commands manually while PDPS is in a "learn mode". An important feature is a help command, providing information about the command set. Figure 3.7 shows the structure of PDPS, and table 3.1 lists the available subprograms. PDPS consists of 1) a main program, performing command interpretation from terminal or batch-file, providing helpful information to the user and starting subprograms on request, 2) a sub-program to perform data recording; 3) a sub-program to handle a file containing parameters for the record session; 4) sub-programs to calibrate the gas-fraction signals or the flow signal and 5) sub-programs to perform preliminary analysis on recorded data and to produce results in the form of graphs. Parameters needed for the system to run properly are stored in two files. The settings file (text file, changeable with a text editor) contains pre-set values of parameters in the program, concerning among others debugging level and mode (interactive vs. batch). It also contains the commands to be executed when in batch mode. The calibration file contains the parameters needed for the data acquisition and the calibration of the data.

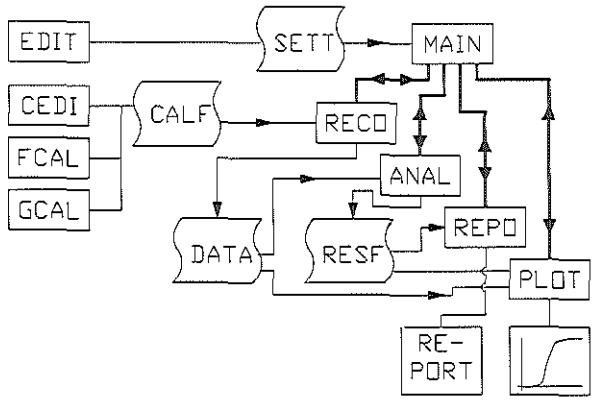

FIGURE 3.7: Scheme of the software system. A small main program MAIN performs command interpretation and passes temporary control to other small programs. The function of the programs and files are listed in table 3.1

Program:	Purpose:
MAIN	Command interpretation and control.
RECO	Performs data acquisition during wash-out. Writes obtained samples to file DATA.
ANAL	Analysis of the signals in file DATA; writes calculated results to file RESF.
REPO	Reports result of analysis (read from RESF) in the form of a table (fig. 3.8).
PLOT	Produce plots.
CEDI	List or change calibration file CALF manually.
FCAL	Perform flow calibration and write the results in CALF.
GCAL	Perform calibration of gas-fractions and write the results in CALF.
File:	**Purpose:**
SETT	Settings file (changeable by a text editor). Contains global parameter settings.
CALF	Contains measurement set-up (sample-frequency, scheme of connections to the ADC channels) and calibration data.
DATA	Contains the obtained samples of a wash-out session in digital form.
RESF	Contains data obtained by analysis of the data file.

TABLE 3.1: List of the available sub-programs and the files used in PDPS

Description of data acquisition and calibration

Before PDPS can start a wash-out measurement, the channels of the analog-digital converter (ADC) with which the flow- and gas-fraction signals are sampled have to be configured, and the signals have to be calibrated (i.e. the values of these signals have to be mapped to the digital sampled values). In order to avoid the need to re-enter this information before each measurement, PDPS stores the following parameters in a calibration file: the sample frequency, the time delay of the gas fraction signals due to the capillary leading to the mass spectrometer, and a table. The table contains for each signal to be used an identification code (e.g. 1=flow, 2=helium etc.), and data for a two point calibration (a calibration point consists of the physical value of a signal (e.g. gas fraction), and the digital value to which the physical value is converted). The sub-program "GCAL" in figure 3.7 serves to calibrate gas fractions. When invoked, it continuously samples gas fractions from a gas mixture of known composition, plotting the obtained signals on the screen, until the user issues a stop command. Then the sub-program stores for each gas the mean of the last 8 samples (in order to reduce influence of noise) as the digital value of one of the calibration points (the user decides which one). The physical value is obtained from a file associated with the gas mixture used. The calibration subprogram "FCAL" serves to calibrate the flow sampling channel using a calibration cylinder with movable piston displacing a test volume of 1000 ml. The sub-program first calibrates the data corresponding to zero flow. Next, it samples the flow while the user moves the test volume in and out of the cylinder through the flow measuring device. The volume displacement is derived from the obtained signal and plotted on the screen, to enable the user to detect nonlinearities. From the obtained data a calibration factor for expiration as well as for inspiration is calculated and displayed. The user is asked to accept one of the two values, or the mean of the two. If the flow measuring device is non-symmetric (it has a different calibration factor for inspiratory and expiratory flow) the user should choose the calibration factor for expiratory flow. Otherwise he should use the mean of inspiratory and expiratory flow. The sub-program calculates the digital values belonging to flow values of 0 and 1000 ml/sec, and stores them in the recording description file.

Data acquisition

The data acquisition sub-program asks the user for the maximum duration of the measurement, the name of the file to store the data, and comments to be included in this data file. Recording is started by manual (one-key) command or external triggering. The signals are sampled

in a swept mode, and the samples are stored, unaltered, in the data file. After the measurement time has been elapsed or the user interrupted the sub-program by a key, sampling stops, and a trailer block containing the information from the calibration file and the user comments is appended to the file. After the measurement the computer plots the acquired signals on the screen.

Analysis of the signals

The analysis sub-program performs the detection of the expirations and performs the preliminary analysis (as described in a previous section). The results are written in a file, and are used by other subprograms.

Presentation of the results

The plotting sub-program draws plots on the terminal, with a hard copy option. The following plots can be made: 1) Breath-by-breath expirograms of one or more of the gases carbon dioxide, helium or SF_6 (figure 3.2). Expirograms of one breath are drawn in the same frame. For ordinate, a choice can be made between relative volume ($0 \ldots V_{Ti}$), absolute volume ($0 \ldots 500$ml, in order to compare phase II of expirograms with different tidal volume) or time ($t_{bi} \ldots t_{ei}$). The y-axis is normalized (scaled between the end-inspiratory and the end-expiratory fraction) for each of the gases separately. The sub-program plots by default 15 subsequent expirograms on the same screen (three rows of 5 frames). 2) Gas exchange ratio of each subsequent expiration as a function of time, relative or absolute volume (figure 3.5). Optionally expirograms of carbon dioxide and oxygen are included; 3) Dead space: To analyse variations of the shape of the expirograms the differences of the dead space of the chosen gases and the dead space of carbon dioxide of the same breath is plotted breath-by-breath as a function of time (figure 3.4); 4) Wash-out curve (figure 3.6). The carbon dioxide corrected wash-out curve is plotted a decade below the actual curve; 5) F_{An}/F_{En} as a function of time. In addition to the plots, the report sub-program can print a table containing a breath-by-breath list of the following quantities: time; tidal volume; for each of the gases oxygen, carbon dioxide, helium and SF_6 the end expiratory fraction, the mean expiratory fraction, and Bohr "dead space"; carbon dioxide production, oxygen consumption and gas exchange ratio. Figure 3.8 is an example of such a table.

Hardware and software specification

The software is written in Fortran-77 to run on DEC PDP11 computers. There is a version running under RT11, and a version for RSX-11M-PLUS.

G A S T R A N S P O R T Page. 1

Filename..... GS:XXXXXX.GAS Version..... 1
Date..... 10- 4-1991 Labnumber..... 6
Time..... 11:33 Samplefrequency... 100.00 Hz

Comment..... XXXXXXXX; 17 hPa PEEP

zwo/4a-11-APR-91

Hemax : 187.8 Hem1 : 185.9 CO2max : 335.8 mtx :, -1

1 :	2 :	3 :	4 :	5 :	6 :	7 :	8 :	9 :	10 :	11 :	12 :	13 :
1	0.0	714	188	188	0.0	336	191	0.0	0.00	0.000	0.000	0.00
2	2.5	897	163	137	36.5	342	190	44.4	1.22	0.317	0.391	0.81
3	5.0	705	140	101	37.3	337	192	42.9	1.16	0.321	0.390	0.82
4	7.5	701	114	76	39.0	338	191	43.2	1.23	0.321	0.385	0.83
5	10.0	703	98	60	40.1	333	190	42.7	1.36	0.321	0.386	0.83
6	12.5	701	82	49	43.4	333	189	43.4	1.47	0.320	0.381	0.84
7	15.0	691	69	41	42.7	329	189	42.5	1.51	0.319	0.383	0.83
8	17.5	702	53	34	36.6	337	189	43.9	1.48	0.319	0.387	0.82
9	20.0	703	49	28	43.7	334	189	43.3	1.58	0.319	0.389	0.82
10	22.6	702	41	24	42.5	334	189	43.5	1.59	0.319	0.389	0.82
11	25.1	703	36	21	41.5	333	190	42.9	1.63	0.319	0.388	0.82
12	27.6	887	31	18	42.0	337	188	44.0	1.66	0.318	0.388	0.82
--	2.5	734							0.00			

Column explanation :

1 ---> Breathnumber
2 ---> Time.....[sec]
3 ---> Expiration Volume....[mL]
4 ---> End exp. He conc.....[%*100]
5 ---> Mean ,, ,, ,,.....[%*100]
6 ---> Deadspace for He.....[%]
7 ---> End exp. CO2 conc....[%*100]
8 ---> Mean ,, ,, ,,.....[%*100]
9 ---> Deadspace for CO2....[%]
10 ---> FRC(He).....[Liter]
11 ---> CO2-Production.....[L/min]
12 ---> O2 consumption.....[L/min]
13 ---> Respiratory quotient

FIGURE 3.8: Table containing breath by breath results. This table contains tidal volume, mean- and end expiratory fractions and Bohr "dead space fractions" of He and CO_2, EEV derived from He wash-out, and gas exchange data (O_2 uptake, CO_2 delivery and respiratory quotient).

The software supports a programmable clock, and analog-digital converters. Graphical output is presented on graphical terminals of the DEC VT series. The pictures can be captured by the computer to make hard copies on REGIS compatible printers. A new version of the program has been made that runs on the MS-DOS operating system.

Discussion

PDPS is a software system that has a purpose to gain insight in the distribution of ventilation and ventilation/perfusion ratio in the lung. As far as we know this is the first system that uses the advantage of the capacity of a mass spectrometer to measure simultaneously the fractions of the metabolic gases (oxygen and carbon dioxide) and of poorly soluble indicator gases washing out of the lung. This type of measurement enables combination of several calculations on data obtained during the same train of breath-cycles. Besides established parameters being calculated we introduce new methods (the reconstruction of the ratio of the mean alveolar to end-expiratory indicator gas-fraction, and the breath-by-breath Bohr dead space analysis as indication of a changing shape of the expirogram) as a means of evaluating the efficacy of ventilation. Combining information from the various calculations leads to a more comprehensive description of the ventilation and the ventilation/perfusion process than the individual methods alone would permit. For example in patients with obstructive pulmonary disease or bronchus carcinoma the lungs can be divided in compartments with different ventilation ratios ($\dot{V}/V$), that empty asynchronously (best ventilated compartments empty at the beginning of the expiration) and in which the ventilation inhomogeneity is not compensated by complementary perfusion inhomogeneity. In that case the ventilation inhomogeneity shows up in multi-exponential decay of the expiratory indicator gas-fraction and the ventilation/perfusion mismatch shows up in a sloping alveolar plateau of the carbon dioxide expirograms and a gas exchange ratio that diminishes in the course of a single expiration. Furthermore the asynchronous emptying of the parallel compartments causes the Bohr "dead space" fractions of the subsequent expirograms during the wash-out process to rise. The phenomena are illustrated in figures 3.2B, 3.4 and 3.5B. However in many cases wash-out tests show multi-exponential wash-out and a sloping alveolar plateau of carbon dioxide, but the gas exchange ratio does not change in the course of a single expiration and the Bohr "dead space" fraction does not change significantly in the course of the wash-out [95]. In that case the ventilation inhomogeneity can not be caused by unequally ventilated, asynchronously emptying volumes, but it must be

caused by a stable longitudinal gas-fraction gradient at the level of the respiratory bronchioli where the gas-transport is predominantly caused by diffusion [32]. It is only by the combination of the techniques that this difference can be recognized.

An alternative way to study the diffusion-related ventilation inhomogeneity is offered by PDPS allowing the combination of the washout of two gases with different diffusion coefficient, like helium and SF_6 (the former being seven times more diffusible than the latter). The origin of diffusion-related inhomogeneity is not yet fully understood. Von Nieding et al. [70] performed an extensive study on He/SF_6 washout and found that F_E/F_0 of helium was larger than F_E/F_0 of SF_6 at the beginning of the wash-out, but smaller at the end of wash-out. In the healthy volunteers and bronchitis patients the moment of cross-over was much earlier than in emphysema patients. The delayed cross-over was ascribed to gross dilation of the airways of the 17–18 generation causing the inspiratory gas to penetrate less far into the lung than in a normal lung. Luijendijk et al. [64] showed by mathematical simulation that existence of small closed volumes in the acini, in which gas-exchange takes place by collateral ventilation, could explain the cross-over retardation. These studies strongly suggest that diffusion can be a limiting factor in the gas-transport in the lung, and this can only be studied with wash-out techniques using gases with different diffusability.

Although not described in this paper, the analysis of the data is complete enough to calculate conventional indices of ventilation inhomogeneity from the wash-out data (like Becklake index, moment ratio index etc. [39, 36]) Using the described software system we have recently developed a new ventilation inhomogeneity index [51] capable of identifying COPD patients. The accuracy of the mass spectrometer enables the addition of only small fractions of the indicator gases (2%) into the inspiratory gas-mixture during wash-in. This has the advantages that no secondary gas effect occurs, that the inspiratory oxygen fraction can be kept constant, so that metabolic measurements can be performed during the wash-out, and that the wash-out can be performed on critically ill patients needing very high inspiratory oxygen levels. PDPS enables calculations to be made for wash-in as well as wash-out tests. This has the advantage of utilizing the time preceding wash-out, that is needed to wash the indicator gas into the lungs, by performing a measurement. This results in an optimal use of measurement time which can be advantageous in the rapidly changing condition of the critically ill patient. The obtained data, besides providing patient lung-function tests [95, 48, 44], can be used for basic lung-physiological research. With the described system measurements have been performed on 60 spontaneously breathing

patients. Measurements can be performed using a special device to inject the indicator gas into the inspired gas-mixture [48]. We performed wash-out tests on 65 mechanically ventilated Intensive Care patients in order to evaluate the effect of ventilation settings (e.g. application of positive end-expiratory pressure ventilation) and medication (e.g. bronchodilators) on the end-expiratory lung-volume and ventilation inhomogeneity [44].

Mode of availability

The program sources are available on tape or MS-DOS diskette. Requests should be addressed to the author.

Acknowledgment

This investigation was sponsored by the Dutch organization for pure research ZWO, and in part by the Netherlands Asthma Foundation. The authors thank W.P.J. Holland MSc and Dr.Ir. C. Ince for careful reading of the manuscript.

Chapter 4

Accuracy of wash-out tests[1]

P. Huygen, C. Ince and H.A. Bruining

Abstract

We have analysed the effect of several factors on the accuracy of the lung volume calculation with multiple breath wash-out tests, using different analysis techniques. The analysed factors include noise in the flow or gas-fraction signal, misestimation or variation of the delay of the gas-fraction measurement, the dynamic response of the gas-fraction measuring device, metabolic gas-exchange and solubility of the indicator gas. The analysis was applied to a set-up using an Airspec MGA3000 mass spectrometer for gas-fraction measurements and a Fleisch flow meter for flow measurements, with argon, helium or SF_6 as indicator gases.

It was found that the main factor of limitation of the accuracy of the lung volume measurement was the delay of the gas-fraction measurement. A delay misestimation of 10 ms could induce an error of up to 7% in the lung volume measurement. Another important factor was gas-fraction noise, that in our set-up could cause a variability of up to 3% in argon wash-out tests. Solubility of argon may cause a slight but otherwise undetectable over-estimation of the lung volume if this gas is used as indicator gas.

It is concluded that with our set-up an overall accuracy within 10%, or 200 ml, can be reached.

Introduction

If a subject, after inspiration from a gas-mixture containing a poorly soluble, inert indicator gas until the indicator gas has been homogeneously distributed in the lung, inspires from an indicator gas-free gas mixture, the alveolar indicator gas-fraction decreases with each subsequent inspiration. The indicator gas is 'washed out" from the lungs, and the course of this wash-out process is determined by the distribution of the inspired gas in the alveolar space [13, 21]. Therefore, such an "open-circuit indicator gas wash-out test" can provide important parameters related to

1. *Submitted*

the distribution of the ventilation in the lung [4, 95, 49, 50, 60]. Furthermore, the end-expiratory lung-volume can be measured. Especially during mechanical ventilation or other forms of ventilatory support the wash-out test shows its advantages [48] since other lung-function measurement techniques are rarely applicable at the bed-side because they interfere with the ventilation equipment or because they are dependent on active cooperation of the subject.

The most common modality of indicator gas wash-out test is the multiple breath nitrogen wash-out (MBNW) test [33, 38, 4] in which the subject originally breathes room air, and switches to pure oxygen during the wash-out phase, using nitrogen as indicator gas. Advantages of this method are the simple set-up, the availability of the inspiratory gas-mixture and the accessibility of sensitive nitrogen fraction meters. Disadvantages are the large change of the fractions of nitrogen and oxygen that influences the dynamics of the indicator gas (secondary gas effects), promotion of atelectasis in poorly ventilated parts of the lung by the oxygen uptake by the blood, the toxicity of high inspiratory oxygen fractions and non-negligible solubility of nitrogen in blood. These disadvantages can be avoided by using a low fraction of poorly soluble indicator gases such as helium or sulfurhexafluoride (SF_6). Combinations of helium and SF_6 in a single wash-out procedure can provide information on gas-transport by diffusion since the diffusion coefficient of the two gases differs sevenfold. The main disadvantage of this approach is that sensitive detectors for these indicator gases are not always available. Mass spectrometers are very suitable, but they are expensive and bulky and need trained staff. An infra-red meter for measuring low fractions of SF_6 has been described [55] and has been used for wash-out tests [56, 27], but it is not yet commercially available.

The wash-out technique has a disadvantage in that while being more sophisticated it requires more care than conventional techniques. Small calibration inaccuracies can accumulate during the wash-out and result in large deviations in the final calculation. Various studies have been done to variations of individual factors such as the dynamic response and delay of mass-spectrometers [1, 2, 7, 10, 22, 85] and the accuracy of Fleisch pneumo-tachographs [68, 89] on the accuracy of wash-out tests. Investigations of the impact of the instrumental inaccuracies on the outcome of indicator gas wash-out tests have, as far as we know, only been made by Brunner [10], who measured the effect of misestimation of the delay of the gas-fraction measurement on the calculation of the volume of a dummy lung. Until now no comprehensive study has been undertaken that takes into account the cumulative effect of the different factors on the calculated variables.

We analysed the effects of several types of instrumental inaccuracies on the calculation of the lung volume from indicator gas wash-out tests by the volumes regression method [50]. The factors that induce inaccuracy of the wash-out test can be classified as follows: 1) Stochastic factors that diminish the accuracy of the results but do not cause a systematic deviation; 2) Scaling errors (such as calibration errors), that influence the result of the lung volume calculation, but have no influence on, for example, the shape of curves that can be drawn with the data. Therefore, these errors have no influence on calculations of ventilation inhomogeneity; 3) Cumulative errors. An important part of the calculations of ventilation inhomogeneity and lung volume is integration of the flow signal as a function of time and the integration of the product of gas-fraction and flow signal as a function of time. This causes small offset-like errors to grow in the course of the wash-out and result in a major inaccuracy.

The effects of instrumental inaccuracies on the outcome of wash-out tests was studied by simulating the effects that these inaccuracies would have on the signals from wash-out tests on a number of representative subjects. The effect of solubility of the indicator gas by the blood was studied by simulations with a mathematical model. The effect of a computational error, e.g. metabolic gas uptake, is calculated by omitting the computational correction.

Theory

If at the begin of the wash-out test the indicator gas is homogeneously distributed in the lungs to a fraction of $F_{a,0}$ and the subject inspires during the wash-out test from a gas-mixture with a different indicator gas-fraction (F_I) then the end-expiratory lung volume (EEV) can be calculated at the end of every breath of the wash-out test by division of the amount of indicator gas removed from the lung with the dilution of the indicator gas in the lung. At the end of the n^{th} expiration after the beginning of the wash-out this can be expressed in formula by

$$\text{EEV} = \frac{\sum_{i=1}^{n} \Delta V_{P,i}}{F_{A,0} - F_{A,n}} \tag{4.1}$$

where $\Delta V_{P,i}$ is the partial volume of indicator gas washed out of the lung during breath cycle i (the integral of the product of flow and gas-fraction over the breath cycle: $\Delta V_{P,i} = \int_{t_{b,i}}^{t_{e,i}} F(t)\dot{V}(t)\,dt$), $F_{A,n}$ is the mean alveolar indicator gas-fraction of breath cycle n and $F_{A,0}$ is the

mean alveolar indicator gas-fraction of the last breath cycle before the beginning of wash-out.

It is, however, not possible to measure $F_{A,n}$ since this would involve gas-fraction measurements in all of the alveolar spaces. Instead the method of Haldane and Priestley [45] is used in which $F_{A,n}$ is approximated by the end-expiratory indicator gas-fraction $F_{E,n}$ which is easily measured. If the distribution of the indicator gas in the lung is homogeneous, then $F_{A,n}$ is equal to $F_{E,n}$, and the following estimation of the lung volume is then valid:

$$\text{EEV}_n^* = \frac{\sum_{i=1}^{n} \Delta V_{P,i}}{F_{E,0} - F_{E,n}} \tag{4.2}$$

EEV_n^* denotes the lung volume estimated at the end of breath cycle nr. n. The difference between $F_{A,n}$ and $F_{E,n}$ will cause a difference between the actual and the estimated lung volume. However, in the course of the wash-out the difference between the two will decrease. We have shown previously that a good estimation of the EEV is obtained by application of the "Volumes regression technique" [50]. In this technique EEV_n^* is calculated breath by breath and plotted as a function of the relative amount of indicator gas washed out of the lung (calculated as the quotient $w = (F_{E,n} - F_{E,0})/(F_I - F_{E,0})$). A regression line is drawn through the volume estimations in which $0.7 \leq w \leq 0.9$ and this line is extrapolated to $w = 1$. This is illustrated in figure 4.1 . The volume that belongs to the intersection of the extrapolated line with the line $w = 1$ is denoted as EEV^* and considered as a best estimation of the end-expiratory lung volume of the subject.

Ventilation inhomogeneity. The slope of the regression line is determined by the difference between the mean alveolar and the end-expiratory gas-fraction. Therefore the normalized slope of the regression line (quotient of the slope and EEV^*) is a sensitive index of ventilation inhomogeneity and is called "volumes regression index" [50].

Wash-in vs. wash-out The described calculation of the lung-volume and ventilation inhomogeneity is independent of the actual value of the inspiratory gas-fraction before or during the actual wash-out; it is essential that both fractions are constant and not equal. This implies that the calculations are valid for a true wash-out procedure in which the indicator gas is added to the inspiratory gas-mixture before, but not during the test ($F_{A,0} > 0$; $F_I = 0$), but also for a wash-in procedure in which the indicator gas is present in the inspiratory gas-mixture only during the

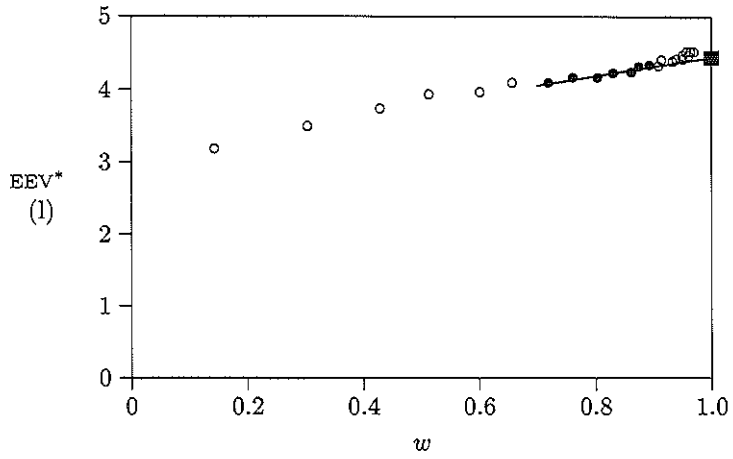

FIGURE 4.1: Breath-by-breath estimations of EEV, plotted as a function of the relative amount of indicator gas washed out w (bottom). The final EEV is calculated by extrapolating the regression line drawn through the estimations in which $0.7 \leq w \leq 0.9$ (• symbols) to $w = 1$ (■ symbol).

test ($F_{A,0} = 0$; $F_I > 0$). This has the advantage that the wash-in of the indicator gas, prior to the wash-out procedure, can be utilized for a calculation. We developed an indicator gas injector [48] that starts a wash-out procedure by replacing the indicator gas in the inspiratory gas-mixture by another indicator gas, thereby keeping the inspiratory oxygen fraction constant. In this set-up the calculations can be performed on both indicator gases. The calculation can also be performed when argon, that is present in air, is injected as indicator gas.

If during a wash-out the inspiratory gas-fraction is zero, the inspirations do not contribute to the integral in the numerator of equation 4.2. Thus only the partial volume of the expired indicator gas has to be calculated. This is advantageous because differences in the temperature and the composition of the inspiratory and the expiratory gas-mixture cause small flow calibration differences that will cause an error in the calculation. If the inspiratory gas-fraction is not zero during the wash-out, the inspirations can be neglected provided that the inspiratory indicator gas-fraction, F_I, is subtracted as an offset from the gas-fraction , i.e. the integral in the numerator of equations 4.1 and 4.2 is calculated as

$$\int_{t_{b,i}}^{t_{e,i}} [F(t) - F_I]\, \dot{V}(t)\, dt \tag{4.3}$$

The sum of the integral 4.3 over n breath-cycles is equal to the sum of the original integral provided that the sum of the inspired tidal volumes is equal to the sum of the expired tidal volumes:

$$\sum_{i=1}^{n} \int_{t_{b,i}}^{t_{e,i}} [F(t) - F_I]\,\dot{V}(t)\,dt = \sum_{i=1}^{n} \int_{t_{b,i}}^{t_{e,i}} F(t)\dot{V}(t)\,dt - F_I \sum_{i=1}^{n} \int_{t_{b,i}}^{t_{e,i}} \dot{V}(t)\,dt \tag{4.4}$$

The second term of the right part of equation 4.4 is the product of a constant and the integral of the flow over the n breath-cycles, which is zero if the subject expires the same amount of air as he inspired. In fact there is a small difference between inspired and expired tidal volume due to the addition of water vapor and the uptake of oxygen in the blood which is not completely compensated by the delivery of carbon dioxide. This difference is, however, difficult to measure and in the set-up that we use the calibration of the inspiratory flow is multiplied by a factor that makes the measured sum of the inspiratory tidal volumes equal to the sum of the expiratory tidal volumes in order to compensate for calibration differences between inspiratory and expiratory flow. This means that factors that cause the expiratory tidal volume to be different from the inspiratory tidal volume (like metabolic gas uptake) cause, when not corrected for, an inaccuracy of the results of a test in which $F_I > 0$, but not of a test in which $F_I = 0$.

Factors causing inaccuracy of the lung volume measurement

The factors that cause inaccuracy of the lung volume measurement by indicator gas wash-out can be divided into instrumental errors, physical errors and computational factors. Instrumental factors involved are measurement noise and dynamic response limitation of the gas-fraction measuring device. Physical factors are the solution of indicator gas in blood and body tissue and delay variations of the gas-fraction measurement due to changes of the viscosity of the gas-mixture. A computational factor is the net metabolic gas uptake if the Haldane correction can not be applied.

Delay of gas-fraction measurement

In order to calculate the amount of indicator gas washed out of the lung (numerator of equation 4.2) the gas-fraction may not be shifted in time with respect to the flow signal. However, most gas-fraction measuring instruments transport the sampled gas to a measuring chamber, which causes a delay that has to be corrected for. The delay time is sensitive for the pressure at the inlet of the capillary and for the viscosity of

the gas mixture. In this paper we address the effect of inaccurate delay correction on the EEV calculation.

Limited dynamic response of the measuring device

While the sample gas is transported to the measuring chamber, diffusion and convection processes cause some mixing of the sample gas in the transport direction of the gas. This mixing causes deformation of the gas-fraction signal. In devices in which the gas-fraction is measured directly near the mouth of the subject by infra-red absorption the same signal deformation is caused by electronic post-processing of the measured signal in order to obtain a reasonable signal-to-noise ratio [9]. Deformation of the flow signal will generally not occur due to limitations of the flow measuring device, since the frequency response of the device is generally flat up to more than 50 Hz, whereas typical flow signals of breathing subjects do not contain frequencies of more than 20-25 Hz [67].

Metabolic gas exchange.

The blood normally takes up more oxygen from the alveolar gas than it delivers CO_2. The quotient of the volume of CO_2 released and the volume of O_2 taken up by the blood (respiratory quotient, RQ) has usually a value of about 0.8. If the rate of the oxygen uptake is denoted as $\dot{V}_{O_2}$ and the rate of carbon-dioxide release as $\dot{V}_{CO_2}$, the mean inspiratory flow exceeds the mean expiratory flow by $\dot{V}_{O_2} - \dot{V}_{CO_2}$. This difference can usually not be measured and is ignored. As a consequence a flow of indicator gas of $F_I(\dot{V}_{O_2} - \dot{V}_{CO_2})$ enters the lungs unnoticed. If the wash-out tests lasts a time Δt, this causes an over-estimation of the lung volume of $\Delta t(\dot{V}_{O_2} - \dot{V}_{CO_2})F_I/(F_I - F_{A,0})$. Thus the metabolic gas exchange does not cause an error in a true wash-out with $F_I = 0$. In a wash-in with $F_{A,0} = 0$, the error is $\Delta t(\dot{V}_{O_2} - \dot{V}_{CO_2})$. In healthy subjects the wash-out lasts less than 2 minutes, and the net metabolic gas uptake will be approximately 50 ml/min, resulting in an overestimation of the lung volume of less than 100 ml. In patients with severe inhomogeneously ventilated lungs the wash-out test may last as long as 5 minutes and in that case the error can amount to 250 ml. If the inspiratory and expiratory gas-fractions of the metabolic gases are measured during the wash-out and the inspiratory oxygen fraction can be kept constant, the influence of the metabolic gas uptake on the wash-out calculation can be eliminated by application of the Haldane transformation. However, measurement of the metabolic gas fractions, especially oxygen, complicates the measurement set-up and is only possible if suitable sensors are available. Therefore we have calculated the effect of metabolic gas exchange when the Haldane transform is not applied.

Solution of indicator gas in blood and body tissues.

All gases are slightly soluble in blood and body tissues. Argon, for example, has a solubility of 56 ml/l/Bar, nitrogen 23 ml/l/Bar, helium 9.4 ml/l/Bar and SF_6 7 ml/l/Bar. Therefore, during an indicator gas wash-out a certain amount of indicator gas will be released from tissue into the lungs. If the body tissues were allowed to become in equilibrium with the lungs before and at the end of the wash-out, the dissolved indicator gas could in a 75 kg subject potentially cause an over-estimation of the lung-volume between 0.5 l for SF_6 and 3.5 l for argon. However in the relatively short duration of a wash-out test only a few well-perfused organs such as the lungs, kidney, brain and heart are capable of releasing more than 50% of the gas that they contain. Moreover, if the indicator gas is washed into the lung before the wash-out, most of the organs in the body have not had enough time to become saturated with the indicator gas. Therefore, Robertson et al. [80] made for nitrogen wash-out tests a more realistic estimation by mathematical simulation using existing data [80, 53, 54] of the typical perfusion and weight of the organs of a 70 kg normal man with a cardiac output of 5.89 l/min. The wash-out model is explained in the appendix.

Methods

Wash-out technique

In order to perform indicator gas wash-out tests on patients who were mechanically ventilated with a Servo 900B (Siemens-Elema, Solna, Sweden) ventilator, we developed a device [48] that injects indicator gas into the oxygen-air mixture entering the ventilator. This indicator gas injector can also be used for wash-out tests on spontaneously breathing subjects. During the wash-out procedure the respiratory flow and the fractions of the indicator gases used (argon and/or SF_6) are continuously measured at the end of the tracheal tube. The flow is measured with a Fleisch nr. 2 pneumotachograph (Sensormedics, Bilthoven, the Netherlands) connected to a Validyne type MP45-14-871 (Northridge, CA) pressure transducer. The gas-fractions are measured with a quadrupole mass spectrometer (MGA3000, Airspec, Biggin Hill, UK). The flow and gas-fraction signals are sampled with a frequency of 100 Hz and stored on disk.

The subject inspires gas with a constant, low fraction (approximately 2%) of indicator gas until the difference between the end-expiratory indicator gas-fraction and the inspiratory indicator gas-fraction is smaller than 10^{-4}. Then, to start the wash-out, the indicator gas in the

inspiratory gas-mixture is replaced with another inert gas in order to keep the inspiratory oxygen fraction constant. After the procedure the obtained flow and gas-fraction signals are analysed [49] and the end-expiratory volume of the lung and the volumes regression index are calculated [50].

In order to establish the effect of the equipment used on the EEV calculation we performed bench tests. The linearity of the mass spectrometer was measured using a Digamix (Wüsthoff, FRG) gas-mixer to make helium/air mixtures with accurately known compositions. The helium fractions varied between 0% and 10% with steps of 1%. In order to measure noise-levels of the mass-spectrometer for the indicator gases the mass spectrometer sampled gas-mixtures with fractions between 0% and 5% of helium or SF_6 and fractions between 1% and 5% of argon. The dynamic response and delay of the mass spectrometer has been measured by sampling while the tip of the sampling capillary was pulled from a tube through which a gas-mixture, consisting of 3% argon, 3% helium, 3% SF_6, 5% CO_2 and 30% O_2 in nitrogen flowed, concomitantly disconnecting an electrical signal. Additional delay measurements were performed to determine the influence of viscosity and pressure variations on the delay. In these measurements the sample opening of the capillary of the mass spectrometer was mounted inside the measuring chamber of a flow-through infra-red capnograph (Novametrix 7000A). The measuring chamber was connected to the outlet of the indicator gas injector that produced a constant flow of an oxygen/air mixture to which a small fraction (3%) of carbon dioxide could be added step-wise. The appearance and disappearance of the carbon dioxide was measured simultaneously by the capnograph and the mass-spectrometer and the time difference between the output signals of both instruments was caused by the delay in the mass spectrometer. In order to measure the pressure dependence of the delay pressure differences were imposed by connecting the outlet of the measuring chamber to a variable pneumatic resistance and a pressure meter. To measure the viscosity dependence of the delay, the sample gas was changed by varying the oxygen fraction.

Of the flow-measuring device we measured the linearity and signal-to-noise ratio using calibrated flows produced by a flow generator (Gould-Godard, The Netherlands).

Simulations on actual wash-out signals.

To evaluate the effect of the mentioned error sources in wash-out tests on the EEV calculations we performed simulations of the effect of the error sources on existing recordings of wash-out tests on mechanically ventilated as well as spontaneously breathing patients. The recordings have

been selected to cover a wide range of situations (large lungs, small lungs, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS)). Most of the recordings are from wash-out tests in which the inspiratory fraction of argon changes from 0.03 before the wash-out to 0.01 after the wash-out. Recording 3 is a wash-in test in which the argon fraction changes from 0.01 before to 0.03 during the wash-in. The recordings used are listed in table 4.1 .

TABLE 4.1: List of the subjects on whose wash-out recordings noise simulations have been performed.

Nr.	EEV	*description*
1	0.78	Mechanically ventilated, female patient
2	3.16	Mechanically ventilated dummy lung.
3	3.35	Spontaneously breathing subject with COPD
4	4.65	Male volunteer with a large EEV
5	2.41	Female volunteer, mechanically ventilated
6	1.80	Ventilated ARDS patient with PEEP of 17 hPa

Noise simulations

In order to simulate the effect of signal noise on the EEV calculations Gaussian distributed random numbers with a mean value of zero and standard deviation of σ were added to one of the signals. Random numbers with a uniform distribution between 0.0 and 1.0 were created using the internal random number generator of the computer system. In order to avoid sequential correlation of the random numbers, the numbers were shuffled before use [76]. The Box-miller transformation [76] converted the obtained random numbers into random numbers with a Gaussian distribution with standard deviation equal to unity and a mean value of zero. The obtained numbers were multiplied by a scaling factor to obtain the requested value of σ, and added to the samples of either the flow or the indicator gas signal. The scaling factor was either a constant value (absolute noise) or a constant fraction of the value of the sample to which the random number was added (relative noise; constant signal-to-noise ratio). On these contaminated signals the EEV calculation was performed. In order to determine the accuracy the contamination and EEV determination was repeated 40 times, after which the standard deviation of the distribution of the obtained EEV values was calculated. Using this method we performed simulations of flow noise with a constant standard deviation of 0, 25, 50, 75 and 100 ml/sec and with a constant coefficient of variation of 5% and 10%. We performed gas-fraction noise simulations adding noise with a constant standard deviation of 1%, 2% and

5% of the difference between the inspiratory fraction before and after the beginning of the wash-out. Finally we performed gas-fraction noise simulations adding noise with a constant coefficient of variation of 1%, 2% and 5%.

Delay of gas-fraction relative to the flow signal

Misestimations of the delay between the gas-fraction and the flow signal have been simulated by adding extra delay to the gas-fraction signal. Delays between -100 msec and $+100$ msec were added in steps of 10 msec.

Dynamic response limitation of gas-fraction signal

In order to simulate the effect of response limitations in the gas-fraction signal we convoluted the gas-fraction signal with Gauss-functions with values of the second moment σ of 20, 50, 100, 150 and 200 msec before performing the EEV calculation.

Solubility of the indicator gas in blood and body tissues

In order to estimate the effect of indicator gas uptake by the blood we performed wash-out tests combining wash-out of argon with wash-in of SF_6. The tests were performed on 6 subjects. Three of the subjects suffered from chronic obstructive pulmonary disease (COPD), two suffered from pulmonary emphysema and one from cystic fibrosis. The lung volume was measured from both the argon and the SF_6 signal using the volumes regression technique. In addition to the measurements simulations on a mathematical model of the lung were done. The model consists of a single compartment with volume V_L, that is ventilated with a constant tidal volume V_T, as described in the appendix. It incorporates interaction with blood and body tissues as derived from data of Robertson [80], but scaled for the solubility of argon (0.056 vol/vol/Bar) or SF_6 (0.006 vol/vol/Bar) instead of nitrogen (0.023 vol/vol/Bar). The results of the actual wash-out tests on our subjects were compared with the results of model simulations using the same lung volume, effective tidal volume and breath cycle duration as the subjects. The effective tidal volume was calculated as the mean of the difference between the tidal volume and the Bohr dead space fraction and the duration was calculated as the mean of the durations of the breath-cycles of the subject.

Metabolic gas exchange

In order to calculate the effect of metabolic gas exchange on the lung volume and volumes regression calculation we calculated the lung volume from the SF_6 wash-in tests of the 6 subjects with and without the correction for the metabolic gas uptake.

Results

Properties of the equipment used. Figure 4.2 shows the measured noise

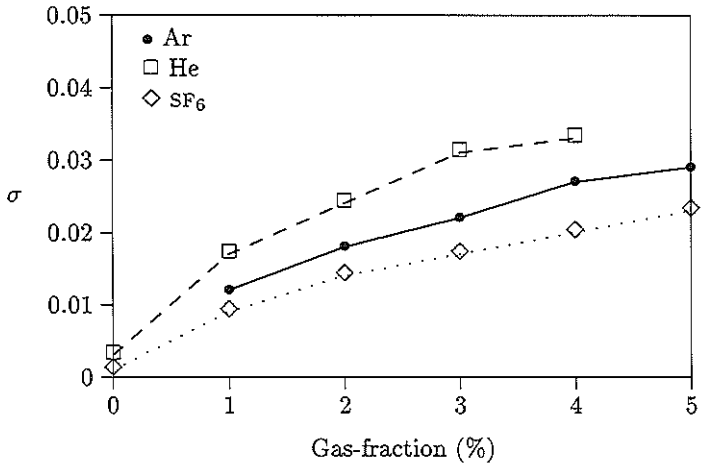

FIGURE 4.2: Standard deviation (σ) of the noise in the gas-fraction signals measured by the Airspec MGA3000 mass-spectrometer

level of the gas-fraction signals of helium, argon and SF_6. The standard deviation of the measured gas-fraction signal (in %) is plotted as a function of the gas-fraction in the mixture that was analysed by the mass spectrometer (in %). For a signal of 1% helium the N/S ratio (the quotient of the standard deviation and the signal-value) is 1.7%. The standard deviation of the noise in the helium signal in the absence of helium is equal to 0.003% helium.

Figure 4.3 shows the linearity of the mass-spectrometer. The maximum deviation of the measured gas-fraction from the regression line is 0.02%, and the correlation coefficient of the regression line is almost unity. Figure 4.4 shows the step response of the mass spectrometer for helium and SF_6. The rise-time from 10% to 90% is for helium shorter than 40 msec, and for SF_6 shorter than 50 msec. The delay during sampling at barometric pressure (100.3 kPa) was 228 ± 8 ms.

Figure 4.5 shows the delay of the CO_2 signal as a function of effective pressure. Effective pressure variations caused delay variations of -0.28 msec/hPa. With the Hagen-Poiseuille formula, modified to take the large density variation in the capillary into account [7], a theoretical delay variability of -0.23 msec/hPa was calculated (dotted line in figure 4.5). Figure 4.6 shows the delay as a function of oxygen fraction.

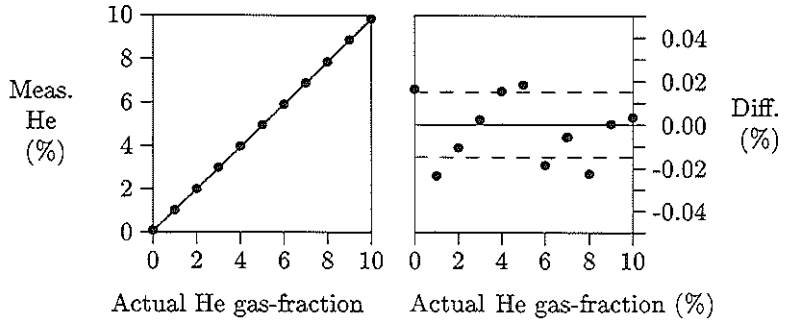

FIGURE 4.3: Linearity of the mass-spectrometer. Left: The measured He fractions are compared with the regression line ($y = 0.020 + 0.979x$, $r = 1.0000$). Right: Differences between measured values and regression line. Dashed lines represent one standard deviation difference.

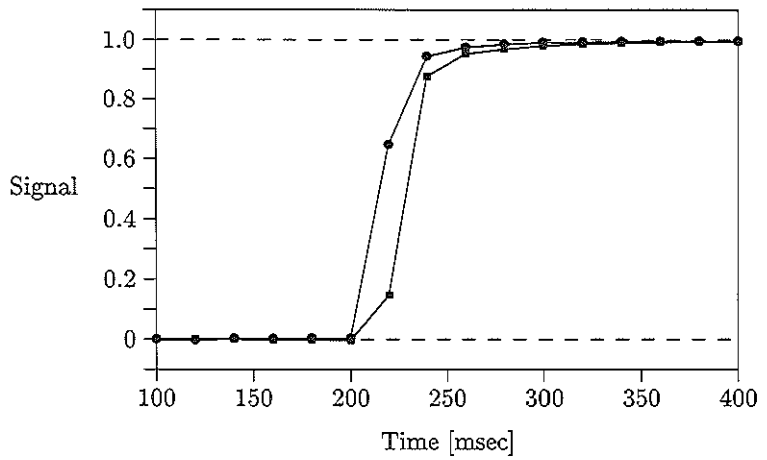

FIGURE 4.4: Step response of the mass-spectrometer for helium (•) and SF_6 (▪). The figure is obtained by adding six individual response curves and then normalizing the sum.

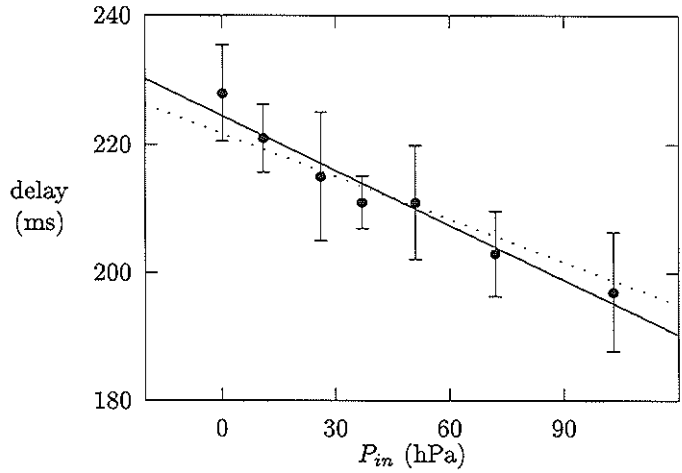

FIGURE 4.5: Delay of the mass spectrometer signal as a function of effective pressure. Solid line: Regression line. Dotted line: Regression line using modified Hagen-Poiseuille formula.

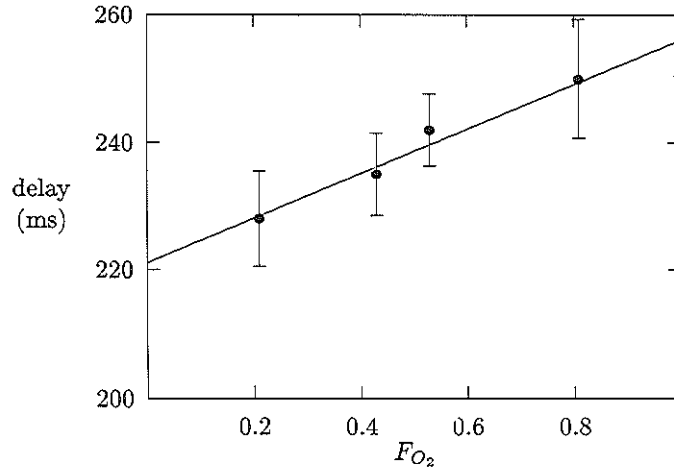

FIGURE 4.6: Delay of the mass spectrometer signal as a function of oxygen fraction. Solid line: Regression line.

The solid line in this figure is the regression line through the data points, according to the Hagen-Poiseuille equation. The relationship between the delay and the viscosity of the test gas was $\Delta t = 1.25 \pm 0.16\eta$ (Δt represents the mass spectrometer delay in msec. and η the viscosity of the test gas in μ-Poise).

Figure 4.7 shows the static linearity of the Fleisch nr 2 flow mea-

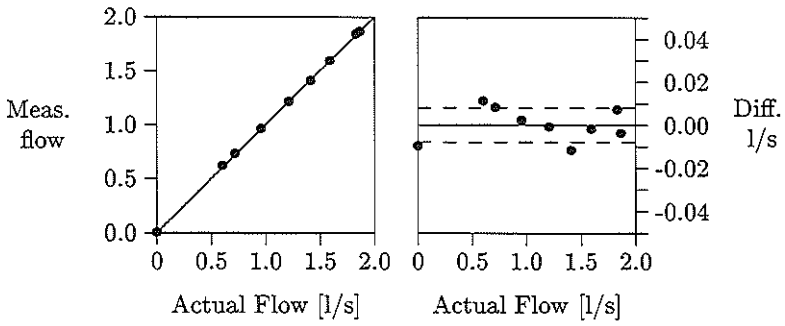

FIGURE 4.7: Linearity of the flow-measuring device. Left: measured flow values compared to the regression line ($y = 0.037 + 0.977x$, correlation coefficient: 1). Right: differences between measured flow and regression line. Dashed lines represent one standard deviation difference.

suring device. The noise in the flow signal during constant flow was difficult to measure because no flow generator with known characteristics was available. During zero flow the noise level is smaller than 2 ml/s, and is caused by the discretisation of the analog flow-signal in the ADC (Analog-Digital-Converter). Using a Gould-Godard flow generator an overall signal-to-noise ratio of better than 100 was measured. It is uncertain to what extend the measured noise is caused by the flow generator.

Effects of noise in the flow signal. Tables 4.2 and 4.3 list the results for lung volume calculations after the addition of noise with constant standard deviation ($\sigma_{\dot{V}}$) resp. with constant signal-to-noise ratio to the flow.

Figure 4.8 shows the mean, the minimum and the maximum of the standard deviation and misestimation of the volume calculations. Addition of noise with standard deviation up to 50 ml/sec resulted in coefficients of variation and mean drift of the COV of the calculated lung volume that remained well below 2%. Addition of noise with larger standard deviation resulted in major deterioration of the accuracy. This is caused by a decrease of the performance of the algorithm that determines the beginning of inspirations and expirations. To ensure the error in the

TABLE 4.2: Mean and standard deviation of 40 EEV values in liters, calculated after contamination of the flow signal with Gaussian noise with constant standard deviation.

Nr.	Flow noise standard deviation (ml/sec)				
	0	25	50	75	100
1	0.78	0.78±0.01	0.79±0.01	0.79±0.08	0.72±0.44
2	3.16	3.16±0.01	3.16±0.02	3.16±0.02	3.17±0.04
3	3.35	3.31±0.03	3.33±0.03	3.40±0.08	3.48±0.12
4	4.65	4.65±0.01	4.66±0.01	4.65±0.02	4.65±0.03
5	2.41	2.41±0.01	2.41±0.01	2.40±0.02	2.40±0.03
6	1.80	1.80±0.01	1.81±0.01	1.81±0.02	1.82±0.02
mean	2.7	2.7 0.01	2.7 0.01	2.7 0.04	2.7 0.11
sd	1.3	1.3 0.01	1.3 0.01	1.3 0.03	1.4 0.16

TABLE 4.3: Mean and standard deviation of 40 EEV values in liters, calculated after contamination of the flow signal with Gaussian noise with constant coefficient of variation (COV).

Nr.	Flow noise COV		
	0%	5%	10%
1	0.78	0.78±0.00	0.78±0.00
2	3.16	3.15±0.00	3.15±0.01
3	3.35	3.35±0.00	3.34±0.02
4	4.65	4.64±0.00	4.64±0.01
5	2.41	2.40±0.00	2.40±0.01
6	1.80	1.80±0.01	1.81±0.01
mean	2.7	2.7 0.00	2.7 0.01
sd	1.3	1.3 0.00	1.3 0.01

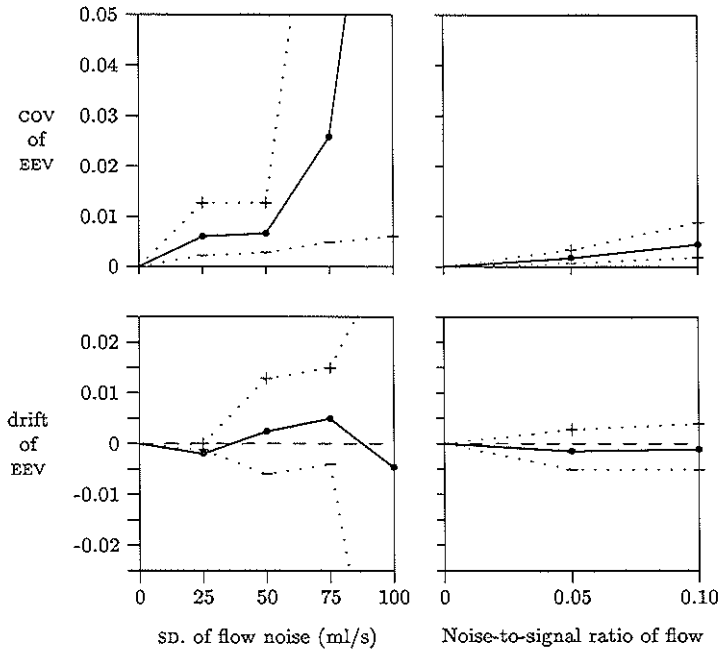

FIGURE 4.8: Influence of noise in the flow signal on the accuracy of the calculation of the lung volume. *Left:* coefficient of variation COV (top) and mean of the deviation (bottom) of the lung volume estimation due to addition of noise with uniform second moment to the flow signal. *Right:* coefficient of variation COV (top) and mean of the deviation (bottom) of the lung volume estimation due to addition of noise of which the second moment is a fraction of the flow signal itself. + symbols: Maximum; dots: mean; −: minimum COV/drift

EEV estimation to be below 1% the noise in the flow signal needs to be below 25 ml/s. The effect of noise with constant coefficient of variation on the accuracy of the lung volume calculation is very small.

Noise in gas-fraction signal. Table 4.4 and the right side of figure 4.9

TABLE 4.4: Mean and standard deviation of 40 EEV values in liters, calculated after contamination of the gas-fraction signal with Gaussian noise with constant standard deviation.

Nr.	gasfraction noise $\frac{\sigma}{\lvert F_I - F_{A,0} \rvert}$			
	0%	1%	2%	5%
1	0.78	0.78±0.02	0.80±0.10	0.79±0.59
2	3.16	3.16±0.02	3.16±0.04	3.16±0.10
3	3.35	3.35±0.05	3.41±0.11	3.35±0.17
4	4.65	4.63±0.07	4.65±0.09	4.65±0.33
5	2.41	2.40±0.03	2.41±0.07	2.45±0.14
6	1.80	1.82±0.03	1.83±0.05	1.90±0.14
mean	2.7	2.7 0.04	2.7 0.08	2.7 0.24
sd	1.3	1.3 0.02	1.3 0.03	1.3 0.19

show the results of the addition of noise with constant standard deviation to the gas-fraction signals of the measurements on the subjects. Table 4.5

TABLE 4.5: Mean and standard deviation of 40 EEV values in liters, calculated after contamination of the gas-fraction signal with Gaussian noise with constant coefficient of variation.

Nr.	Gasfraction noise COV			
	0%	1%	2%	5%
1	0.78	0.79±0.03	0.79±0.02	0.81±0.11
2	3.16	3.16±0.02	3.17±0.03	3.14±0.06
3	3.35	3.37±0.07	3.36±0.14	3.26±0.25
4	4.65	4.65±0.04	4.64±0.08	4.63±0.19
5	2.41	2.41±0.02	2.40±0.03	2.44±0.11
6	1.80	1.80±0.02	1.81±0.02	1.83±0.06
mean	2.7	2.7 0.03	2.7 0.05	2.7 0.13
sd	1.3	1.3 0.02	1.3 0.05	1.3 0.08

and the left side of figure 4.9 show the results of the addition of gas-fraction noise with a constant noise-to-signal ratio.

Delay misestimation. Table 4.6 shows for each of the recordings the

TABLE 4.6: EEV calculation in liters as a function of the delay time between the gas-fraction signal and the flow signal, if the delay time is not corrected for in the calculation.

Nr.	Delay (ms)								
	-40	-30	-20	-10	0	10	20	30	40
1	0.69	0.70	0.72	0.75	0.78	0.81	0.84	0.85	0.88
2	2.87	2.96	3.03	3.12	3.16	3.21	3.24	3.32	3.25
3	3.16	3.20	3.21	3.26	3.35	3.36	3.46	3.51	3.68
4	4.37	4.46	4.56	4.61	4.65	4.70	4.77	4.85	4.88
5	2.14	2.20	2.26	2.33	2.41	2.45	2.51	2.55	2.58
6	1.48	1.58	1.64	1.71	1.80	1.92	2.01	2.05	2.13
mean	2.45	2.52	2.57	2.63	2.69	2.74	2.80	2.85	2.90
sd	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.4

results of the EEV calculations on the signals of the subjects as a function of the difference between the estimated delay time that is used in the calculation and the actual delay time. The left panel of figure 4.10 shows the mean, the minimum and the maximum of the relative EEV errors of all the recordings as a function of the delay misestimation.

Influence of dynamic response limitation of the gas-fraction measuring device. Table 4.7 and the right part of figure 4.10 show the re-

TABLE 4.7: EEV calculations in recordings in which the gas-fraction signal has been filtered with gauss functions with different second moments.

Nr.	σ of filter (msec):					
	0	20	50	100	150	200
1	0.78	0.77	0.79	0.78	0.77	0.76
2	3.16	3.15	3.10	3.05	2.97	2.53
3	3.35	3.34	3.32	3.23	3.18	2.84
4	4.65	4.63	4.59	4.56	4.43	4.36
5	2.41	2.37	2.35	2.29	2.24	2.20
6	1.80	1.82	1.77	1.72	1.61	1.51
mean	2.69	2.68	2.65	2.60	2.53	2.37
sd	1.3	1.3	1.3	1.3	1.3	1.2

sults of EEV values calculated after filtering the gas-fraction signal with Gaussian functions with different values of the second moment σ. Dynamic response limitation of the gas-fraction causes generally an underestimation of the lung volume. However, when the gasfraction signal of

the patient recordings was convoluted with a Gaussian function with $\sigma = 50$ msec, causing a 10–90 step response of 125 msec, the calculated lung volume deviated less than 3%. When $\sigma = 20$ msec, the deviations were less than 2%

Solubility of the indicator gas. Table 4.8 shows the result of the combined argon wash-out–SF_6 wash-in measurements on 7 subjects. The lung volume, calculated with the Ar signal was on average 4% larger than the volume calculated with the SF_6 wash-out. The maximum difference was 15% in an emphysema patient and the minimum was -6% in the cystic fibrosis patient. In the patient-equivalent mathematical models the mean of the difference was also 4%.

Metabolic rate. In table 4.9 the lung volumes, calculated with and without correction of the metabolic gas uptake from the SF_6 wash-in of the 7 subjects are compared. When not corrected for, the metabolic gas uptake causes in these subjects an underestimation of the lung volume between 0.12 l and 0.3 l. The mean of the under-estimations was 0.2 l or 6%.

TABLE 4.8: Results of combined SF_6 wash-in and Ar wash-out

Subj.	description	Measured			Diff. Ar/SF_6	
		V_L	$V_T - V_D$	τ	Act.	Model
		l	l	s	%	%
m1	Healthy male	4.88	0.66	5.2	+5	4
m2	Emphysema	4.48	0.44	3.1	−3	3
m3	Cystic fibrosis	2.88	0.38	3.6	−6	5
m4	COPD	3.30	0.31	3.3	+7	5
m5	Emphysema	2.56	0.69	5.1	+15	4
m6	COPD	3.35	0.73	5.3	+2	4
m7	COPD	2.09	0.40	4.3	+7	6
mean		3.4	0.5	4.3	+4	4
sd		1	0.2	0.9	+7	1

V_L Lung volume measured with SF_6 wash-in.
$V_T - V_D$ Mean effective tidal volume (difference between tidal volume and Bohr dead space
τ Mean duration of the breath cycle.
Diff. Ar/SF_6 Relative difference of lung volume calculated from Ar wash-out to lung volume calculated from SF_6 wash-in.
Act. Relative difference measured in actual wash-out test.
Model Relative difference found in mathematical model with the same V_L, effective tidal volume and τ as the subject.

TABLE 4.9: Result of volumes regression calculation before and after application of correction of metabolic gas uptake in SF_6 wash-in on 7 subjects.

subj.	V_L		
	raw	corr.	diff.
	l	l	%
m1	4.76	4.88	−2
m2	4.24	4.48	−5
m3	2.74	2.88	−5
m4	3.01	3.30	−9
m5	2.41	2.56	−6
m6	3.21	3.35	−4
m7	1.87	2.09	−11
mean	3.18	3.36	−6
sd	1.01	1.00	3

raw: results before metabolic correction.
corr: result after metabolic correction.
diff: relative difference of raw result with respect to corrected result.

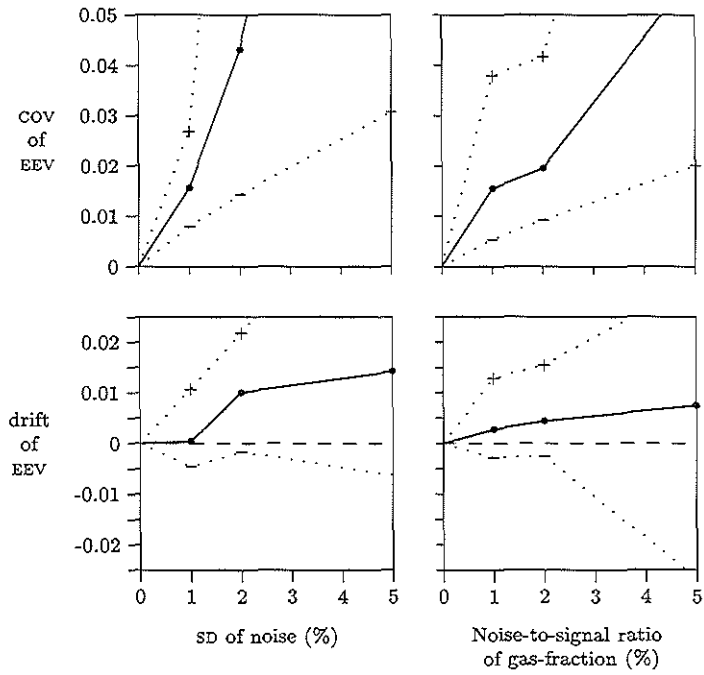

FIGURE 4.9: Influence of noise in the gas-fraction signal on the accuracy of the calculation of the lung volume. *Left:* coefficient of variation COV (top) and mean of the deviation (bottom) of the lung volume estimation due to addition of noise with uniform second moment to the flow signal. *Right:* coefficient of variation COV (top) and mean of the deviation (bottom) of the lung volume estimation due to addition of noise of which the second moment is a fraction of the gas-fraction signal itself. + symbols: Maximum; dots: mean; −: minimum COV/drift

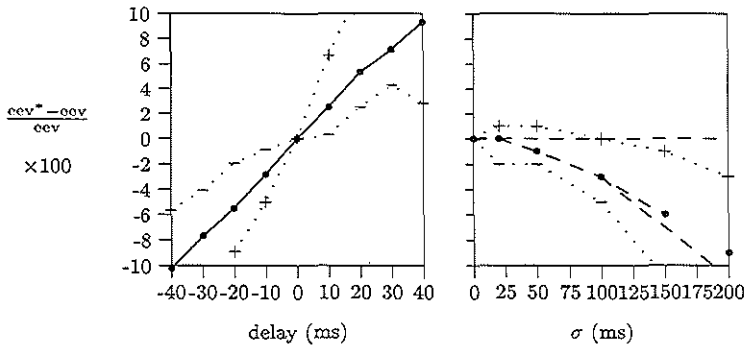

FIGURE 4.10: Relative misestimation of EEV due to misestimation of gas-sample delay (left) or due to dynamic response limitation of the gas-fraction measuring device (right). + symbols: Maximum; dots: mean; −: minimum deviation

Discussion

We analysed the effect of several error sources in wash-out tests on the estimation of the end-expiratory lung volume. Two techniques have been used for these estimations. The effects of signal noise, misestimation of the delay of the gas-fraction signal and the dynamic response limitation of the gas-fraction measurement device have been estimated by modification of the signals of actual wash-out tests in the same fashion as the error sources would do and comparison of the lung volume calculations with and without the modifications. The recordings chosen for these tests are representative for a wide range of illnesses and circumstances in adult subjects with normal lungs, extremely stiff lungs (subject 6) and extremely compliant lungs with inhomogeneous ventilation (subject 3). The effects of solubility of the indicator gas in blood and of metabolic gas exchange have been simulated in a mathematical model of indicator gas wash-out.

Time delay and mass-spectrometer response

Misestimation of the delay between the flow and the gas-fraction measurement is potentially the most important source of inaccuracy. A misestimation of only 10 ms gave rise to a relative error of up to 7% (or an absolute error of up to 120 ml) of the lung volume measurement. In the standard sample capillary that we use with our mass spectrometer a delay change of 10 ms can be caused by a CO_2 fraction of 15%, an inspiratory oxygen fraction of 40% instead of 20% or a pressure difference of 3 kPa. Brunner [10] analysed the effect of delay time variations on the calculations of multiple breath nitrogen wash-out tests and found that the changes in gas composition during the wash-out caused an error in the lung volume calculation of up to 17%, using a sample capillary with a delay time of 757 ms and replacing air by an argon-oxygen mixture during the wash-out. Our results, obtained with a shorter capillary, comply with these findings. Boutellier et al. [7] studied the effect of gas-fraction delay variations on metabolic rate measurements and found that a delay misestimation of 100 ms could cause errors up to 100% in subjects having breathing patterns with extremely fast onsets of the expiratory phase as seen in exercise.

It is clear that delay misestimation can be an important source of error and that steps have to be taken to reduce its influence. The best precaution is to use part of the tubing of the wash-out device itself as a measuring chamber, e.g. by measuring the indicator gas-fraction by infra-red absorption near the mouth of the subject. Unfortunately, although flow-through infra-red devices for measurement of SF_6 have been

used [55, 27], they are not yet generally available. Problems of these devices include poor signal-to-noise-ratio due to a small optical pathway of the infra-red light beam [11]. If sample capillaries have to be used, they should be as short as possible, in order to make the delay time as short as possible. The composition of the inspiratory gas should be as constant as possible, i.e. the variation of the indicator gas-fraction should be small. The influence of elevated inspiratory oxygen fractions on the delay time should be accounted for. During mechanical ventilation the increased pressure during inspiration will reduce the delay time. However, unless the subject is ventilated with an extremely high positive end-expiratory pressure, the pressure is only high in the course of the inspiration and at the very beginning of expiration. In these periods the gas fraction is constant, and equal to the inspiratory fraction, and the delay misestimation has no effect on the calculation of the displaced volume. In devices where the pressure at the outlet of the capillary is much lower than atmospheric pressure, the delay varies proportionally with the absolute pressure near the mouth of the subject. This is the case for mass spectrometers. However, devices like infra-red meters require relatively high pressures in their measuring chambers, and the measurement delay is for these devices more sensitive for pressure variations. The variability can however be reduced by connecting the outlet of the sample pump to the respiration system, so that both the inlet and the outlet of the sampling system feels the same pressure.

The limited dynamic response of the mass spectrometer turns out to have only a minor effect on the accuracy of the lung volume measurement. The 10–90% response time of mass spectrometers is usually well below 100 ms, causing an inaccuracy of the lung volume calculation of well below 2%.

Noise

The influence of flow noise on the EEV measurements is very limited. Even a signal-to noise ratio of as low as 10 causes an inaccuracy of the EEV calculation of much less than 1%. If the strength of the noise in the flow signal is independent of the amplitude of the signal, then the contribution of the flow noise in the inaccuracy of the EEV calculation will be below 1% if the standard deviation of the noise is below 20 ml/sec. The insensitivity of the calculation for the noise level of the flow signal can be expected from the fact that only the integral of the product of the flow and the gas-fraction is used in the lung-volume calculation and that integration smoothes out noise. However, the inaccuracy of the lung volume determination increases disproportionally for noise levels of more than approximately 50 ml/s. This is because the noise causes errors in

the determination of the times at which the inspirations and expirations start. We conclude that under normal circumstances flow noise does not contribute significantly to the inaccuracy of the measurement.

The influence of noise in the gas-fraction signal on the EEV calculation is much larger than that in the flow-signal. This is because in equation 4.2 the flow is only integrated in the numerator, whereas the gas-fraction signal is also used to determine the dilution of the indicator gas (in the denominator) which involves subtraction of two gas-fraction values. It should however be possible to change the gas-fraction calculation and make it less vulnerable to noise (currently the end-expiratory gas-fraction is determined as the mean of the last three gas-fraction samples of the expiration, but it could also be computed by a kind of fitting technique). In our mass-spectrometer the noise level of the Ar signal when sampling air is smaller than 0.015%. Table 4.5 shows that the accuracy of the calculation of the lung-volume from the wash-in test (recording nr. 3) is more vulnerable for the presence of gas-fraction noise with a constant coefficient of variation than the calculation from a wash-out test. This can be expected because in a wash-out test the indicator gasfraction, and thus the noise level, has low values most of the time whereas the reverse is true in a wash-in test.

Solubility of the indicator gas

In the combined argon wash-out/SF_6 wash-in measurements the mean of the differences between the lung volume calculated with both methods was 4%. A large difference of 15% (0.4 l) was found in subject 5. It is possible that this patient who suffered from pulmonary emphysema, had compartments in his lungs in which the ventilation took place predominantly by diffusion. In that case the low diffusion coefficient of SF_6 can cause an under-estimation of the actual lung volume. If subject 5 were excluded the mean difference between the lung volume calculated with argon and SF_6 would be 2%. The difference between the lung volumes measured with argon and SF_6 are not significant ($p > 0.05$ with Wilcoxon test), but this is probably due to the small number of measurements. The model simulations predicted a mean difference of 4%. The model simulation might be not completely representative for critically ill subjects in whom the cardiac output is larger than in healthy subjects. However, those patients the indicator gas uptake will often be limited due to ventilation-perfusion mismatch and enhanced recirculation because the non-vital organs will often be less perfused. In conclusion, due to the fact that perfusion of the body organs is very unevenly distributed, recirculation will reduce the uptake or release of indicator gas by the blood. The solubility of argon can cause an over estimation of the lung volume

of less than 5%. When gases like helium or SF_6 are used the effects of indicator gas uptake by the blood are negligible.

Metabolic gas exchange

Our results show that, if no correction for the metabolic gas uptake is made, a mean under-estimation of the lung volume of 0.18 l or 6% would result in our SF_6 wash-in tests. The metabolic gas exchange has no influence on the calculation of an indicator gas wash-out with $F_I = 0$. Therefore, if the metabolic gas-fractions can not be measured, it is better to analyse the wash-out tests ($F_I = 0$) only.

The accuracy of our measurement set-up

In our set-up the accuracy is limited by the noise levels of the gas-fraction and flow signal, the accuracy of the delay measurement and the solubility of the indicator gas in tissue. If the delay can be estimated to an accuracy of ± 10 ms, it causes a systematic error that is well below 10%. We measured an error of 7% (120 ml) after the addition of 10 ms extra delay in the gas-fraction signal of recording 3. In the other recordings the error was much smaller.

Our mass spectrometer has a signal-to noise ratio for helium that is better than 50 (figure 4.2). We found that this signal-to-noise ratio caused a standard deviation of the calculated lung volume of better than 100 ml and a coefficient of variation of better than 3% in a true wash-out ($F_I = 0$). If $F_I > 0$, then for most of the wash-out the gas-fraction signal is nearly equal to F_I. In the case of helium wash-in with $F_I = 0.02$, the noise level is 1% of $F_I - F_{A,0}$ and then deviations of the lung volume measurement are better than 100 ml and coefficient of variation values are better than 2% (table 4.4). In summary, the accuracy of our system is better than 10% or 200 ml when helium or SF_6 is used as indicator gas, and when the inspiratory oxygen fraction has been taken into account in the calculation of the delay.

Appendix: Theoretical model of a wash-out process, and the influence of the error sources on this model.

In this appendix a simple, one-compartmented, model of the wash-out process of the lungs is presented. The model incorporates tissue wash-out. The lung model consists of a simple alveolar compartment with volume V_L that contains gas with a homogeneous composition. This compartment is ventilated with a constant tidal volume V_T. When the wash-out starts the indicator gas fraction in the lung is equal to $F_{A,0}$

and during the wash-out the inspiratory gas-fraction is equal to F_I. In the absence of leakage or interaction with pulmonary capillary blood the alveolar indicator gas-fraction at the end of breath-cycle $i+1$ (upon wash-out) can be calculated from the alveolar gas-fraction of the previous breath. The partial volume of indicator gas at the end of inspiration number $i+1$ is equal to the sum of the partial volume that was present at the end of expiration i and the partial volume of indicator gas in the inspired tidal volume:

$$F_{A,i+1}(V_A + V_T) = F_{A,i}V_A + F_I V_T \tag{4.5}$$

$$F_{A,i+1} = \frac{V_A}{V_A + V_T}F_{A,i} + \frac{V_T}{V_A + V_T}F_I \tag{4.6}$$

The alveolar gas-fraction is a mono-exponential function of i. Substitution of

$$F_{A,i} = F_I - (F_I - F_{A,0})e^{-\gamma i} \tag{4.7}$$

into equation 4.6 results in:

$$\gamma = -\ln\left(\frac{1}{1+\frac{V_T}{V_A}}\right) \tag{4.8}$$

Substitution of equation 4.7 into equation 4.2 shows that the lung volume estimations EEV^*_n are all equal to V_A, independent of n.

In our model the relationship between the breath number n and w can be calculated. Substitution of equation 4.7 into

$$w(n) = \frac{F_{A,0} - F_{A,n}}{F_{A,0} - F_I} \tag{4.9}$$

results in:

$$w(n) = 1 - e^{-\gamma n} \tag{4.10}$$

$$n = \frac{-\ln(1-w)}{\gamma} \tag{4.11}$$

Tissue wash-out The partial volume of indicator gas that washes out of an organ into the lungs can be calculated as follows: Suppose an organ has a volume of V_o, with an indicator gas solubility of S_o vol/vol/Bar. The perfusion flow of the organ is denoted as Q_o and the solubility of the indicator gas in the blood as S_b. F_T is the quotient of the indicator gas volume that is stored in the tissues of the organ and the gas volume that can be stored when the nitrogen pressure is equal to 1 B (tissue

fraction). Diffusion limitation in the transport of indicator gas from the tissue to the blood is neglected. F_a is the fraction of the indicator gas in the blood. The flow of indicator gas from the blood to the tissue is given by:

$$\dot{V}_T(t) = Q_o S_b \left[F_a(t) - F_T(t)\right] \tag{4.12}$$

Since $V_T = V_o S_o F_T$, the rate of change of the tissue indicator gas-fraction is equal to:

$$\dot{F}_T(t) = \frac{Q_o S_b}{V_o S_o} \left[F_a(t) - F_T(t)\right] \tag{4.13}$$

If at time $t = 0$ the input F_a changes step-wise from 0 to 1, then the tissue fraction responds as

$$F_T(t) = 1 - e^{-\Gamma t} \tag{4.14}$$

with $\Gamma = Q_o S_b / V_o S_o$. The indicator gas volume that is taken up by the organ after the step input is:

$$\dot{V}_T(t) = \dot{V}_{T0} e^{-\Gamma t} \tag{4.15}$$

with $\dot{V}_{T0} = Q_o S_b$.

Table 4.10 lists for several organs the values of $\dot{V}_0$ and Γ as we

TABLE 4.10: Theoretical unit step response parameters of nitrogen elimination from several organs of a man of 70 kg with cardiac output of 5.98 l/min. (after Robertson [80]

organ	$\dot{V}_0$ ml/s	Γ s^{-1}
lung	1.04	0.0800
liver, spleen, pancreas and intestines	0.31	0.0023
kidneys	0.25	0.0798
muscle	0.20	0.0003
brain	0.14	0.0083
bone marrow	0.09	0.0025
connective tissue	0.07	0.0010
thyroid	0.04	0.0067
heart	0.03	0.0064
fat	0.02	0.0001
skin	0.02	0.0003
adrenal glands, testes, prostate	0.02	0.0153

have recovered them from the data of Robertson et al [80]. An estimation

of the parameters $\dot{V}_o$ and Γ for other gases can be made by scaling up, using the quotient of the solubility of the other gas and the solubility of nitrogen.

To estimate the volume of indicator gas that is washed out of the organ during a breath cycle it is assumed that the indicator gas-fraction in the arterial blood entering the organ during the breath cycle is equal to the end-expiratory breath-cycle of the previous breath. If the tissue fraction at the begin of breath-cycle i (at time t_i) is denoted as x_i, then

$$F_T(t) = F_{A,i-1} - (x_i - F_{A,i-1})\, e^{-\Gamma(t-t_i)} \tag{4.16}$$

where $F_{A,i-1}$ denotes the alveolar gas-fraction at the end of the previous breath and t_i the time at the begin of the current breath-cycle. Thus:

$$x_{i+1} = F_{A,i-1} - (x_i - F_{A,i-1})\, e^{-\Gamma(t_{i+1}-t_i)} \tag{4.17}$$

The volume of indicator gas released by the organ during the breath-cycle is equal to:

$$\Delta V_i = V_o S_o (x_i - x_{i+1}) \tag{4.18}$$

$$= \frac{\dot{V}_{T0}}{\Gamma}(x_i - x_{i+1}) \tag{4.19}$$

Assuming that the partial pressure of the indicator gas in the arterial blood is equal to the partial pressure in the alveolar space ($F_a = F_A$) the alveolar gas-fraction at the end of breath-cycle $i+1$ ($F_{A,i+1}$) can be calculated from the gas fraction during breath-cycle i as

$$F_{A,i+1} = \frac{V_A}{V_A + V_T} F_{A,i} + \frac{V_T}{V_A + V_T} F_I + \frac{\sum_{j=i}^{k} \Delta V_{ji}}{V_A + V_T} \tag{4.20}$$

where ΔV_{ji} denotes the partial volume of indicator gas that is released by organ nr. j during breath cycle i. ΔV_{ji} is calculated according to equation 4.19, assuming that all breath cycles have the same duration τ. The model consists of a compartment with a volume V_L that is ventilated with a tidal volume V_T. Each breath-cycle has a duration of τ.

Chapter 5

A sensitive ventilation inhomogeneity index from multiple breath indicator gas wash-out tests, applied in mechanically ventilated patients[1]

P.E.M. Huygen, I. Gültuna, C. Ince, A. Zwart, J.M. Bogaard, B.W.A. Feenstra and H.A. Bruining

Abstract

Objectives: a) To determine the validity of a new method to analyze indicator gas wash-out tests on mechanically ventilated patients. This method takes into account the difference between the end-expiratory gas fraction and the mean fraction in the lung and provides the end-expiratory lung volume and a new index of ventilation inhomogeneity called *volumes regression index*. b) To determine the validity of this index as a predictor of chronic pulmonary disease. c) To compare this index with the moment ratio index and the Becklake index.
Design: Prospective study of diagnostic test. Criterium standards: Closed-circuit indicator gas dilution technique and Tiffeneau index.
Setting: Surgical Intensive Care Unit of a University Hospital.
Patients: A total of 38 mechanically ventilated post-operative patients, divided into two groups: the obstructive group ($n = 21$) and the non-obstructive group ($n = 17$), based on their pre-operative lung function.
Interventions: None.
Measurements and Main Results: a) The mean coefficients of variation of all lung volume measurements in a group of nine healthy volunteers was 5% and the difference between this technique and the closed circuit He dilution measurements was $-2 \pm 5\%$. In patients, the mean coefficient of variation of the lung volume measurements was 3.5%. The volumes regression index was measured as 0.02 ± 0.04 in a dummy lung, 0.37 ± 0.08 in the healthy volunteers, 0.64 ± 0.23 in the non-obstructive patients and 1.1 ± 0.3 in the obstructive patients. The volumes regression index provided a better correlation ($r^2 = 0.46$) with pre-operatively determined Tiffeneau index than the Becklake index ($r^2 = 0.11$) or Moment ratio index ($r^2 = 0.18$).
Conclusions: The volumes regression technique provides a means for accurate

1. *Crit Care Med* **21**(*1993*):*1149–1158*

measurement of the end-expiratory lung volume and the amount of ventilation inhomogeneity in mechanically ventilated ICU patients.

Introduction

Assessment of the pulmonary status of mechanically ventilated patients is generally limited to physical examination, chest radiology, pulse-oximetry and blood gas analysis. Recently, several methods have been described to measure the end-expiratory volume (EEV) in the lungs during mechanical ventilation by multiple breath indicator gas wash-out tests [52, 56, 27, 30, 48, 42]. The end-expiratory lung volume is an important parameter to determine the optimal end-expiratory pressure during mechanical ventilation with Positive End-Expiratory Pressure (PEEP) [29]. However, in many cases e.g. in COPD patients more information about the ventilation process is desirable to determine the optimal ventilation setting. One factor that can reduce the efficiency of the ventilation process is ventilation inhomogeneity, especially if the ventilation inhomogeneity is not matched by perfusion. Therefore, a simple test to quantify the amount of ventilation inhomogeneity benefits the assessment of the severity of existing lung disease and the efficacy of the mechanical ventilation.

Several methods to derive ventilation inhomogeneity from washout tests have been developed [36, 39]. Attempts have been made to recover a continuous [41, 59, 69] or discrete [38, 46, 87] distribution of specific ventilation-to-volume ratios. This sometimes mathematically sophisticated approach can be useful in physiological research, but has some difficulties concerning complex computations, non-unique fittings and sensitivity for experimental error [58], that makes it less suitable for clinical use. Therefore, simplified tests were designed, based on the decreasing rate of the decay of the end-expiratory indicator gas caused by the ventilation inhomogeneity [3, 5, 77, 94]. The disadvantage of these methods is that the obtained indices depend on tidal volume and on variations of tidal volume and lung volume during the washout process. Moreover, the latter methods use only one point from the wash-out curve and therefore do not utilize the information contained in the entire wash-out curve. A practical disadvantage of most of the techniques for use in the Intensive Care unit is that they need a relatively long wash-out period (up to 15 minutes [5]). Recently Crawford et al [16, 15] elaborated one of the methods [19] and measured breath-by-breath the ratio of the amount of indicator gas actually washed out and the amount that should be washed out in a perfect ventilating lung. This method is potentially interesting for physiological investigation but is critically dependent of

the determination of the dead space, therefore also on breath-by-breath tidal volume variations. Zwart [95] developed a qualitative measure of ventilation inhomogeneity by a breath-by-breath reconstruction of the relation between the end-expiratory gas-fraction and the mean indicator gas-fraction in the lung. Although offering significant improvement over previous methods, the method is not quantitative or standardized. Saidel et al. [82] proposed a model-free method, based on a mathematical analysis of the breath-by-breath end-expiratory fractions as a function of the cumulative amount of gas inspired from the beginning of the wash-out (moment analysis) [36, 35]. However, this method does not take into account the fact that the rate of the wash-out process decreases as time elapses. Each wash-out breath has the same weight in the calculated index, although the amount of gas washed out per breath decreases during the wash-out. In the present study, we propose a new index, the volumes regression index S, that is based on the difference between the end-expiratory measured indicator gas-fraction and the mean indicator gas-fraction over the lung. The difference is caused by ventilation inhomogeneity. This new method accounts for the decreasing rate of the wash-out of the indicator gas, also providing a best estimate of the lung volume, and provides an index that is sensitive for ventilation inhomogeneity. This index was measured in normal subjects and in mechanically ventilated patients with varying degree of obstructive pulmonary disease.

Materials and methods

Measurement set-up: Figure 5.1 shows the measurement set-up. The subject is ventilated by a ventilator (Servo 900B, Siemens-Elema, Solna, Sweden). The ventilator obtains the oxygen-air mixture from an indicator gas injector [48], that provides a stepwise change in the indicator gas-fraction. The indicator gas used was argon, with a fraction of 2%. The respiratory flow was measured by a Fleisch nr. 2 pneumotachograph (SensorMedics, Bilthoven, The Netherlands) connected to a pressure transducer (MP45-14-871, Validyne, Northridge, CA). A mass spectrometer (MGA3000, CASE, Biggin Hill, UK) measured the fractions of the indicator gas and of the metabolic gases oxygen and CO_2. Flow and gas-fraction signals were sampled at a rate of 100 Hz and analyzed off-line by a computer (PDP-11, DEC, Maynard, MA).

Analysis and lung volume calculation: The computer program for analysis of the multiple-breath wash-out test has been described elsewhere [49].

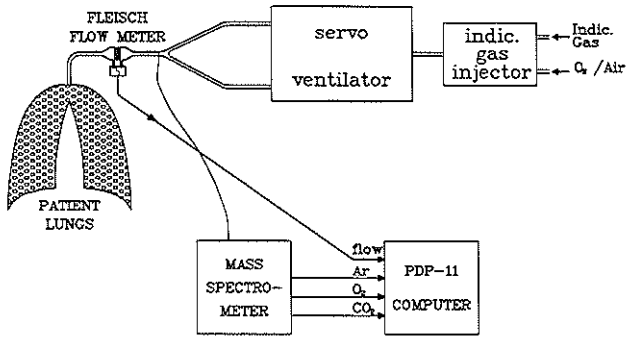

FIGURE 5.1: Measurement set-up. The indicator gas injector provides a constant flow of air/oxygen mixture to which a constant flow of one out of two indicator gases can be mixed. Immediately stopping of the indicator gas injection causes a wash-out process. The gas-fractions are continuously measured by a mass spectrometer, and the respiratory flow by a Fleisch pneumotachograph. The output signals are sampled by a computer and stored for off-line analysis.

It detects the beginning and end of sequential inspirations and expirations and calculates breath by breath inspired and expired tidal volume, end-expiratory indicator gas-fractions, and flow-weighted mean inspiratory and expiratory gas-fractions. To calculate the end-expiratory lung volume from indicator gas wash-out curves a modified approach of the algorithm of Zwart [95] was used [49]. This method is based on the relation between the net amount of indicator gas washed out from the lung and the alveolar dilution caused by this indicator gas-transport. The alveolar dilution of the indicator gas is estimated as the difference between the indicator gas-fraction before the start of the wash-out and the end-expiratory gas-fraction (see appendix). Ventilation inhomogeneity causes an enhanced discrepancy between the end-expiratory and the mean alveolar gas-fraction (F_{EE} resp. F_A). This methodology is the basis for the volumes regression method. At the end of the wash-out, when nearly all of the indicator gas has been washed out, the influence of the dilution misestimation on the end-expiratory lung volume is negligible. However, at earlier moments, when less indicator gas has been washed out, the difference between F_{EE} and F_A will have influence on the end-expiratory lung volume estimations. Thus, the course of the subsequent end-expiratory lung volume estimations reveals information about the difference between F_{EE} and F_A and hence about ventilation inhomogeneity. Figure 5.2A shows an example of the breath-by-breath end-expiratory lung volume estimations as a function of breath number. Initially, the end-expiratory lung volume is largely underestimated

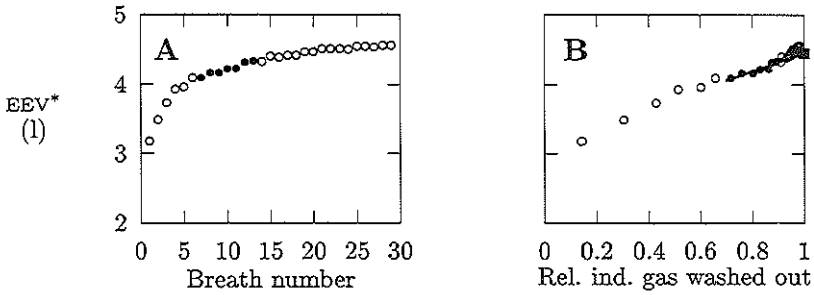

FIGURE 5.2: Breath-by-breath end-expiratory lung volume estimations. A: Plotted against breath number or time, the breath-by-breath estimated end-expiratory lung volume seems to approach, after initial under-estimation, a stable situation. B: Plotted against w, the estimated end-expiratory lung volume increases monotonously. An accurate value of the end-expiratory lung volume can be obtained by extrapolation of the regression line through the data in the range $0.7 < w < 0.9$ (filled circles) to $w = 1$ (filled square). The slope of this regression line is caused by an increasing discrepancy between the end-expiratory and the mean alveolar indicator gas-fraction. This means that the slope is sensitive for ventilation inhomogeneity, when this discrepancy is enhanced.

due to the difference between F_{EE} and F_A. In the course of the wash-out the end-expiratory lung volume estimations approximate the actual end-expiratory volume of the lung in an asymptotic fashion. The asymptotic character is not caused by the development of a steady-state situation in which the estimation of the end-expiratory lung volume does not change systematically, but by the decrease of the rate of the wash-out process. During the wash-out, the amount of indicator gas that is removed from the lung per breath decreases. This circumstance causes a decrease in the breath-by-breath variability of the end-expiratory lung volume estimations, which gives an impression of the development of a steady-state situation in which sequential end-expiratory lung volume estimations are constant. In order to take the effect of the decreasing rate of wash-out into account, we introduce to plot the breath-by-breath EEV_k^* estimations

against the amount of indicator gas washed out, relative to the amount of indicator gas originally present (w, estimated as $(F_0 - F_{EEk})/F_0$). In figure 5.2B, the same breath-by-breath end-expiratory lung volume estimations as in figure 5.2A are plotted as a function of the relative amount of indicator gas washed out of the lung. The figure shows a monotonous increase in the estimated end-expiratory lung volume, whereas in figure 5.2A the asymptote is difficult to assess. In order to get an optimal estimation of the end-expiratory lung volume the regression line through the EEV vs. w data for $0.7 < w < 0.9$ is drawn and extrapolated to $w = 1$ (the volumes regression method). The EEV belonging to $w = 1$ is denoted as EEV_e^*, the best estimation of the end-expiratory lung volume. The slope of this regression line (caused by the discrepancy of the end-expiratory indicator gas-fraction (F_{EEk}) over the mean gas-fraction in the lungs (F_{Ak})), normalized by division by EEV_e^*, provides a measure for ventilation inhomogeneity, and is denoted as the volumes regression index S.

Validation: To assess the sensitivity of the volumes regression index S with respect to the ventilation inhomogeneity that accompanies obstructive pulmonary disease, we made correlations between the volumes regression index and (pre-operatively determined) Tiffeneau index in post-operative, mechanically ventilated patients. We compared our index with two accepted inhomogeneity indices: the Becklake index [3] and the quotient of the first and zero^{th} moment of the wash-out curve (M_1/M_0, the moment ratio index [82]), both modified according to the method of Felton et al. [35], in order to allow for a non-stepwise transition of the indicator gas at the beginning of the wash-out process. To compare the three ventilation inhomogeneity indices Volumes regression index, Becklake index and moment ratio index with each other we determined their relationship with Tiffeneau index (i.e. quotient of forced expiratory volume in one second (FEV_1) and vital capacity) in post-operative, mechanically ventilated patients.

To test the accuracy of the present method in measuring the end-expiratory lung volume 16 consecutive wash-in/wash-out tests were performed on a dummy lung (Dräger, Lübeck FRG), ventilated in intermittent positive pressure ventilation (IPPV) mode with a rate of 10 breaths per minute and a tidal volume of 1 l. Next, in 9 healthy volunteers, lung volume measurements were performed with the volumes regression method, and the results were compared with a standard closed circuit helium dilution test (EEV_c) [75]. For the wash-out test the subjects were instructed to allow themselves to be ventilated as passively as possible via a mouth-piece (nose closed by a clip). The (seated) subjects were

ventilated in the IPPV mode. The ventilation rate and tidal volume were set in a manner comfortable to the subjects (the range was between 8 and 13 l/min with frequencies between 9 and 12 cycles per minute). Four wash-in followed by wash-out tests were performed on each subject. Since the inspiratory tidal volume is constant during IPPV, variations of the expired tidal volume equal variations of the end-expiratory lung volume. To avoid these breath-by-breath end-expiratory lung volume variations, the data from tests in which the standard deviation of the expired tidal volumes exceeded 100 ml were discarded. The lung volume measurement in relaxed state that is obtained from this procedure is denoted as EEV_o.

Patients: Wash-out tests were performed in 38 post-operative intensive care patients who had undergone a standard pre-operative lung-function test in which the Tiffeneau index had been determined. FEV_1 and Tiffeneau index are the best clinical criteria for obstructive pulmonary diseases. Because these patients had not undergone detailed lung function studies, only these indices were chosen as measure for the impairment of lung mechanics. The measurements were approved by the Medical Ethical Committee of the University Hospital of Rotterdam. The Committee judged informed consent not necessary because the measurements were done during routine lung volume measurements that were needed for optimal ventilation support. 17 of the 38 patients had Tiffeneau index values that were more than two standard deviations lower than their reference value [78], indicating the existence of obstructive pulmonary disease. The remaining 21 patients had Tiffeneau values larger than their reference value minus two standard deviations and were thus classified as "non-obstructive". All patients were ventilated in the IPPV mode. As with the volunteers each patient underwent four measurements, each one consisting of a wash-in followed by a wash-out test. A Wilcoxon test was used to determine whether the three indices volumes regression index, Becklake index and moment ratio index differed significantly between the non-obstructive and the obstructive group.

Results

Dummy lung measurements: The mean and standard deviation of the EEV values calculated from the 16 dummy lung measurements were 3.04 ± 0.01 l, whereas with the helium dilution method 3.05 ± 0.01 l was measured. The mean and standard deviation of the volumes regression index S was 0.02 ± 0.04.

TABLE 5.1: End Expiratory lung volume and Volumes regression index, measured in healthy volunteers.

subj.	age [yr]	lth [m]	EEV_c [l]	EEV_o [l]	sd [l]	S	sd
1	51	1.77	2.71	2.67	0.12	0.42	0.11
2	42	1.72	3.37	3.26	0.31	0.38	0.12
3	35	1.92	4.46	4.73	0.22	0.37	0.08
4	30	1.73	2.61	2.37	0.06	0.34	0.04
5	24	1.91	4.52	4.43	0.36	0.30	0.09
6	28	1.79	3.40	3.65	0.20	0.28	0.21
7	31	1.72	2.62	2.52	0.22	0.51	0.12
8	51	1.70	2.32	2.26	0.09	0.49	0.08
9	29	1.70	3.15	3.36	0.14	0.29	0.04
Mean			3.2	3.2	0.19	0.38	0.10
sd			0.8	0.9		0.08	

Explanation of abbreviations:
EEV_c EEV, measured with the closed helium dilution technique.
EEV_o EEV, measured with the volumes regression technique.
S Volumes regression index.

Healthy volunteers: The results of the measurements on the nine healthy volunteers are listed in table 5.1. The observed intra-individual coefficients of variation of the lung volume measurements were less than or equal to 10%. They had a mean value of 5%. The largest range was measured in subject 2, from -11% to $+18\%$ of the mean value. Figure 5.3 shows the differences of the EEV measured using the volumes regression method and the EEV using the helium dilution test. The mean of the differences equaled $-2 \pm 5\%$. The inter-individual mean value of S equaled 0.37 ± 0.08. The mean intra-individual standard deviation of S equaled 0.10.

Patients: The results of the measurements on the 21 non-obstructive patients are listed in table 5.2 and gave a mean volumes regression index of 0.6 ± 0.2. The 17 obstructive patients (table 5.3) had a mean volumes regression index of 1.1 ± 0.3. In 12 patients the moment ratio index could not be determined because insufficient time was available for the wash-out process to reach the required turn-over rate of eight [83]. In the tables 5.2 and 5.3 the mean and standard deviations of the lung-function parameters are calculated for all patients and for the group of patients with known moment ratio index only (denoted as "sub-group"). The volumes regression index, Becklake index and moment analysis index

TABLE 5.2: Results of measurements on the non-obstructive patients.

N/sx	age [yr]	lth [m]	$\frac{EEV}{ref}$ [%]	FEV_1 [L]	VC [L]	Ti_r [%]	S	BI	$\frac{M_1}{M_0}$
1/M	62	1.73	41	1.4	1.6	118	0.85±.14	6.9±.3	2.48±.05
2/F	48	1.59	67	2.9	3.5	103	0.47±.11	5.1±.2	1.84±.12
3/F	41	1.54	25	1.7	2.0	102	0.22±.08	5.8±.3	2.03±.03
4/M	61	1.57	45	2.5	3.3	100	0.53±.22	5.5±.2	2.02±.07
5/M	76	1.65	62	2.8	3.7	100	0.74±.05	5.5±.2	2.05±.06
6/M	63	1.80	53	2.7	3.6	100	1.13±.10	6.0±.2	2.20±.00
7/M	68	1.71	61	3.3	4.4	99	0.36±.08	4.8±.1	1.63±.06
8/M	67	1.67	50	2.4	3.3	98	0.53±.12	5.2±.2	1.78±.08
9/M	35	1.83	57	1.4	1.7	98	0.66±.08	6.3±.2	2.24±.09
10/M	69	1.67	47	1.6	2.3	95	0.79±.04	6.1±.2	2.11±.10
11/M	64	1.85	89	3.2	4.5	93	0.62±.08	5.6±.0	
12/F	57	1.50	43	0.9	1.3	91	0.32±.13	4.9±.2	2.02±.13
13/F	49	1.61	57	2.4	3.3	90	0.77±.03	5.5±.4	1.87±.13
14/M	54	1.68	67	2.9	4.2	90	0.47±.11	5.1±.2	
15/M	77	1.78	44	2.7	4.1	90	0.80±.07	6.4±.4	2.15±.05
16/F	58	1.57	64	1.2	1.7	90	0.54±.10	5.0±.1	1.68±.01
17/M	64	1.82	52	2.2	3.2	89	0.57±.17	5.9±.1	2.17±.07
18/F	75	1.59	45	2.1	3.1	89	0.47±.16	5.3±.3	1.91±.10
19/M	68	1.65	45	2.3	3.7	85	0.96±.09	6.2±.4	2.20±.05
20/M	66	1.74	42	2.0	3.2	84	1.03±.09	7.2±.0	2.20±.04
21/F	67	1.70	48	2.1	3.3	84	0.62±.05	5.7±.2	2.09±.06
Mean			53	2.2	3.1	95	0.6 .10	5.7 .3	
sd			13	0.7	1.0	8	0.2	0.6	
Mean sub-group			50	2.1	3.0	95	0.7 .10	5.8 .3	2.0 .07
sd			10	0.6	0.9	8	0.2	0.6	0.2

Explanation of abbreviations:

N/sx:	Identification and sex of the patient.
EEV/ref:	quotient of measured end-expiratory lung volume and reference value.
Ti_r:	quotient of measured Tiffeneau index and the reference value for the patient.
S:	volumes regression.
BI:	Becklake index.
M_1/M_0:	moment ratio index.
subgroup:	only patients with known M_1/M_0.

TABLE 5.3: Results of measurements on the obstructive patients.

N/sx	age [yr]	lth [m]	$\frac{EEV}{ref}$ [%]	FEV_1 [L]	VC [L]	Ti_r [%]	S	BI	$\frac{M_1}{M_0}$
22/F	46	1.58	39	2.3	3.5	82	1.02±.06	6.6±.3	2.27±.10
23/M	71	1.78	77	2.1	3.7	78	1.39±.09	7.0±.3	
24/M	73	1.75	47	1.5	2.6	76	0.70±.06	5.6±.2	1.99±.07
25/M	64	1.79	88	2.6	4.8	73	1.15±.09	5.9±.2	
26/M	57	1.72	78	2.2	4.0	72	0.94±.15	4.9±.4	
27/M	59	1.73	40	2.6	4.6	74	0.79±.05	6.2±.2	2.22±.03
28/F	66	1.72	92	1.3	2.5	67	1.13±.07	5.9±.2	
29/M	61	1.91	62	2.8	5.7	66	1.74±.17	6.2±.3	
30/M	52	1.73	99	1.6	3.2	66	0.76±.17	4.9±.2	
31/M	62	1.78	86	1.6	3.3	63	1.22±.08	6.2±.1	2.12±.10
32/M	75	1.75	90	2.0	4.3	62	1.38±.08	6.3±.2	
33/M	66	1.71	60	2.0	4.7	57	1.10±.12	6.9±.4	2.21±.15
34/M	67	1.85	50	1.1	2.8	50	0.92±.01	6.4±.2	2.50±.14
35/M	65	1.75	76	1.7	4.4	50	1.11±.07	6.4±.1	
36/M	67	1.75	70	1.5	4.3	46	1.18±.10	6.6±.4	2.42±.05
37/F	78	1.65	97	0.8	2.5	41	1.33±.09	6.6±.2	
38/M	72	1.65	103	0.7	2.6	34	1.17±.04	5.9±.2	
Mean			74	1.8	3.7	62	1.1 .09	6.1 .2	
sd			21	0.6	1.0	14	0.3	0.6	
Mean sub-group			56	1.8	3.7	64	1.0 .07	6.4 .3	2.2 .09
sd			17	0.5	0.9	14	0.2	0.4	0.2

Legends: see table 5.2

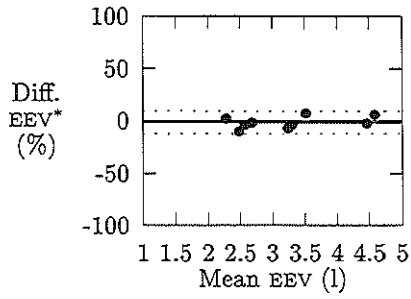

FIGURE 5.3: Comparison of EEV measurement methods. The EEV measured on healthy volunteers using the volumes regression method (EEV_o) is compared to that measured with a closed circuit helium dilution method (EEV_c). The relative difference (i.e. $200 \times (EEV_o - EEV_c)/(EEV_o + EEV_c)$) is plotted as a function of the mean value of the estimations ($(EEV_o + EEV_c)/2$) and shows that the differences are smaller than 10%. Thick line: mean of the differences; dotted line: mean±2sd of the measurements.

were higher in the obstructive than in the non-obstructive patients. The volumes regression index S, however, was more significantly correlated to the pre-operatively determined Tiffeneau index than the Becklake or the moment analysis index were ($p < 0.01$, $p < 0.05$ and $p < 0.05$ respectively). Figure 5.4 shows the ventilation inhomogeneity index as

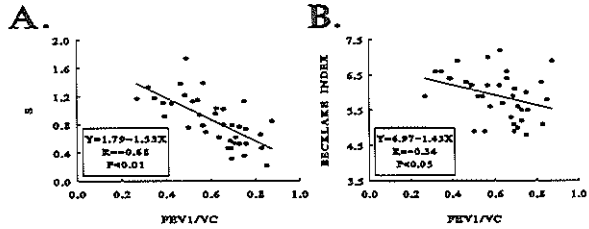

FIGURE 5.4: Ventilation inhomogeneity index S (A) and Becklake index (B) plotted as a function of Tiffeneau index. This figure shows that S is correlated more strongly to FEV_1 than the Becklake index.

a function of Tiffeneau index (correlation coefficient: $r^2 = 0.46$) and the Becklake index as a function of Tiffeneau index ($r^2 = 0.11$). Both volumes regression index and Becklake index are significantly correlated to the Tiffeneau index, but the volumes regression index more strongly

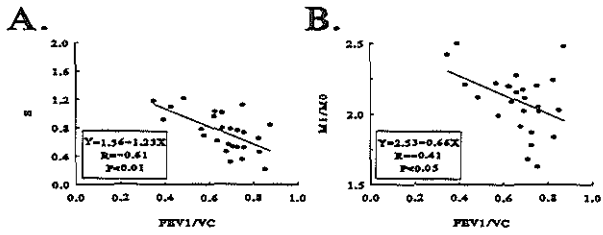

FIGURE 5.5: M_1/M_0 (part A) and S (of those patients of whom M_1/M_0 could be derived, part B) as a function of FEV_1/VC. The degree of correlation of S values to FEV_1 in the patients with available M_1/M_0 value is lower than the correlation of S and FEV_1 in the group of all patients, but still slightly better than the correlation of M_1/M_0 to FEV_1/VC.

than the Becklake index. Figure 5.5 shows, of the patients in whom the moment ratio index could be measured, the volumes regression index as a function of Tiffeneau index ($r^2 = 0.37$) and moment ratio index as a function of Tiffeneau index ($r^2 = 0.18$). The volumes regression index is stronger correlated with the Tiffeneau index than is the moment ratio index.

The reproducibility of the end-expiratory lung volume measurements is better than 6%, with a mean value of 3.5%. Tables 5.2 and 5.3 give the quotient of the measured end-expiratory lung volume and the reference value (FRC_{ref}, calculated according to length, weight, mass and sex of the subject [78]) of each patient is given. The end-expiratory lung volume tends to increase with a decreasing Tiffeneau index (correlation coefficient: 0.31). It is significantly higher for the patients with low Tiffeneau index than for those with normal Tiffeneau index ($p < 0.05$, determined with the Wilcoxon test). This finding is expected and demonstrates that the obstructive patients tend to hyperinflate due to the obstruction or due to accompanying loss of lung elasticity.

Discussion

A technique to calculate the end-expiratory volume of the lung and provide a measure of ventilation inhomogeneity from wash-out tests during mechanical ventilation is presented. We compared the determination of the end-expiratory lung volume by the wash-out technique with the closed volume helium rebreathing method in healthy subjects. The values obtained with both methods showed good agreement. The differences between the paired values were of the same order as the standard error of

the mean of repeated end-expiratory lung volume determinations, showing that both types of determination of the lung volume are compatible.

The reproducibility of the end-expiratory lung volume measurement by the volumes regression wash-out technique meets the European requirement of 10% [78]. The fact that the reproducibility in the patients, who are sedated and mechanically ventilated, is better than in the healthy subject suggests that a large part of the intra-individual variability in the latter group is not due to measurement inaccuracy but to actual variations of the end-expiratory lung volume caused by small changes in posture or tidal volume in the subjects. The advantage of the open-circuit wash-out measurement above the closed circuit procedure includes the facts that the wash-out procedure is easier to apply during mechanical ventilation and that the obtained data contain more information about the gas-exchange process. An important step in obtaining the high reproducibility of the end-expiratory lung volume calculation in the open-circuit wash-out measurements was our development of the volumes regression method, in which breath-by-breath estimates of end-expiratory lung volume are plotted as a function of the relative amount of indicator gas washed out. The low values of the end-expiratory lung volume in the mechanically ventilated patients, expressed in percent of reference EEV, can be explained by the supine position and the post-operative status of the patients, and are in agreement with previous findings [14].

There are several important reasons to measure the lung volume during mechanical ventilation. PEEP therapy as it is used in adult respiratory distress syndrome (ARDS) patients is aimed at restoring the volume of the lung which has collapsed due to lack of surfactant and development of edema. Therefore, it is important to measure the parameter that is to be controlled by the therapy. East et al. [29] showed that positive end-expiratory pressure titration based on lung volume measurements can reach optimal levels sooner than standard PEEP management using blood gas measurements, and enables quick adaptation to the patient's changing condition. This fact is especially important since there is recent evidence that it is primary overdistention of the lung rather than excessive pressure that causes barotrauma [25]. PEEP titration by lung volume has the advantage over PEEP titration by measuring the inflection point in the static pressure-volume curve that it does not interfere with the ventilation of the patient (Measurement of the static pressure-flow curve takes several minutes during which the patient is not ventilated, and requires that the positive end-expiratory pressure has to be taken away temporarily, which can cause re-collapse of previously recruited alveoli). Another reason to monitor the lung volume is that the reduc-

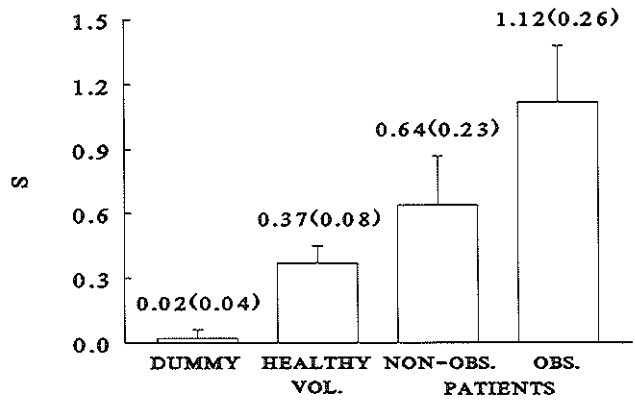

FIGURE 5.6: Results of volumes regression measurements. Mean (and s.d.) of the volumes regression index S on resp. a dummy lung, healthy volunteers, non-obstructive and obstructive patients. This shows that the volumes regression index detects the ventilation inhomogeneity in healthy subjects, and that it is sensitive for the existence of obstructive pulmonary disease.

tion of the lung volume in post-operative patients is the main cause of post-operative pulmonary complications [14].

We found that the normalized slope of the breath-by-breath end-expiratory lung volume estimations as a function of the relative amount of indicator gas washed out, the volumes regression index, is a sensitive parameter for the amount of ventilation inhomogeneity in our patient group as assessed by the pre-operative Tiffeneau values. Figure 5.6 demonstrates that the volumes regression index reveals the ventilation inhomogeneity present in healthy subjects [32]. Comparison of the mean value of the volumes regression index in patients with a normal Tiffeneau index with the mean in patients with low Tiffeneau values shows that it is a potentially valuable diagnostic parameter in defining the degree of ventilation inhomogeneity in patients suffering obstructive lung disease. The volumes regression index is better correlated to the Tiffeneau index than the Becklake index or the moment ratio index.

The regression line for the lung volume estimation and volumes regression index is determined in the interval $w = 0.7$ to $w = 0.9$. As a consequence the wash-out has to be continued until the end-expiratory indicator gas-fraction has been decreased to 10% of the initial value, which, in most cases, is reached within 2 minutes. This short measurement time is an additional advantage of the use of the volumes regression index over the use of most other inhomogeneity indices (like the

moments method), in which much longer durations of the washout tests are required. The choice of the boundaries ($0.7 \leq w \leq 0.9$) has been made heuristically. Calculations obtained from data with very high w-values do not increase the accuracy of the result due to the integration of small random and systematic errors (e.g. due to water vapor production, metabolic gas exchange etc.). On the other hand lung volume estimations of the very first wash-out expirations are not accurate, because they are very sensitive to measurement errors of the end-expiratory indicator gas-fraction.

The origin of the linear character of the relationship between the end-expiratory lung volume estimations and w is currently under investigation. It results from ventilation inhomogeneity which could have a serial character or could originate from sequential emptying of unequally ventilated parallel compartments [32, 65, 17, 18]. From our data it can not be concluded whether this pattern of inhomogeneity is a general property of COPD or that it represents a subclass of COPD due to an accidental selection of the investigated patients.

The ability to measure ventilation inhomogeneity (and obstructive disease) in an ICU setting is important for the identification of patients with no known history of pulmonary complications (e.g. trauma patients). The described method can also be used for monitoring the progress of some essential lung-function parameters in the course of the illness (e.g. development of ARDS, pulmonary oedema or exacerbation of COPD) and the effects of therapy (e.g. ventilation setting or medication) [42]. Currently, the main techniques used for this purpose are measurement of auto-PEEP and measurement of compliance. However, the amount of auto-PEEP is largely determined by the ventilatory method used, and, therefore, cannot be standardized. Moreover, the obstruction that causes the auto-PEEP is usually a distributed phenomenon that causes a distribution of the pressure over the lung at the end of the expiration, causing ventilation inhomogeneity and reduction of the efficacy of the gas transport. This distribution cannot be measured by the auto-PEEP method, whereas the resulting ventilation inhomogeneity can be measured with our method. The same is true for the distribution of the inspired air in lungs of ARDS patients. Gattinoni et al. [40] showed that, in the lungs of ARDS patients, three regions with different properties can be identified, i.e. a healthy zone, a recruitable zone, and a diseased zone that does not respond to pressure changes. It is to be expected that measurement of ventilation inhomogeneity can help in the identification of these zones [24]. However, since our method is still new, the precise effect of the method on ventilatory care has yet to be defined.

In our research, we made use of a mass spectrometer that is a

costly instrument and not available in most ICU's. However, the described method can also be applied with other gas fraction measuring devices. For example, East et al. [27] and Jonmarker et al. [56]described measurement of wash-out tests measuring sulfurhexafluoride by infra-red absorption. Currently, we are developing a method to measure helium that is based on heat transport. If, however, a mass spectrometer is used and the inspiratory oxygen fraction can be kept constant (as is the case in our measurement set-up) the metabolic rate can be measured during the wash-out test [49] using the same measurement set-up. In our surgical ICU the described wash-out test is routinely performed [42]. It provides important parameters for optimal setting of ventilation in for example COPD and ARDS patients.

Appendix: Calculation of the end-expiratory lung volume

The end-expiratory lung volume V_L is calculated at the end of each wash-out breath-cycle (inspiration followed by expiration) as the quotient of the amount of indicator gas washed out from the lung from the start of wash-out and the indicator gas dilution caused by the wash-out. Before the start of the wash-out, the amount (partial volume, V_p) of indicator gas present in the lung is equal to the product of the lung volume and the gas-fraction:

$$V_{p,0} = F_0 \times V_L \tag{5.1}$$

where F_0 is the gas-fraction in the lung before the wash-out. From the expiratory flow and indicator gas-fraction the amount of indicator gas that has been washed out during breath-cycle i, $\Delta V_{p,i}$ can be calculated [49]. At the end of breath cycle k after the begin of the wash-out a total amount of indicator gas of $\sum_{i=1}^{k} \Delta V_{p,i}$ has been removed. This causes the partial volume of indicator gas in the lung to change to a new value:

$$V_{p,k} = V_{p,0} - \sum_{i=1}^{k} \Delta V_{p,i} \tag{5.2}$$

On the other hand (analog to equation 5.1):

$$V_{p,k} = F_{Ak} \times V_L \tag{5.3}$$

where F_{Ak} equals the mean fraction of the indicator gas in the lung (mean alveolar gas-fraction) at the end of breath-cycle k. From equations 5.1,

5.2 and 5.3 V_L can be derived as:

$$V_L = \frac{\sum_{i=1}^{k} \Delta V_{p,i}}{F_0 - F_{Ak}} \tag{5.4}$$

There is however no way to measure the mean indicator gas-fraction in the lungs (F_{Ak}). Therefore, the lung volume is estimated by replacing F_{Ak} in equation 5.4 by the end-expiratory indicator gas-fraction F_{EEk}:

$$V^*_{L,k} = \frac{\sum_{i=1}^{k} \Delta V_{p,i}}{F_0 - F_{EEk}} \tag{5.5}$$

At the end of the wash-out, when nearly all of the indicator gas has been washed out, the influence of the difference between the end-expiratory fraction and the mean fraction of the indicator gas in the lung becomes negligible compared to the difference between F_0 and F_{EEk}. If, for example, at the moment that 99% of the indicator gas has been washed out, F_{Ak} is twice as large as F_{EEk}, then EEV^*_k would be in error of only 1%.

Chapter 6

Analysis of the shape of volumes regression curves.[1]

P.E.M. Huygen, C. Ince, R.F. Peters, A. Zwart, J.M. Bogaard, B.W. Kooi and H.A. Bruining

Abstract

Ventilation inhomogeneity causes a difference between the mean composition of the alveolar gas and the composition of the end-expiratory gas, which in turn causes systematic errors in the breath-by-breath estimations of the end-expiratory lung volume. We have recently shown that analysis of these systematic deviations can be used to quantify ventilation inhomogeneity by a volumes regression index which increases with increasing ventilation inhomogeneity. In this study the effect of several types of ventilation inhomogeneity on breath-by-breath lung volume estimations is analysed. Wash-out tests were performed on 9 healthy subjects, on 3 emphysematous patients and on 3 Chronic Obstructive Pulmonary Disease (COPD) patients. The volumes regression indices found were 0.3 ± 0.2 in the healthy subjects, 1.1 ± 0.0 in the COPD patients and 2.2 ± 0.3 in the emphysema patients. The breath-by-breath lung volumes estimations in these subjects were compared to those in a model consisting of two parallel compartments with a common dead space compartment. The results suggest that the stronger ventilation inhomogeneity of the COPD and the emphysema patients have a parallel origin.

Introduction

Ventilation inhomogeneity causes the composition of the alveolar gas to vary in different parts of the lungs resulting in a discrepancy between the composition of the expired gas and the composition of the mean alveolar gas. Indicator gas wash-out tests can provide a means to analyse this difference. The analyses of wash-out tests currently applied are aimed at either determination of a delay in the rate of the wash-out compared

1. *Submitted*

to the wash-out of a homogeneous ventilated lung with the same volume [6, 31, 3, 19, 82, 38], or at a description of the breath-by-breath expired indicator gas-fraction as the sum of a few [38, 46, 87], or a continuous distribution [41, 59, 69], of mono-exponential functions. In this way the wash-out test gives an indication on the severity of the ventilation inhomogeneity, but it provides no information on the origin of the ventilation inhomogeneity, like existence of different time constants or a longitudinal gradient.

A method that does provide information on the nature of the ventilation inhomogeneity is the analysis of the slope of the alveolar plateau in the course of the wash-out or, equivalently, analysis of the breath-by-breath Bohr dead space fraction [71, 96, 49]. If the lungs contain parallel ventilating units with different ventilation rates that empty sequentially, then generally the best ventilating units will empty early in the expiration. Since in the best ventilated units the indicator gas is more rapidly diluted than in the other units, the indicator gas-fraction will be lower early in the expiration than at the end of the expiration and the ratio of the indicator gas-fractions early and late in the expiration will decrease in the course of the wash-out. This gives rise to an increased slope of phase III of the expirogram and an increasing Bohr dead space fraction [71]. However, if the parallel, unequally ventilating units empty synchronously, the slope of phase III of the expirogram and the Bohr dead space fraction will remain constant in the course of the wash-out.

We recently introduced the Volumes Regression Technique [50], that gives a sensitive index of ventilation inhomogeneity, and that is based on the difference between the end-expiratory gas-fraction and the mean alveolar gas-fraction of the indicator gas that is washing out. We hypothesized that the shape of these curves could provide information about the nature of ventilation inhomogeneity. In this paper we applied the method on models of serial and parallel compartments. Consequently, wash-out tests have been performed on healthy subjects and on chronic obstructive pulmonary disease (COPD) patients, in some of whom emphysema was present, and the results were compared to those of the theoretical models.

Theory

The difference between the end-expiratory indicator gas-fraction and the mean indicator gas-fraction in the lung causes a misestimation of the volume of the lung. This can be quantified as follows; before the start of the wash-out the lung is filled with indicator gas to a fraction F_o. The partial volume of indicator gas in the lung (the quotient of the

volume that the indicator gas occupies if it could be separated from the other gases and the lung volume) at end-expiration is $F_o V_L$ where V_L is the end-expiratory lung-volume. During the wash-out the inspiratory gas-mixture has a constant indicator gas fraction of F_f. At the end of breath n after the start of the wash-out the partial volume of indicator that is left in the lung is equal to the difference of the partial volume of indicator gas that was in the lung before the start of the wash-out and the partial volume of indicator gas that has been expired during the first n expirations:

$$F_{An} V_L = F_o V_L - \sum_{i=1}^{n} \Delta V_i \tag{6.1}$$

where F_{An} is the mean indicator gas-fraction in the lung at the end of expiration n, and ΔV_i the partial volume of indicator gas that has been expired during expiration number i. From equation 6.1 V_L can be solved:

$$V_L = \frac{\sum_{i=1}^{n} \Delta V_i}{F_o - F_{An}} \tag{6.2}$$

Equation 6.2 can however not be used to calculate the volume of the lung, because the mean indicator gas-fraction in the lung F_{An} can not be measured. Instead we use the end-expiratory indicator gas-fraction F_{En}, which is easily measured [45]. If the distribution of the indicator gas in the lung is homogeneous, then F_A is equal to the end-expiratory indicator gas-fraction F_{En}, and the following estimation is valid:

$$V^*_{Ln} = \frac{\sum_{i=1}^{n} \Delta V_i}{F_o - F_{En}} \tag{6.3}$$

(the asterix signifies that the quantity is an approximation). At the end of the wash-out both F_{An} or F_{En} are nearly equal to F_f, and their difference is negligible compared to their difference with F_o. Therefore, the estimated volume will generally approach the actual volume of the lung for large n. Earlier in the wash-out the difference between the mean alveolar indicator gas-fraction and the end-expiratory gas-fraction may cause a difference between the estimated and the actual lung volume. The quotient of the estimated and the actual lung volume can be expressed as a function of the quotient of the mean alveolar and the end-expiratory gas-fraction. The quotient of equations 6.3 and 6.2 is:

$$\frac{V^*_{Ln}}{V_L} = \frac{F_o - F_{An}}{F_o - F_{En}} \tag{6.4}$$

The derivation can be made independent of the actual values of F_o and F_f by rescaling of the gas-fractions to a range between 0 and 1. Defining

F' as the quotient of the difference between the (alveolar or expiratory) indicator gas-fraction and the inspiratory gas-fraction during the wash-out F_f and the gas-fraction step at the beginning of the wash-out $F_o - F_f$ (i.e. $F'_{An} = (F_{An} - F_f)/(F_o - F_f)$, $F'_{En} = (F_{En} - F_f)/(F_o - F_f)$, $F'_o = 1$ and $F'_f = 0$) then:

$$\frac{V^*_{Ln}}{V_L} = \frac{1 - F'_{An}}{1 - F'_{En}} \tag{6.5}$$

Instead of the end-expiratory fraction we use a dimensionless variable w [50], defined as

$$w = 1 - F'_{En} \tag{6.6}$$

The quantity w is an indication of the progress of the wash-out process, running from zero at the start of the wash-out, when the expired gas contains an indicator gas fraction of F_o, to unity at the end of the wash-out, when the expired gas contains an indicator gas-fraction of F_f. Therefore, it is more instructive to plot the lung volume estimations as a function of w than to plot them as a function of time or breath number. The curve through the breath-by-breath volume estimations as a function of w is called the *volumes estimation curve*. Substituting equation 6.6 in equation 6.5, and writing the gas-fractions and volume estimations as a function of w instead of n shows that:

$$\frac{V^*_L(w)}{V_L} = \frac{1}{w} - \frac{1-w}{w} q_{ae}(w) \tag{6.7}$$

where

$$q_{ae}(w) = \frac{F'_A(w)}{F'_E(w)} \tag{6.8}$$

is the quotient of the alveolar and end-expiratory gas-fraction. Due to the definition of $F'_A(w)$ and $F'_E(w)$ the derivation is independent of the actual values of F_o and F_f, in other words, it is valid for wash-out as well as for wash-in tests (when $F_f > F_o$). In the case of perfectly homogeneous ventilation F'_{An}/F'_{En} is equal to unity, independent of n, and so is the quotient of the estimated lung volume and the actual lung volume. If F'_{An}/F'_{En} does not approach infinity, then in the limit $w \to 1$ the quotient of the estimated and the actual lung volume is equal to unity. If $q_{ae}(w) > 1$ then the quotient of the estimated and the actual lung volume is smaller than unity for $w < 1$. The breath-by-breath lung volume estimations plotted as a function of w follow an ascending curve that ends on V_L for $w = 1$. Conversely, if $q_{ae}(w) < 1$ then the breath-by-breath lung volume estimations follow a descending curve that leads to the actual lung volume V_L at $w = 1$.

The volumes estimation curve in some simple theoretical models.

Invariant distribution of indicator gas in the lung. If the ventilation inhomogeneity in the lung is caused by the interaction of diffusion and convection due to unequal branching of the bronchial tree at the acinar level [65, 32], or if the ventilation of parts of the lung occurs by way of collateral ventilation, it is expected that soon after the start of the wash-out a constant distribution pattern of the indicator gas develops in the lung, because the gas-fraction decreases in all compartments of the lung with the same decay constant. As a result the ratio of the indicator gas-fraction in different compartments of the lung will remain invariant in the course of the wash-out. In this case the same holds true for the quotient of the mean alveolar gas-fraction in the lung and the end-expiratory gas-fraction. If this constant, q_{ae}, is known, equation 6.7 gives directly the curve through the volume estimations. Figure 6.1 shows volumes

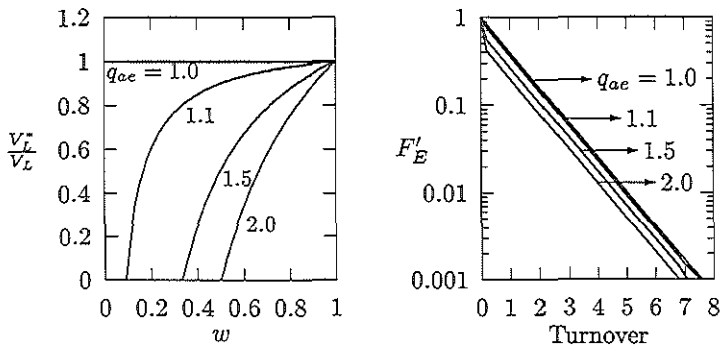

FIGURE 6.1: Simulation of a wash-out test in which the quotient of the mean alveolar gas-fraction and the end-expiratory gas-fraction has a constant value throughout the wash-out ($q_{ae}(w) = q_{ae}$ in equation 6.7). Left: Volumes estimation curves show the curves of the quotient of the estimated and the actual lung volume as a function of the relative amount of indicator gas washed out (w, see equation 6.6), calculated for 4 fixed values q_{ae}. Right: The normalised end-expiratory gas-fraction as a function of the quotient of the cumulative expired gas volume and the lung volume (turnover volume) of a simulated wash-out on a model with a ratio of tidal volume to lung volume of 0.17, for the same values of q_{ae}. The inhomogeneity manifests itself only in the first breath-cycle.

estimation curves for a number of values of q_{ae}, as well as curves of

the end-expiratory fraction as a function of the turnover volume, which is the quotient of the cumulative expired volume (CEV) and the lung volume. Since $q_{ae} > 1$ the volumes estimation curves have positive but decreasing slopes. The effect of the inhomogeneity is clearly visible in the volumes estimations curve, but in the end-expiratory fractions curve it is only apparent as a discontinuity of the first breath, the so-called end-expiratory dead space [81], after which a mono-exponential decay follows.

Two parallel, unequally ventilating compartments. The lung can be modeled as a set of parallel compartments with unequal ventilation rate [4]. An example of a model with 2 parallel compartments is described in the appendix. Figure 6.2 shows the Volumes Estimation Curves and the end-expiratory fraction curves of simulated two-compartment models with different volumes and ventilation ratios. The bi-exponential behavior can be recognized easily in the end-expiratory fraction curves. The volumes estimation curves have all upward slopes. Initially they are concave upward, but in the region near $w = 1$ there is an inflection point. The inflection point is poorly discernable because of its closeness to $w = 1$. An inflection point must however exist: both the mean composition of the alveolar gas and the end-expiratory gas-fraction are linear combinations of the gas-fractions in the two parallel compartments, $F_{1,n}$ and $F_{2,n}$. If compartment 1 is the best ventilating compartment, then eventually $F_{1,n}$ will become negligible compared to $F_{2,n}$, and both the mean alveolar and the end-expiratory fractions will degenerate into linear functions of $F_{2,n}$ only so that the quotient of the two will degenerate into a constant. Figure 6.2 shows only cases in which $q_{ae} > 1$, which is common in practice. Theoretically configurations with $q_{ae} < 1$ are also possible. In those cases the quotient of the lung volume estimations and the actual lung volume would be larger than unity.

Two parallel compartments with a common dead space. If the parallel compartments are connected to athmosphere via a common dead space compartment with finite volume, some transport of indicator gas from the least ventilated compartment to the best ventilated compartment takes place, because at the end of an expiration the dead space compartment contains gas from both compartments that will be redistributed among the compartments in the next inspiration. This causes a stabilization of q_{ae} at an earlier moment than would be the case when the dead space compartment was absent. The three-compartment model is described in the appendix. Figure 6.3 shows the volumes estimation curve and the end-expiratory gas-fraction curves of simulated three-

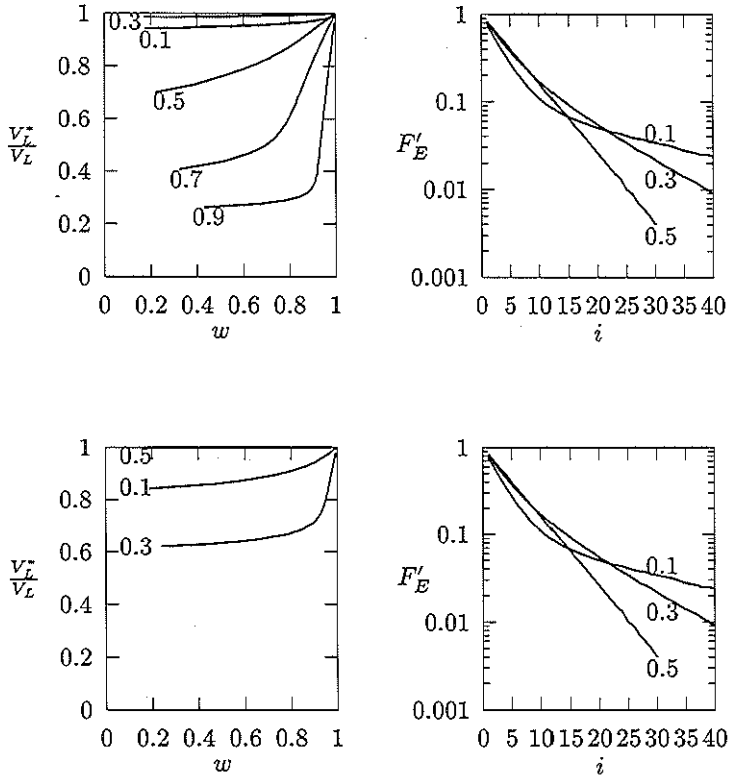

FIGURE 6.2: Simulation of a wash-out test in a model consisting of two parallel compartments with different ventilation. The ratio of tidal volume to lung volume is equal to 0.2. Left: volumes estimation curves. Right: Curve of the normalized end-expiratory indicator gas-fraction as a function of breath number. Top: The volume of the smallest compartment is one fourth the volume of the largest compartment and the ratio of tidal volume of the smallest compartment to that of the largest compartment is equal to 0.1, 0.3, 0.5, 0.7 and 0.9. Bottom: The volumes of both compartments are equal and curves are drawn for ratios of the tidal volumes of both compartments of 0.1, 0.3 and 0.5 (the latter case represents homogeneous ventilation).

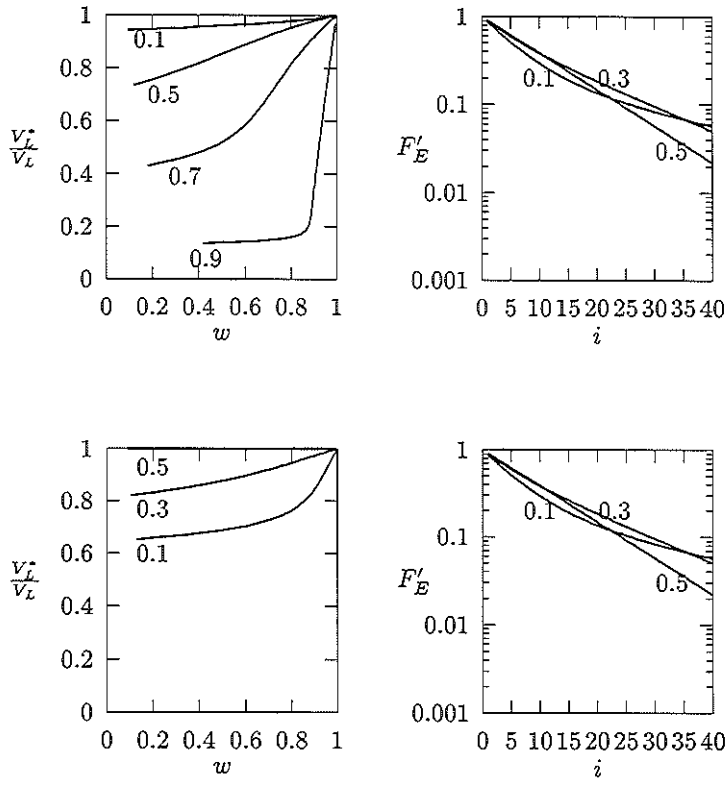

FIGURE 6.3: Simulation of a wash-out test in a model consisting of two parallel compartments with different ventilation that share a common dead space compartment. The ratio of tidal volume to lung volume is equal to 0.2 and the volume of the dead space is 10% of the total volume. Left: Volumes estimation curves. Right: Curve of the normalized end-expiratory indicator gas-fraction as a function of breath number. Top: The volume of the smallest compartment is one fourth the volume of the largest compartment and the ratio of tidal volume of the smallest compartment to that of the largest compartment is equal to 0.1, 0.3, 0.5, 0.7 and 0.9. Bottom: The volumes of both compartments are equal and curves are drawn for ratios of the tidal volumes of both compartments of 0.1, 0.3 and 0.5 (the latter case represents homogeneous ventilation).

compartment models.

Subjects and methods

In order to study the behavior of the *volumes estimations curve* we performed wash-out tests on 9 healthy subjects with normal lung function parameters (4 females and 5 males, age between 22 and 43 year) and on 6 patients with a severe obstruction and with a forced expiratory volume in 1 second (FEV_1) ranging from 30 to 64% of their reference value (mean: 45%, sd 14%). 3 of the patients had strong clinical and physiological signs of emphysema. The lung-healthy subjects are denoted as S1 to S9, the patients with strong indications for emphysema as E13 to E15, and the 3 other patients as C10 to C12. The results of the measurement were compared to the results with a three-compartment model.

The subjects breathed through a T-shaped tubing system with a Fleisch pneumotachochometer head in the common tube, the capillary inlet to an Airspec 3000 mass spectrometer (CASE, Biggin Hill, UK) on the junction of the three tubes, and one-way-valves. The inspiration tube was the common tube of another T-tube that was connected to an indicator gas injector [48]. The indicator gas injector provides a constant flow of air to which one of two indicator gases could be mixed. During the measurement the flow signal and the signals of the metabolic gases, oxygen and CO_2, were continuously sampled with a personal computer. The flow was sampled with a rate of 100 Hz, and the gas-fractions with 50 Hz. The delay of the gas-fraction signals relative to the flow-signal was compensated by shifting and interpolation of the gas-fraction signals off-line. The wash-out process starts by cessation of the mixing of the indicator gas to the inspiratory gas-mixture. Two gases were used as indicator gas: helium and SF_6, with inspiratory fractions of 2%. During a wash-out of helium, SF_6 was washed in and vice versa. This has the advantages of being a faster procedure with absence of secondary gas effects. On each healthy subject 4 helium and 4 SF_6 wash-out tests were performed in one session. On the COPD patients and the emphysema patients only a single wash-out could be performed as the procedure is too laden for them. The subjects were not instructed to breath according to a specific pattern. After the measurement, analysis of the signals took place as described earlier [49]. Plots of the volumes estimation curves and of the breath-by-breath mean- and end-expiratory gas-fractions were made. The three-compartment model, described in the Appendix, was fitted to the gas-fraction curves. The tidal volumes in the model were made equal to those of the subject. In the fit procedure the volumes of the three compartments and the distribution of the tidal volume over the

parallel compartment were allowed to vary until the difference between the mean and end-expiratory fractions of the subject and those of the model was minimized. The model and the fit procedure are described in the Appendix. In order to evaluate the existence of sequential emptying, inhomogeneously ventilated regions of the lung plots were made of the breath-by-breath Bohr dead space of the indicator gas washing out as well as CO_2 as a function of breath number. The Bohr dead space fraction (i.e. the ratio between the Bohr dead space and the tidal volume) is calculated as the difference between unity and the quotient of the flow weighted mean expiratory fraction and the end-expiratory gas-fraction. If the sequential emptying regions exist, the Bohr dead space fraction of the indicator gas will increase during the wash-out test, whereas the CO_2 fraction will not [95, 49].

Results

The left part of figure 6.4 shows the breath-by-breath lung-volume es-

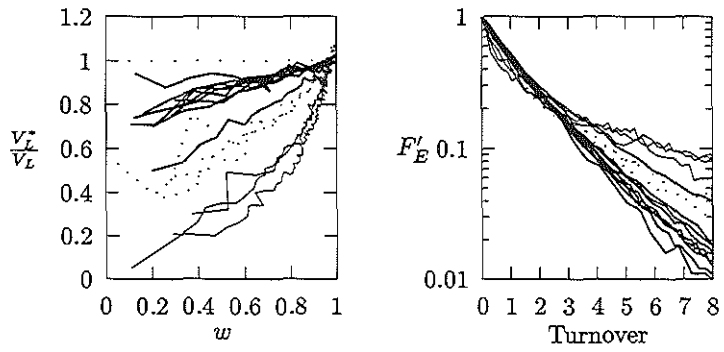

FIGURE 6.4: Volumes estimation curves (left) and curves of the normalised end-expiratory indicator gas-fraction as a function of turn-over volume (right) of the wash-out tests on the subjects. Thick lines: curves of the healthy subjects; thin lines: curves of the emphysema patients and dotted lines: curves of the COPD patients.

timation of the first wash-out test of each subject. In order to make the curves comparable the volume estimations are divided by a reference value obtained by extrapolation of the part of the curve between $w = 0.8$ and $w = 0.95$. The graph shows that the inter-subject variation of the

curves for each group are small, with exception of the curve of S6, whose curve is similar to that of the COPD patients. In the healthy subjects the lung volume estimations increase monotonously with w, and seem to be oriented along a straight line with a slope of approximately 0.3. In the emphysematous patients the curves have a more pronounced upward bend and have a steep slope near $w = 1$. The curves of the COPD patients and of healthy subject S6 are in between. The right part of figure 6.4 shows the quotient of the end-expiratory fraction and the gas-fraction before the wash-out as a function of turnover volume (the quotient of the cumulative amount of indicator gas washed out and the lung volume). In order to diminish the influence of variations of the tidal volume the gas-fractions were divided by the end-expiratory CO_2 fraction [95, 49]. The (semi-logarithmic) curves of the healthy subjects have a slight nonlinearity, revealing the presence of ventilation inhomogeneity. The curves of the patients have a marked nonlinearity.

Table 6.1 lists the mean and the standard deviations of the lung volumes and the normalized slopes of the part of the volumes estimation curves between $w = 0.8$ and $w = 0.95$ for each wash-out test of the healthy subjects and the patients. In the volumes regression technique [50] the normalized slope of the curve in the interval $0.7 \leq w \leq 0.9$ is called the *volumes regression index* and is used as an index of ventilation inhomogeneity. We decided to calculate the slope S in the interval $0.8 \leq w \leq 0.95$, because in the region near $w = 0.7$ the volumes estimation curves of the patients still have a marked curvature. The normalized slope S of the healthy subjects is significantly smaller than S of the COPD patients or emphysematous patients ($p < 0.005$, Wilcoxon test) and S of the COPD patients is significantly smaller than S of the emphysematous patients ($p < 0.05$). The mean of the volumes regression indices of the healthy subjects is 0.3 ± 0.2. In subject S6 a value of 0.7 ± 0.3 was measured, which is two standard deviations away from the mean of the group. If this subject was left out the mean and standard-deviation of the volumes regression index in the remaining group was 0.3 ± 0.1

Figure 6.5 and 6.6 compares the actual volumes estimation curves and breath-by-breath gas-fraction curves to the curves of the three-compartment model with synchronous emptying that fit the actual gas-fraction curves best. The mean expiratory gas-fractions of the model follows well the actual curves. The volumes regression curves of the model match the actual volumes regression curves for high values of w, but for low values of w the lung volume estimations of the model are higher than the volume estimations from the actual data.

Figure 6.7 shows the breath-by-breath Bohr dead space values for the indicator gas and for CO_2 of the first 15 wash-out breath-cycles of the

TABLE 6.1: Lung volume (V_L) and volumes regression indices (S) of nine subjects, each undergoing 8 wash-out tests each, of three emphysema patients and three COPD subjects each having a single wash-out tests. The quotient of the forced expiratory volume in 1 second (FEV_1) and the reference value [78] is given for the patients.

subj.	age yr	$\frac{FEV_1}{ref.}$	V_L l	S $0.8 \leq w \leq 0.95$
S1	27		3.14 ± 0.36	0.21 ± 0.05
S2	43		3.65 ± 0.09	0.37 ± 0.16
S3	24		2.74 ± 0.27	0.19 ± 0.08
S4	32		3.31 ± 0.06	0.24 ± 0.03
S5	23		2.73 ± 0.26	0.45 ± 0.15
S6	26		3.86 ± 0.05	0.69 ± 0.25
S7	22		4.02 ± 0.10	0.39 ± 0.20
S8	40		5.27 ± 0.04	0.27 ± 0.06
S9	34		4.33 ± 0.19	0.25 ± 0.02
mean healthy	30		3.67 ± 0.16	0.34 ± 0.11
sd healthy	08		0.81 ± 0.12	0.16 ± 0.08
E10	70	0.34	4.3	2.1
E11	57	0.40	3.2	2.2
E12	68	0.30	5.1	2.6
mean emphysema	65	0.35	4.2	2.3
sd emphysema	07	0.05	0.9	0.3
C13	61	0.64	3.6	1.1
C14	58	0.41	2.1	1.1
C15	83	0.61	3.6	1.1
mean COPD	67	0.55	3.1	1.1
sd COPD	14	0.12	0.9	0.0

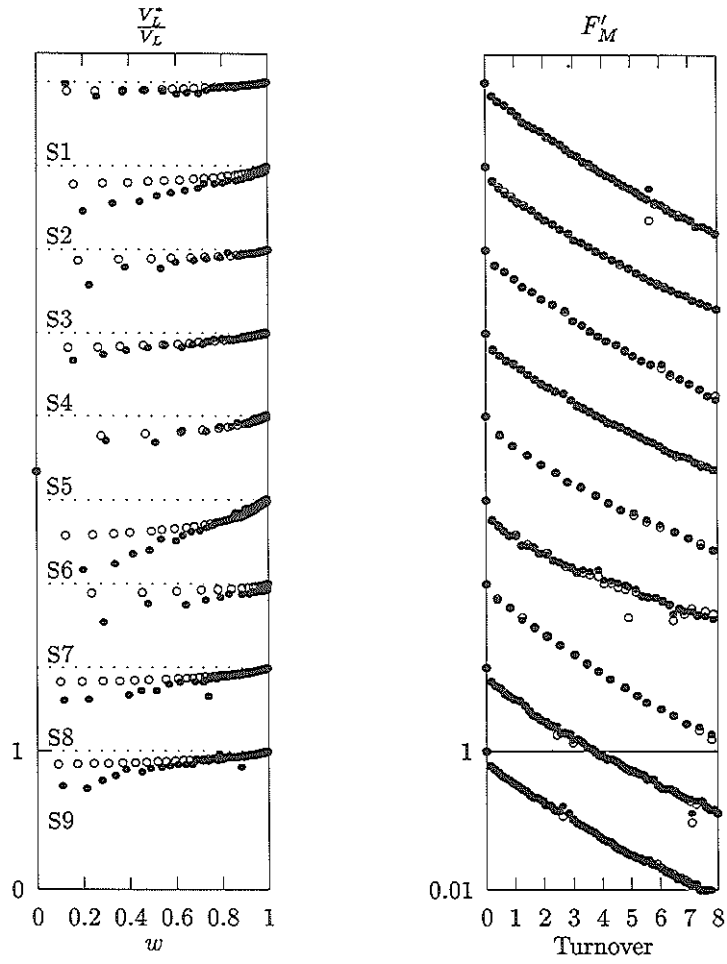

FIGURE 6.5: Comparison of the breath-by-breath volumes estimation curves (left) and of the mean expiratory fractions (right) of the actual wash-out curves of the healthy subjects (filled circles) and the fit of the mean expiratory and end expiratory gas-fractions with a three-compartment model with synchronous ventilation (open circles). The model fits the mean expiratory fractions very well, but over-estimates the lung-volume estimations of the first wash-out breaths.

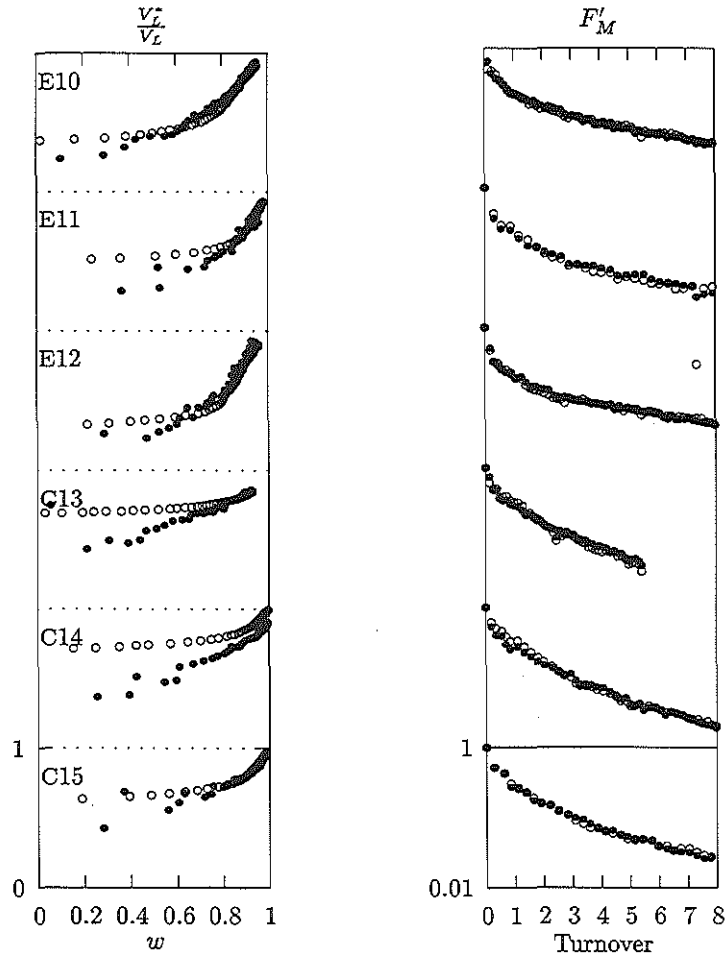

FIGURE 6.6: Comparison of the volumes estimation curves (left) and of the mean expiratory fractions (right) of the actual wash-out curves of the COPD and emphysema patients (filled circles) and the fit of the mean expiratory and end expiratory gas-fractions with a three-compartment model with synchronous ventilation (open circles). The model fits the mean expiratory fractions less well than it does in the healthy subjects.

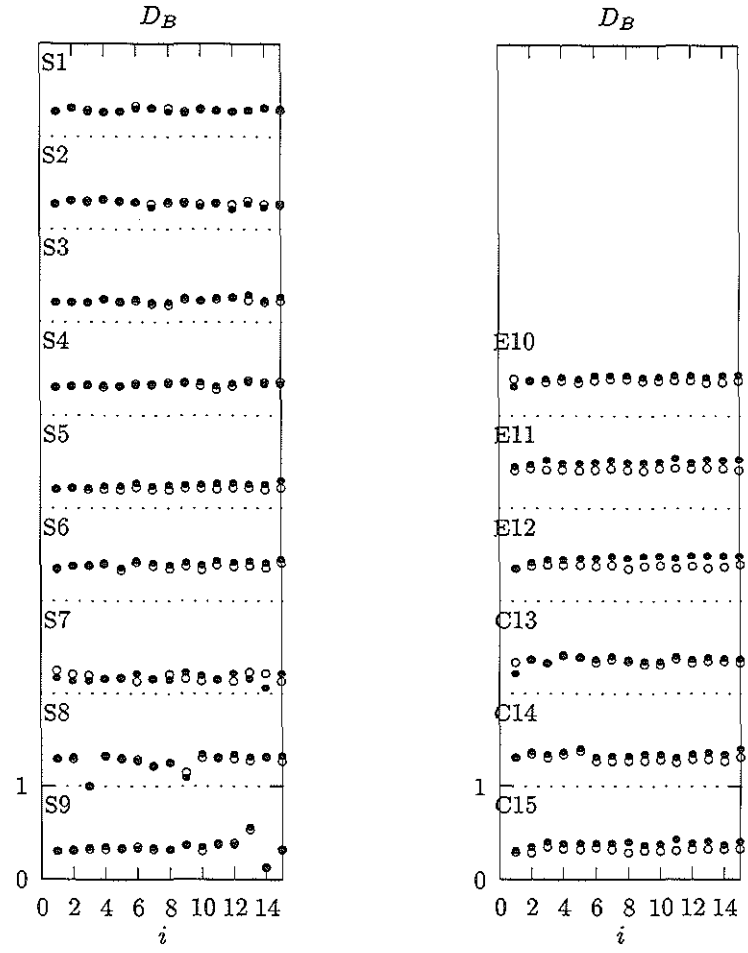

FIGURE 6.7: Comparison of the breath-by-breath Bohr dead space fractions of carbon dioxide (open circles) and indicator gas (closed circles) of the subjects (S, left) and the emphysema (E, right) and COPD (C, right) patients. In most of the subjects the indicator gas dead space follows the dead space fraction of carbon dioxide, indicating that sequential emptying is not present. In the patient group the indicator gas dead space increases during the wash-out, indicating that in this group sequential emptying is an important phenomenon.

subjects and the patients. In subjects S5 and S6 and in the 6 patients the Bohr dead space fraction of the indicator gas increases with respect to the Bohr dead space of CO_2, whereas in the other healthy subjects the Bohr dead spaces of the two gases follow the same trend. Table 6.2

TABLE 6.2: Parameters and eigenvalues of the three-compartment model with synchronous emptying for the subjects.

Subj.	V_1 l	V_2 l	V_D l	τ	$\overline{V}_T$ l	e_1	e_2
S1	2.38	0.75	0.19	0.89	0.67 ± 0.08	0.91	0.85
S2	2.70	1.04	0.26	0.90	1.02 ± 0.09	0.91	0.80
S3	2.30	0.57	0.27	0.93	0.97 ± 0.14	0.90	0.79
S4	2.31	0.75	0.28	0.91	0.73 ± 0.06	0.92	0.85
S5	1.61	0.91	0.37	0.87	1.33 ± 0.13	0.85	0.68
S6	2.48	1.49	0.36	0.91	0.98 ± 0.30	0.94	0.83
S7	2.70	1.38	0.26	0.83	1.81 ± 0.19	0.82	0.68
S8	3.67	1.42	0.26	0.88	0.78 ± 0.11	0.94	0.89
S9	3.15	1.22	0.21	0.88	0.62 ± 0.09	0.96	0.90
mean healthy	2.59	1.06	0.27	0.89	0.99 ± 0.13	0.91	0.81
sd healthy	0.58	0.33	0.06	0.03	0.38 ± 0.07	0.05	0.08
E1	1.16	3.90	0.32	0.85	0.73 ± 0.05	0.95	0.78
E2	1.10	2.04	0.51	0.92	1.05 ± 0.12	0.96	0.74
E3	0.38	3.68	0.36	0.87	0.76 ± 0.06	0.98	0.62
mean emphysema	0.88	3.21	0.40	0.88	0.85 ± 0.08	0.96	0.71
sd emphysema	0.43	1.02	0.10	0.03	0.18 ± 0.04	0.02	0.08
C4	2.23	1.58	0.20	0.93	0.50 ± 0.07	0.98	0.89
C5	1.27	1.02	0.13	0.89	0.41 ± 0.09	0.96	0.84
C6	1.75	1.90	0.40	0.91	1.08 ± 0.13	0.95	0.76
mean COPD	1.75	1.50	0.24	0.91	0.66 ± 0.10	0.96	0.83
sd COPD	0.48	0.44	0.14	0.02	0.36 ± 0.03	0.02	0.07

V_1, V_2 Volume of parallel compartments.
V_D Volume of dead space compartment.
τ Fraction of the tidal volume that is absorbed by compartment 1
$\overline{V}_T$ Mean and sd of the tidal volume
e_1, e_2 Eigenvalues corresponding to the model.

shows the results of the parameter estimations on the healthy subjects and patients. The table lists the estimated volumes of the three compartments and the distribution of the inspired volume over the two parallel compartments, the mean and standard deviation of the tidal volume and the two eigenvalues of the transition matrix A (see appendix; the mean of the tidal volumes during the wash-out is used for V_T). The eigenvalues represent the relaxation constants of two exponential functions of

the breath number of which the mean expiratory gas-fraction and the end-expiratory gas-fraction are both linear combinations.

Discussion

A new method for analyzing of indicator gas wash-out tests is described. The method is based on visualization of the difference between the end-expiratory gas-mixture and the mean alveolar gas-mixture. The results of mathematical simulations (figures 6.1 and 6.2) show that this method discriminates ventilation inhomogeneity with parallel origin from inhomogeneity with serial origin. The former type of ventilation inhomogeneity results in an upwards curled curve through the breath-by-breath lung volume estimations as a function of w, whereas the latter type results in a downwards curled curve. The curves of the lung volume estimations as a function of w of the healthy subjects follow a nearly straight line. They have thus neither a pure parallel nor a pure serial character. One explanation for this behavior is that the dead space compartment promotes the development of a steady state situation by compensating differences in ventilation rate by redistribution of indicator gas. The effect of this mechanism is illustrated in the curves from the mathematical simulations. However, the results of the fit procedure with the three compartment model show that the fitted volume estimation curves are markedly more curved than the actual volume estimations of the subject and that thus the compensation of the dead space compartment alone can not fully explain the shape of the volumes estimation curves. Other mechanisms that have the same effect as a longitudinal gradient are collateral ventilation of compartments with very low ventilation via the normal airways [63, 86] or convection-diffusion driven ventilation inhomogeneity [65, 32]. The curves of the COPD patients and the emphysematous patients have a more "parallel" character than those of the healthy subjects (except S6).

Volumes regression index. The large difference of the volumes regression index for the three groups (healthy subjects, COPD patients and emphysematous patients) shows that this method is sensitive for indicating chronic obstructive pulmonary disease. The breath by breath indicator gas Bohr dead spaces of the two healthy subjects with the largest values of S, S5 and S6, increase in the course of the wash-out, whereas those of the other subjects do not. Moreover, S6 was asthmatic as a child, but is now considered "lung-healthy". His Forced Expiratory Volume in 1 second is 104% of the reference value. This means that probably, although this subject had outgrown his childhood asthma, traces of the

illness were still visible from our gas exchange studies, but did not cause significant airway obstruction.

Shape of the volumes estimation curves and physical interpretation. In the healthy subjects the volumes estimations curves are more or less oriented along straight lines. The volumes estimations curves of the COPD and the emphysematous patients have a more upward curved shape. The mathematical simulations show that an upward curved shape can be associated with existence of parallel ventilation. The stronger influence of parallel inhomogeneity in the patients,with respect to the healthy subjects,is consistent with the fact that the eigenvalues of the three-compartment model fits (and thus the relaxation constants of the exponential functions with which the end-expiratory/mean alveolar gas-fraction curves can be described) are closer to each other in the healthy subjects than in the patients.

The three compartments of the lung model with which the curve fit procedures have been performed can be interpreted as a continuous distribution of volumes with different ventilation ratios. In the simulations of the wash-outs of the majority of the healthy subjects and the COPD patients the obtained dead space values are realistic for humans (the dead space includes the instrumental dead space of 100 ml). In the emphysematous patients the recovered dead space values including instrumental dead spaces are larger than 300 ml. Thus it may be that the dead space compartment of the mathematical model stands for a combination of true anatomical dead space and a gradient of the gas-fraction in the lung, possibly caused by diffusion-convection driven ventilation inhomogeneity [17] or collateral ventilation by diffusion [63] or convection [86]. Another observation in the healthy subjects and the COPD patients is that the larger of the two parallel compartments absorbs the larger part of the tidal volume, but that in the emphysematous patients the smaller compartment absorbs the larger part of the tidal volume. There are thus striking differences in the shapes of the curves between the three groups and more research is needed to find the origin of these differences.

Sequential vs. synchronous emptying. In our study we found in most of the healthy subjects little evidence for the presence of sequential emptying of lung compartments with different ventilation ratio. Figure 6.7 shows that the breath-by-breath Bohr dead space values increase in only two of the subjects (S5 and S6). Furthermore, if in the three-compartment model the parameters f and g, that represent synchronous filling respectively emptying are allowed to vary during the fit proce-

dure, both parameters changed only marginally and the quality of the fit improved only slightly (the resulting deviation between the actual and modeled data diminished with only 10%). Finally, the fact that the volumes estimation curves of all subjects have positive slopes indicates that during the wash-out the mean alveolar gas-fraction is larger than the end-expiratory gas-fraction, and, consequently, the gas from the best ventilating compartments is still over-represented in the end-expiratory mixture. The finding of only a minor amount of sequential emptying is in contrast with studies of Crawford et al. [17] who found that the normalized slope of phase III of the expirograms increased from app. 0.02 l^{-1} to 0.20–0.30 l^{-1} and that the mean Bohr dead space of 6 subjects increased 30% during the first 20 wash-out breaths. One reason for the different findings can be that Crawford trained his subjects to breath in a saw-tooth manner with constant flow and a constant tidal volume, whereas we did not give instructions to the subjects. Possibly variations in tidal volume decrease differences in gas-fractions over the lung, e.g. an occasional deep breath might cause an otherwise unventilated compartment to ventilate.

The right side of figure 6.7 shows that in all COPD patients and emphysematous patients the Bohr dead space rises in the course of the wash-out, demonstrating, as was expected, sequential emptying in these patients [66].

Appendix: Wash-out of simple lung models

Parallel two-compartment model. The parallel two-compartment model consists of two parallel compartments with volumes V_1 and V_2 that are connected to athmosphere via a common "trachea" with zero volume. The tidal volume that is inspired during inspiration i is equal to T_i. A part τ of the tidal volume is absorbed by compartment 1, the rest $(1-\tau)$ by compartment 2. The gas in each compartment is assumed to be homogeneously mixed. The indicator gas-fractions in the compartments at the end of expiration nr i are denoted as $F_{1,i}$ and $F_{2,i}$. In a true wash-out, when the inspiratory gas does not contain indicator gas, the gas-fractions at the end of next breath-cycle can be calculated with the following gas-balance equations:

$$\begin{aligned} (V_1 + \tau T_{i+1})F_{1,i+1} &= V_1 F_{1,i} \\ (V_2 + (1-\tau)T_{i+1})F_{2,i+1} &= V_2 F_{2,i} \end{aligned} \tag{6.9}$$

results in:

$$F_{1,i+1} = \frac{V_1}{V_1 + \tau T_{i+1}} F_{1,i}$$

$$F_{2,i+1} = \frac{V_2}{V_2 + (1-\tau)T_{i+1}} F_{2,i} \tag{6.10}$$

Defining vector $\vec{F}_i$ and matrix $\mathbf{A}_{\Lambda,i}$ as

$$\vec{F}_i = \begin{pmatrix} F_{1,i} \\ F_{2,i} \end{pmatrix} \text{ and } \mathbf{A}_{\Lambda,i} = \begin{pmatrix} \frac{V_1}{V_1+\tau T_i} & 0 \\ 0 & \frac{V_2}{V_2+(1-\tau)T_i} \end{pmatrix} \tag{6.11}$$

we can write:

$$\begin{aligned} \vec{F}_0 &= \begin{pmatrix} F_0 \\ F_0 \end{pmatrix} \\ \vec{F}_{i+1} &= \mathbf{A}_{\Lambda,i+1}\vec{F}_i \quad (i \geq 0) \end{aligned} \tag{6.12}$$

Matrix $\mathbf{A}$ would be independent of i if the tidal volume was independent of i, which is not generally the case. If a fraction g of the end-expiratory gas-mixture originates from compartment 1 and thus a fraction $1-g$ comes from compartment 2, then the end-expiratory gas-fraction is equal to:

$$F_{Ei} = \begin{pmatrix} g & (1-g) \end{pmatrix} \vec{F}_i \tag{6.13}$$

The mean expired indicator gas-fraction is equal to the quotient of the partial volume of indicator gas expired and the tidal volume during a single expiration i :

$$\begin{aligned} F_{Mi} &= \frac{\tau T_i F_{1,i} + (1-\tau)T_i F_{2,i}}{T_i} \\ &= \begin{pmatrix} \tau & 1-\tau \end{pmatrix} \vec{F}_i \end{aligned} \tag{6.14}$$

If both compartments empty synchronously then the end-expiratory gas-fraction F_{Ei} is equal to the mean expiratory gas-fraction.

The mean indicator gas-fraction in the lung at the end of expiration i is:

$$F_{Ai} = \begin{pmatrix} \frac{V_1}{V_1+V_2} & \frac{V_2}{V_1+V_2} \end{pmatrix} \vec{F}_i \tag{6.15}$$

Parallel two-compartment model with common dead space. The parallel model can be extended with a dead space compartment by assigning a finite volume V_d to the common trachea. In inspiration the gas that remained in the dead space at the end of previous expiration is divided over the two parallel compartments: a fraction f flows into compartment 1 and the remainder flows into compartment 2. At the end of the expiration a part g of the gas in the dead space came from compartment 1. The end-expiratory gas-fractions are assumed to be equal to the

gas-fraction in the dead space compartment. The gas-balance equations of this three-compartment model are:

$$\begin{aligned}(V_1 + \tau T_{i+1})F_{1,i+1} &= V_1 F_{1,i} + f V_d F_{d,i} \\ (V_2 + (1-\tau)T_{i+1})F_{2,i+1} &= V_2 F_{2,i} + (1-f)V_d F_{d,i} \\ F_{d,i+1} &= g F_{1,i+1} + (1-g)F_{2,i+1}\end{aligned} \tag{6.16}$$

Eliminating the dead-space fraction in equations 6.16 we get:

$$\begin{aligned}F_{1,i+1} &= \frac{V_1 + fgV_d}{V_1 + \tau T_{i+1}} F_{1,i} + \frac{f(1-g)V_d}{V_1 + \tau T_{i+1}} F_{2,i} \\ F_{2,i+1} &= \frac{(1-f)gV_d}{V_2 + (1-\tau)T_{i+1}} F_{1,i} + \frac{V_2 + (1-f)(1-g)V_d}{V_2 + (1-\tau)T_{i+1}} F_{2,i}\end{aligned} \tag{6.17}$$

Defining vector $\vec{F}_i$ and matrix $\mathbf{A}_{\lambda,i}$ as

$$\vec{F}_i = \begin{pmatrix} F_{1,i} \\ F_{2,i} \end{pmatrix} \quad \text{and} \quad \mathbf{A}_{\lambda,i} = \begin{pmatrix} \frac{V_1 + fgV_d}{V_1 + \tau T_i} & \frac{f(1-g)V_d}{V_1 + \tau T_i} \\ \frac{(1-f)gV_d}{V_2 + (1-\tau)T_i} & \frac{V_2 + (1-f)(1-g)V_d}{V_2 + (1-\tau)T_i} \end{pmatrix} \tag{6.18}$$

we can write:

$$\begin{aligned}\vec{F}_0 &= \begin{pmatrix} F_0 \\ F_0 \end{pmatrix} \\ \vec{F}_{i+1} &= \mathbf{A}_{\lambda,i+1}\vec{F}_i \quad (i \geq 0)\end{aligned} \tag{6.19}$$

and

$$F_{d,i} = \begin{pmatrix} g & (1-g) \end{pmatrix} \vec{F}_i \tag{6.20}$$

The end-expiratory fraction (F_E) in the model is assumed to be equal to $F_{d,i}$, and the mean expiratory fraction is equal to the quotient of the amount of indicator gas expired in a single expiration and the tidal volume:

$$F_{Mi} = \frac{\tau T_i F_{1,i} + (1-\tau)T_i F_{2,i} - V_d F_{d,i}}{T_i} \tag{6.21}$$

or

$$F_{Mi} = \frac{1}{T_i} \begin{pmatrix} (\tau T_i - gV_d) & [(1-\tau)T_i - (1-g)V_d] \end{pmatrix} \vec{F}_i \tag{6.22}$$

In our study we compared the end-expiratory and the mean expiratory gas-fractions of actual wash-out tests with this model. The tidal volumes used in the model were the actual tidal volumes of the wash-out test. In an iterative fit procedure the parameters τ, V_1, V_2 and V_d are varied until the difference between the modeled and the measured mean

and end-expiratory fractions reached a minimum. In this procedure the parameters f and g were set equal to τ (synchronous emptying of the two parallel compartments). As a measure for the difference between the modeled and the measured fractions the sum of the squares of the relative differences between the modeled and actual fractions was used. In other words, the quantity ϵ, defined as

$$\epsilon = \sum_{i=1}^{n} \left(\frac{F_{Mi} - F^*_{Mi}}{F_{Mi}} \right)^2 + \sum_{i=1}^{n} \left(\frac{F_{Ei} - F^*_{E,i}}{F_{Ei}} \right)^2 \tag{6.23}$$

was minimized. The parameter n is the number of breath-cycles needed to reduce the end-expiratory indicator gas-fraction to 1% of the original value.

Chapter 7

Epilogue: Towards routine lung volume measurements in mechanically ventilated patients.

The main subject of this thesis is the design, validation and application of an indicator gas wash-out test, to be used on mechanically ventilated intensive care patients. The goal of the described wash-out test was to measure lung function of a selected number of patients, mainly for research purposes. The first application of the test was the evaluation of a new ventilation mode in which the expiratory flow was not allowed to exceed a certain maximum value (diminished early expiratory flow, DEEF ventilation [92, 43]). This study has been successfully completed and a manuscript is in preparation. The test has also been used in mechanically ventilated pigs, to study mechanical ventilation in obstructive disease and in the adult respiratory distress syndrome ARDS [74, 73].

Although we used it mainly for research, the wash-out method has the potential to become a useful technique to monitor the gas transport and pulmonary function of mechanically ventilated patients. It has advantages over conventional variables such as blood gas values and cardiac output in that it is nearly continuously available and on line, and it provides specific insight into the ventilation of the lungs. This is especially important in cases when the pulmonary gas exchange is compromised, as in the many respiratory distressed patients admitted for intensive care treatment.

When would routine wash-out tests be beneficial.

The most common pulmonary problems in an intensive care unit that necessitate measurement of lung volume are the following:

Adult Respiratory Distress Syndrome (ARDS). This syndrome is characterized by interstitial and alveolar oedema, haemorrhage, cellular debris and proteinaceous fluid in the alveoli and patchy atelectasis. As a result the lung becomes very stiff with a reduced end-expiratory volume. A large fraction of the alveoli collapse and can not be ventilated [40], causing a severe hypoxemia. This hypoxemia is probably caused by increasing ventilation-perfusion inequality due partly to continued perfusion of the collapsed alveoli. Furthermore, perfusion of the ventilated part of the lung is reduced due to the high airway pressure that is required to overcome lung stiffness and maintain as many alveoli open as possible. Dantzker et al [20] concluded from a study in dogs, in which the arterial oxygenation was compared with ventilation-perfusion distributions measured with the multiple inert gas elimination technique, that oxygen transport from gas to blood is not diffusion-limited. In order to maximize oxygenation of the arterial blood, a patient suffering ARDS is ventilated with: 1) an elevated inspiratory oxygen fraction, to increase oxygen uptake by the blood in poorly ventilated alveoli, and 2) positive end-expiratory pressure (PEEP) to recruit as many alveoli as possible and to reduce the amount of functional right-to-left shunt. The optimal PEEP corresponds with maximal oxygen transport by the arterial blood (the product of cardiac output and arterial oxygen content). PEEP below the optimal pressure increases ventilation-perfusion mismatch that lowers arterial oxygenation, whereas PEEP above the optimum decreases cardiac output. Measurement of maximum oxygen transport involves measurement of cardiac output and arterial oxygenation, which can usually only be performed at intervals. Several studies have indicated that PEEP which maintains the end-expiratory lung volume normal causes maximal oxygen transport [28]. In addition, end-expiratory lung volume correlates better with PEEP than other variables, including the lung or thorax compliance [28]. Therefore measurement of the end-expiratory lung volume is an excellent means of ensuring optimal PEEP [29], which is independent of changes in stiffness of the lung during the course of disease.

Obstructive Pulmonary Disease (COPD *and asthma*). COPD is a general term that refers mainly to emphysema and chronic bronchitis. Both syndromes are characterized by morphological changes of the airways that cause airflow obstruction. Emphysema is also characterized by loss of elastic recoil of the lung tissue. Asthma, characterized by increased responsiveness of the airways to various stimuli, results in widespread narrowing of the airways, with varying severity, but it can be influenced by medical treatment. Obstructive pulmonary diseases cause a reduction

in expiratory flow, an increase in static lung volumes and an increase in ventilation inhomogeneity. If patients suffering obstructive pulmonary disease require mechanical ventilation it is important to minimize the dynamic hyperinflation caused by the low expiratory flow rates [57] and to recognize exacerbations of bronchitis or asthma so that they can be treated. The wash-out test is a good means to monitor these patients because the hyperinflation due to the disease results in an increased end-expiratory lung volume while the broncho-constriction results in increased ventilation inhomogeneity and in decreased serial dead space volume [11]. Increased lung volume and ventilation inhomogeneity and decreased serial dead space are specific for broncho-constriction, whereas conventionally available signals like maximum inspiratory airway pressure are not. The presence of hyperinflation is usually detected by measurement of intrinsic PEEP, the end-expiratory alveolar pressure that can be measured after a brief occlusion of the airways at the end of an expiration. It is a good method to apply when weaning a patient from a ventilator, because the patient has to overcome this pressure in order to trigger an inspiratory cycle of the ventilator. This leads to increased work of breathing. However, intrinsic PEEP can not be available as a continuous signal because has to be measured manually and the measurement interferes with ventilation. Moreover, in patients with reduced elastic recoil of lung tissue the lung volume might be more sensitive for hyperinflation than intrinsic PEEP, and therefore intermittent measurement of the end-expiratory lung volume is desirable under these circumstances.

Other complications. Evidence exists that the lung volume increases during hypovolemia and decreases during hypervolemia. Brunner and Wolff [11] illustrated this in a case study on a post-operative patient who developed a haemodynamically significant hypovolemia as a result of a clotting disturbance. During hypovolemia the lung volume was 0.6 l larger than after remedy of the clotting disturbance and blood transfusion of 2.8 l. Gültuna et al [44] described a case of a patient in whom the lung volume decreased reversibly during an episode of hypervolemia. These examples suggest that monitoring lung volume during mechanical ventilation may give early warning of a sudden change in fluid balance. However, it has yet to be established whether lung volume is more sensitive for hypervolemia or hypovolemia than other parameters or clinical signs. The same can be said about measurement of ventilation inhomogeneity and CO_2 expirograms during a sudden pulmonary embolism. Brunner et al [11] simulated pulmonary embolism by inflating the balloon of a pulmonary arterial (Swan-Ganz) catheter. During the inflation they measured expiratory flow, CO_2 fraction, and the airway and oesophageal

pressures and found transient changes in the end-tidal CO_2 fraction, lung compliance, airway resistance and the slope of phase III of the CO_2 expirogram. The regional perfusion blockade caused a transient drop in the excreted CO_2. On the longer term, ventilation was redistributed to match the perfusion inhomogeneity and this caused increased ventilation inhomogeneity.

Other complications that result in decreased end-expiratory lung volume are pneumo-thorax, haemo-thorax, atelectases, mucus plugs in the airways and pneumoniae. Continuous monitoring of lung volume enables early diagnosis and treatment of these complications, which prevents deterioration in arterial bloodgases and facilitates recuperation of the patient.

Devices and procedures.

This section analyses the instruments and techniques needed to implement the wash-out test. Suggestions are made for modifications that could make the technique cheaper, easier to handle with less interference to patient care, so that it can be used routinely to monitor lung volume and ventilation inhomogeneity in mechanically ventilated patients.

Indicator gas mixing. Chapter 2 describes an instrument to inject indicator gas into the air-oxygen mixture that will be inspired by the subject. The instrument produces a constant flow of oxygen-air mixture in which it mixes one out of two indicator gases to a constant, small, fraction of approximately 2%. The produced gas-mixture flows into the low-pressure entrance of a Siemens Servo 900 series mechanical ventilator. When the indicator gas is homogeneously distributed in the lungs of the subject, the indicator gas injector receives a signal and either stops the injection of the indicator gas into the inspiratory gas-mixture or replaces the indicator gas with another indicator gas, ensuring that the wash-out of gas 1 is performed together with the wash-in of gas 2. This has several advantages. The indicator gas injector has the advantages of being simple and built up from standard parts. It has been in use for 5 years, and has proven to be a reliable instrument that has never failed. Although it has been developed for use in combination with a mechanical ventilator, it can also be used alone, to perform wash-out tests on spontaneously breathing subjects. However, the device has some limitations. The main limitation is that the device can not be connected to ventilators that require high driving pressures on their gas-inlets, as most modern ventilators do. Another limitation is that, due to a buffering bellows in the

mechanical ventilator, the indicator gas fraction transition at the begin of the wash-out is not perfectly step-wise. This makes measurement of the inspiratory indicator gas-fraction and a correction in the algorithm for the lung volume calculation necessary. To overcome these disadvantages another device (not described in this thesis) has been made by us that injects, during inspiration, a constant flow of indicator gas into the inspiratory gas mixture near the tracheal tube of the subject [43]. When the subject is ventilated with a constant inspiratory flow, the new device can generate a constant inspiratory indicator gas fraction. The device has the advantages of being uncomplicated (the constant flow is generated with a critical orifice), suitable with all kinds of ventilators and capable of generating a perfect step-wise indicator gas transition at the beginning of the wash-out. Currently we are also developing and commercializing a device that is capable of injecting the indicator gas in a flow-proportional manner near the endotracheal tube [30], that has the advantage of being applicable with all ventilators and in all ventilatory modes including pressure support, assisted breathing and spontaneous breathing.

Flow measurement. In all the measurements that have been described in this thesis the respiratory flow was measured near the mouth using a Fleisch pneumo-tachograph in combination with a Validyne pressure transducer. This combination provides a reliable means of measuring respiratory flow. The frequency response is sufficient (a flat response for frequencies up to 80 Hz is easily attainable) to follow the sudden flow variations at the beginning and end of inspiration and at the beginning of expiration during mechanical ventilation. The pneumatic resistance of the device is small compared to the resistance of the other tubing of the ventilation circuit. The Validyne pressure transducer is extremely sensitive with a range between -2 and +2 hPa, and has nearly symmetric pressure chambers, such that a common mode rejection ratio of better than 50 at 30 Hz can easily be attained [26]. The reliability and favourable characteristics of the combination Fleisch pneumo tachograph-Validyne pressure transducer are the main reasons that they are commonly used. There are also, however, some disadvantages. The placement of the flow head near the endotracheal tube increases the instrumental dead space by 60-100 ml. Sputum production by the patient can partially block the linearizing capillaries in the Fleisch head, causing a calibration error. Although we have seldom encountered a (partially) blocked Fleisch head, it remains a phenomenon that one must be aware of, and reduces the applicability of the system for continuous patient monitoring. To overcome or relieve these problems two approaches are possible. The first

is to develop flow meters that are small, lightweight and insensitive for shock and position changes, but still possess the frequency response and common mode rejection ratio that is needed. A promising example is a flow meter based on heat transfer [91]. Another approach is to measure the flow of the inspiration and expiration separately in or near the mechanical ventilator. In this approach the gas that, due to compression by airway pressure variations, remains in the tubing between the ventilator and the patient, must be calculated and subtracted from the measured flow and a correction must be made for the amount of water vapor that condenses between the tracheal tube and the expiratory flow meter. However, modern heat-moisture exchangers are capable to take up the most part of the water vapor from the expiratory gas, so that no further condensation occurs in the expiratory limb of the tubing system. Preliminary data [90] show that a good heat moisture exchanger reduces the humidity of the expired air from 36 g/m^3 to 8 g/m^3, or a dew temperature of 8 °C.

Gas fraction measurement. In our measurements the inspiratory and expiratory gas was analysed with a quadrupole mass spectrometer. A mass spectrometer can accurately measure the fractions of several gases (pseudo-)simultaneously with high precision and fast response. Because the pressure in the measuring chamber is negligible with respect to atmospheric pressure, the device is relatively insensitive for pressure variations at the capillary inlet. However, if very long capillaries are used, the delay time will be very long and delay variations due to variations of the inlet pressure will become very large. A capillary of 30 m may have a delay time of 19 s and a response times (10-90%) of approximately 150 ms [61]. In that case a variation of the inlet pressure of only 10 hPa (1% of atmospheric pressure) results in a delay variation of 1% [7] or 190 ms, which is too large to for accurate calculation of lung volume and ventilation inhomogeneity. Thus, the mass spectrometer must be placed at the bed-side of the patient, where it interferes with patient care because it takes up much floor space, and produces noise and heat. Furthermore, the device is very costly and requires specialized staff. Therefore, efforts have been made to develop other devices to measure gas fractions without the disadvantages of mass spectrometers. A promising method to measure the fraction of SF_6 involves modifying a mainstream CO_2 analyzer to make it sensitive for SF_6 instead of CO_2 [55, 27]. The main advantage of such a device for use in the intensive care environment is, that the measurement takes place in the airway tubing itself, so that delay between the gas fraction measurement and the flow measurement is of instrumental origin, and not dependent of the composition of the respiratory gas mixture or

the airway pressure [9].

References

[1] A. Arieli and H.D. van Liew. Corrections for the response time and delay of mass spectrometers. *J Appl Physiol*, 51:1417–1422, 1981.

[2] J.H.T. Bates, G.K. Prisk, T.E. Tanner, and A.E. McKinnon. Correcting for the dynamic response of a respiratory mass spectrometer. *J Appl Physiol*, 55:1015–1022, 1983.

[3] M.R. Becklake. A new index of the intrapulmonary mixture of inspired air. *Thorax*, 7:111–116, 1952.

[4] A. Bouhuys. Distribution of inspired gas in the lungs. In W.O. Fenn and H. Rahn, editors, *Handbook of Physiology–Respiration 1*, volume Respiration 1, chapter 29, pages 713–733. Williams and Wilkins, Baltimore, 1964.

[5] A. Bouhuys, K-E. Hagstam, and G. Lundin. Efficiency of pulmonary ventilation during rest and light exercise. a study of alveolar nitrogen wash-out curves in normal subjects. *Acta Physiol Scand*, 35:289–304, 1956.

[6] A. Bouhuys, S. Lichtneckert, C. Lundgren, and G. Lundin. Voluntary changes in breathing pattern and N_2 clearance from lungs. *J Appl Physiol*, 16(6):1039–1042, 1961.

[7] U. Boutellier, Kündig, U. Gomez, P. Pietsch, and E.A. Koller. Respiratory phase detection and delay determination for breath-by-breath analysis. *J Appl Physiol*, 62:837–843, 1987.

[8] H.A. Bruining. Two simple assemblies for the application of intermittent mandatory ventilation with positive end-expiratory pressure. *Intensive Care Med*, 10:33, 1984.

[9] J.X. Brunner and D.R. Westenskow. How the rise time of carbon dioxide analysers influences the accuracy of carbon dioxide measurements. *Br J Anaesth*, 61:628–638, 1988.

[10] J.X. Brunner, G. Wolf, G. Cumming, and H. Langenstein. Accurate measurement of N_2 volumes during N_2 washout requires dynamic adjustment of delay time. *J Appl Physiol*, 59:1008–1012, 1985.

[11] J.X. Brunner and G. Wolff. *Pulmonary function indices in intensive care patients*. Springer Verlag, Berlin Heidelberg, 1988.

[12] G.C. Carlon, S. Miodownik, Y. Guy, and J.S. Groeger. A computerized technique to measure functional residual capacity in patients on mechanical ventilation. *Crit Care Med*, page 274, March 1984.

[13] A Cournand, E. Baldwin, R.C. Darling, and D.W. Richard. Studies of intrapulmonary mixtures of gases. IV. the significance of the pulmonary emptying rate and a simplified open circuit measurement of residual air. *J Clin Invest*, 20:681–689, 1951.

[14] D.B Craig. Postoperative recovery of pulmonary function. *Anesthesia and Analgesia*, 60(1):46–52, januari 1981.

[15] A.B.H. Crawford, D.J. Cotton, M. Paiva, and L.A. Engel. Effect of airway closure on ventilation disribution. *J Appl Physiol*, 66(6):2511–2515, 1989.

[16] A.B.H. Crawford, D.J. Cotton, M. Paiva, and L.A. Engel. Effect of lung volume on ventilation disribution. *J Appl Physiol*, 66(6):2502–2510, 1989.

[17] A.B.H. Crawford, M. Makowska, M. Paiva, and L.A. Engel. Convection- and diffusion-dependent ventilation maldistribution in normal subjects. *J Appl Physiol*, 59(3):838–846, 1985.

[18] JC Cruz. A combined parallel and series distribution model of inspired inert gases. *Respir Physiol*, 86:1–14, 1991.

[19] G. Cumming and A.R. Guyatt. Alveolar gas mixing efficiency in the human lung. *Clin Sci*, 62:541–547, 1982.

[20] D.R. Dantzker, C.J. Brook, P. Dehart, J.P. Lynch, and J.G. Weg. Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis*, 120:1039–1052, 1979.

[21] R.C. Darling, A. Cournand, and D.W. Richards. Studies on intrapulmonary mixture of gases. V. forms of inadequate ventilation in normal and emphysematous lungs, analysed by means of breathing pure oxygen. *J Clin Invest*, 23:55–67, 1944.

[22] N.J.H. Davies and D.M. Denison. The uses of long sampling probes in respiratory mass spectrometry. *Respir Physiol*, 37:335–346, 1979.

[23] W.R. de Vries, S.C.M. Luijendijk, and A. Zwart. Helium and sulfurhexafluoride washout in asymmetric lung models. *J Appl Physiol*, 51(5):1122–1130, 1981.

[24] D. Dreyfuss and G. Saumon. Barotrauma is volutrauma, but which volume is the one responsible? *Intens Care Med*, 18:139–141, 1992.

[25] D. Dreyfuss, P. Soler, G. Basset, and G. Saumon. High inflation pressure pulmonary edema. *Am Rev Respir Dis*, 137:1159–1164, 1988.

[26] C. Duvivier, J. Rotger, J. Felicio Da Silva, R. Peslin, and D. Navajas. Static and dynamic performances of variable reluctance and

piezoresistive pressure transducers for forced oscillation measurements. *Eur Respir Rev*, 1:146–150, 1991.

[27] T.D. East, K.P. Andriano, and N.L. Pace. Automated measurement of functional residual capacity by sulfur hexafluoride washout. *J Clin Monit*, 3(1):14–21, 1987.

[28] Th.D. East, J.C.C.M. in 't Veen, N.L. Pace, and S. McJames. Functional residual capacity as a noninvasive indicator of optimal positive end-expiratory pressure. *J Clin Monit*, 4:91–98, 1988.

[29] Th.D. East, J. C. C. in 't Veen, T.A. Jonker, N.L. Pace, and S. McJames. Computer controlled positive end-expiratory pressure titration for effective oxygenation without frequent blood gases. *Crit Care Med*, 16(3):252–257, 1988.

[30] Th.D. East, P.J.M. Wortelboer, E. van Ark, F.H. Bloem, M.L. Peng, N.L. Pace, R.O. Crapo., D. Drews, and T.P. Clemmer. Automated sulfur hexafluoride washout functional residual capacity measurement system for any mode of mechanical ventilation as well as spontaneous ventilation. *Crit. Care Med*, 18(1):84–91, jan 1990.

[31] N.H. Edelman, A.H. Norris, and N.W. Shock. Effects of respiratory patern on age differences in ventilation uniformity. *J Appl Physiol*, 24(1):49–53, 1968.

[32] L. Engel. Gas mixing within the acinus of the lung. *J. Appl Physiol*, 54(3):609–618, 1983.

[33] A. Engelhardt. Über den verlauf der Entlüftung der lunge bei reiner sauerstoffatmung. *Z Biol*, 99:596–613, 1939.

[34] C.R. Felton, H.D. Montenegro, and G.M. Saidel. Inspiratory flow effects on mechanically ventilated patients: lung volume, inhomogeneity, and arterial oxygenation. *Intensive Care Med*, 10:281–286, 1984.

[35] C.R. Felton, G.M. Saidel, and H.D. Montenegro. Moment analysis of multibreath nitrogen washout with a variable input gas composition. *med & Biol Eng & Computing*, 22:496–492, 1984.

[36] G.M. Fleming, E.H. Chester, J. Saniie, and G.M. Saidel. Ventilation inhomogeneity using multi-breath washout; comparison of moment ratios with other indexes. *Am Rev Respir Dis*, 121:789–794, 1980.

[37] W. S. Fowler. Lung function studies II. the respiratory dead space. *Am J Physiol*, 154:405–416, 1948.

[38] W.S. Fowler, E.R. Jr. Cornish, and S.S. Kety. Lung function studies. VIII. analysis of alveolar ventilation by pulmonary N_2 clearance curves. *J Clin Invest*, 31:40–50, 1952.

[39] G.J. Gallivan and W.N. McDonell. An evaluation of the multiple-breath nitrogen washout as a pulmonary function test in dairy cattle. *Can J Vet Res*, 53:133–142, 1989.

[40] L. Gattinoni, A. Pesenti, L. Avalli, F. Rossi, and M. Bombino. Pressure-volume curve of total respiratory system in acute respiratory failure. *Am Rev Respir Dis*, 136:730–736, 1987.

[41] D.M. Gomez, W.A. Briscoe, and G. Cumming. Continuous distribution of specific tidal volume throughout the lung. *J Appl Physiol*, 19(4):683–692, 1964.

[42] I. Gültuna, P.E.M. Huygen, C. Ince, and H.A. Bruining. A new method of injecting indicator gases for frc determination in mechanically ventilated patients. *Pflüg. Arch.*, 416:S2, 1990.

[43] I. Gültuna, P.E.M. Huygen, C. Jabaaij, W.P.J Holland, C. Ince, and H.A. Bruining. A simple device to inject indicator gas for washout tests during mechanical ventilation. *Int Care Med*, 18:304–308, 1992.

[44] I. Gültuna, P.E.M. Huygen, H. Strijdhorst, C. Ince, and H.A. Bruining. Clinical applications of an indicator washout test during artificial ventilation. *Intensive Care Med*, 16:165, 1990.

[45] J.S. Haldane and J.G. Priestley. The regulation of the lung ventilation. *J. Physiol*, 32:225–266, 1905.

[46] T. Hashimoto, A.C. Young, and C.J. Martin. Compartmental analysis of the distribution of gas in the lung. *J Appl Physiol*, 23(2):203–209, 1967.

[47] J. Hruby and J. Butler. Variability of routine pulmonary function tests. *Thorax*, 30:548, 1975.

[48] P.E.M. Huygen, B.W.A. Feenstra, W.P.J. Holland, C. Ince, H. Stam, and H.A. Bruining. Design and validation of an indicator gas injector for multiple gas wash-out tests in mechanically ventilated patients. *Crit Care Med*, 18:754–759, 1990.

[49] P.E.M. Huygen, B.W.A. Feenstra, E. Hoorn, J.R.C. Jansen, and A. Zwart. PDPS: a pulmonary data processing system for assessment of gas exchange properties by multiple gas wash-out. *Comp Meth Prog Biomed*, 36:223–235, 1991.

[50] P.E.M. Huygen, I. Gültuna, C. Ince, A. Zwart, J.M. Bogaard, B.W.A. Feenstra, and H.A. Bruining. A sensitive ventilation inhomogeneity index from multiple breath indicator gas wash-out tests, applied on mechanically ventilated patients. *Crit Care Med*, 21:1149–1158, 1993.

[51] P.E.M. Huygen, H. Strijdhorst, C. Ince, A. Zwart, B.W.A. Feenstra, and H.A. Bruining. A new measure for pulmonary ventilation inhomogeneity using indicator gas washout test. *Pflüg Arch*, 414:S198, 1989.

[52] B.S. Hylkema, P. Barkmeyer-Degenhart, Th.W. van der Mark, R. Peset, and H.J. Sluiter. Measurement of functional residual ca-

pacity during mechanical ventilation for acute respiratory failure. *Chest*, 81:27–30, 1982.

[53] H.B. Jones. Preoxygenation and nitrogen elimination. Technical Report MCREXD-696-114, US Air Force Medical Laboratory, 1948.

[54] H.B. Jones. Nitrogen elimination. In O. Glasser, editor, *Medical Physics*. Year Book Publishers, Inc., Chicago, 2^{nd} edition, 1950.

[55] C. Jonmarker, R. Castor, B. Drefeld, and O. Werner. An analyser for in-line measurement of expiratory hexafluoride concentration. *Anesthesiology*, 63:89–95, 1985.

[56] C. Jonmarker, L. Jansson, B. Jonson, A. Larsson, and O. Werner. Measurement of functional residual capacity by sulfur hexafluoride washout. *Anesthesiology*, 63:89–95, 1985.

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

[58] Kapitan K.S. Information content of the multibreath nitrogen washout: effects of experimental error. *J Appl Physiol*, 64(4):1621–1627, 1990.

[59] G. Lamedica, V. Brusasco, A. Taino, and R. Ramonio. Analysis of nitrogen multibreath washout curves through a statistical approach. *Respiration*, 39:333–343, 1980.

[60] A. Larsson, C. Jonmarker, and O. Werner. Ventilation inhomogeneity during controlled ventilation. which index should be used? *J Appl Physiol*, 65:2030–2039, 1988.

[61] J.G.C. Lerou. *The use of long sampling tubes in respiratory mass spectrometry*. PhD thesis, Catholic University of Nijmegen, the Netherlands, 1984.

[62] S. M. Lewis, J. W. Evans, and A. A. Jalowayski. Continuous distribution of specific ventilation recovered from indicator gas washout. *J Appl Physiol*, 44:416–423, 1978.

[63] S.C.M. Luijendijk, W.R. de Vries, and A Zwart. Collateral ventilation by diffusion across the alveolar walls and the exchange of inert gases in the lung. *Eur Respir J*, 4:1228–1236, 1991.

[64] S.C.M. Luijendijk, W.R. de Vries, and Zwart A. Collateral ventilation by diffusion and the exchange of inert gases in the lung. *Eur Resp J*, 3(Supp 10):186s, 1990.

[65] S.C.M. Luijendijk, A. Zwart, W.R. de Vries, and W.M. Salet. The sloping alveolar plateau at synchronous ventilation. *Pflügers Archiv*, 384:267–277, 1980.

[66] C.J. Martin, S. Tsunoda, and A.C. Young. Lung emptying patterns in diffuse obstructive pulmonary syndromes. *Respir Physiol*, 21:157–168, 1974.

[67] C.B. McCall, R.E. Hyatt, F.W. Noble, and D.L. Fry. Harmonic content of certain respiratory flow phenomena of normal individuals. *J Appl Physiol*, 10:215–218, 1957.

[68] M.R. Miller and A.C. Pincock. Linearity and temperature control of the fleisch pneumotachograph. *J Appl Physiol*, 60:710–715, 1986.

[69] T. Nakamura, T. Takishima, T. Okubo, T. Sasaki, and H. Takahashi. Distribution function of the clearance time constant in lungs. *J Appl Physiol*, 21:227–232, 1966.

[70] G. von Nieding, H. Löllgen, U. Smidt, and H. Linde. Simultaneous washout of helium and sulfur hexafluoride in healthy subjects and patients with chronic bronchitis, bronchial asthma, and emphysema. *Am Rev Respir Dis*, 116:649–660, 1977.

[71] M. Paiva. Two pulmonary function indexes suggested by a simple mathematical model. *Respiration*, 32:389–403, 1975.

[72] W.H. Paloski, J.C. Newell, D.G. Gisser, H.H. Stratton, S.J. Annest, M.E. Gottlieb, and D.M. Shah. A system to measure functional residual capacity in critically ill patients. *Crit Care Med*, 9:342–346, 1981.

[73] J. Pompe, C. Ince, P.E.M. Huygen, J.M. Hendriks, J. Kesecioğlu, and H.A. Bruining. End expiratory lung volume and ventilation inhomogeneity after intratracheal nebulisation of endotoxine in pigs. *Eur Resp J. (in press)*, 1993.

[74] J.C. Pompe, I. Gültuna, P.E.M. Huygen, J. Kesecioğlu, C. Ince, and H.A. Bruining. End-expiratory lung volume and ventilation inhomogeneity during bronchoconstriction in pigs. *Intens Care Med*, 18:S219 (Abs.), 1992.

[75] L. Powell Zarins. Real-time moment analysis of pulmonary nitrogen washout. In Clausen J.L., editor, *Pulmonary Function testing: guidelines and controversies. Equipment, methods and normal values*. Academic Press, 1982.

[76] W.H. Press, B.P. Flannery, Teukolsky S.A., and Vetterling W.T. *Numerical Recipes, the Art of Scientific Computing*, volume Cambridge, UK. Cambridge University Press, Cambridge, UK, 1986.

[77] K. Prowse and G. Cumming. Effect of lung volume and disease on the lung nitrogen clearance delay. *J Appl Physiol*, 34(1):23–33, 1973.

[78] Ph. Quanjer, ed. Standardized lung function testing; report working party "standardization of lung function tests". *Bull Eur Physiopath Resp*, 19(suppl. 5):1–95, 1983.

[79] H. Rahn and L. E. Fahri. Ventilation, perfusion, and gas exchange — the $\dot{V}_A/\dot{Q}$ concept. In W. O. Fenn and H. Rahn, editors, *Handbook*

of Physiology. Volume I: Respiration, chapter 30, pages 735–766. Am Physiol Soc, Washington DC, 1964.

[80] J.S. Robertson, W.E. Siri, and H.B. Jones. Lung ventilation patterns determined by analysis of nitrogen elimination rates; use of the mass spectrometer as a continuous gas analyser. *J Clin Invest*, 29:577–590, 1950.

[81] A. Roos, H. Dahlstrom, and J.P. Murphy. Distribution of inspired air in the lung. *J Appl Physiol*, 7:645–659, 1955.

[82] G.M. Saidel, R.B. Salmon, and E. H. Chester. Moment analysis of pulmonary washout. *J. Appl. Physiol.*, 38:328–334, 1975.

[83] Jafar Saniie, Gerald M. Saidel, and Edward H. Chester. Real-time moment analysis of pulmonary nitrogen washout. *J Appl Physiol*, 46(6):1184–1190, 1979.

[84] R. Serra and B.F. Visser. Diagramme O_2–CO_2 alveolaire. *Le poumon et le Cœur*, 10:1261–1272, 1963.

[85] B.E. Shykoff and H.T. Swanson. A model-free method for mass spectrometer response correction. *J Appl Physiol*, 63:2148–2153, 1987.

[86] D.P.J. Six, W.R. de Vries, and S.C.M. Luijendijk. Collateral ventilation and the sloping alveolar plateaus of He and SF_6: a model study. *Respir Physiol*, 90:145–158, 1992.

[87] B.A. Sjöqvist, K. Sandberg, O. Hjalmarsson, and D. Olsson. Method for analysing multiple-breath nitrogen wash-outs. *Med Biol Eng Comput*, 24:83–90, 1986.

[88] S. Tsunoda, A.C. Young, and C.J. Martin. Emptying patterns of lung compartments in man. *J Appl Physiol*, 32:644–649, 1972.

[89] M.J. Turner, I.M. MacLeod, and A.D. Rothberg. Measurement of frequency response and common-mode gain of neonatal respiratory pressure and flow measurement systems part 1. apparatus. *Clin Phys Physiol Meas*, 10:–239, 1989.

[90] N. Ünal, J.C. Pompe, I. Gültuna, W.P.J. Holland, P.E.M. Huygen, K. Jabaaij, C. Ince, B. Saygin, and H.A. Bruining. An experimental set-up to test heat-moisture exchangers. Intens Care Med (In press), 1994.

[91] A.F.P. van Putten. Measuring the flow of a medium with an integrated silicon double bridge configuration. VDI *Berichte*, 509:47–51, 1984.

[92] W. van Rooyen. *Respiratory and hemodynamic effects of diminished expiratory flow during artificial ventilation*. PhD thesis, Erasmus Universiteit Rotterdam, 1986.

[93] L.J. Weaver, K.R. Pierson, R. Kellie, B. Bonner, and K.C. Craig. A practical procedure fore measuring functional residual capacity

during mechanical ventilation with or without PEEP. *Crit Care Med*, 9:873, 1981.

[94] G.R. Weygandt. A sensitive five-breath N_2 washout test of distribution of ventilation. *J Appl Physiol*, 40:464–467, 1976.

[95] A. Zwart. Ventilation and perfusion distributions in lungs obtained by mass spectrometry. In *Proceedings of the IEEE Engineering in Medicine & Biology Society* 10^{th} *Annual International Conference*, pages 820–822, 1988.

[96] A Zwart, J.R.C. Jansen, and S.C.M. Luijendijk. Bohr dead space during helium washout. *Bull Europ Physiopath Resp*, 18:261–272, 1982.

Appendix A

Samenvatting

In dit proefschrift wordt de ontwikkeling van een methode beschreven om pulmonale uitwas tests te doen bij beademde patiënten. Voorafgaand aan een uitwas test ademt de patiënt eerst een gasmengsel in met een constante gasfractie van een inert, onoplosbaar indicator gas. Als dit gas homogeen verdeeld is in de longen, dan wordt de toevoeging van het indicator gas aan de inademingslucht gestaakt. Uit de snelheid en de manier waarop het indicator gas in de longen verdunt (gemeten aan de hand van de indicator gas fractie in het uitademingsgas aan de mond) kan het volume van de long en de mate van ventilatie inhomogeniteit worden bepaald. Beide grootheden zijn van belang bij de beademing van intensive care patienten, omdat zij kunnen helpen om het beademingsproces te optimaliseren en om problemen op te sporen.

Hoofdstuk 1 is een inleiding van het proefschrift. Hierin wordt het klinische nut van uitwas tests beschreven en een korte samenvatting van de komende hoofdstukken gegeven.

Hoofdstuk 2 beschrijft het ontwerp van en het onderzoek aan een instrument dat het indicator gas in een constante concentratie kan toevoegen aan het zuurstof-lucht mengsel dat de patient in te ademen krijgt. Het instrument moest voldoen aan de volgende specificaties: 1) De verandering van de indicator gas-fractie aan het begin van de uitwas moet snel genoeg zijn om visuele beoordeling van de uitwas curves mogelijk te maken; 2) De inspiratoire zuurstof-fractie moet constant blijven tijdens de uitwas procedure ondanks het veranderen van de indicator gasfractie; 3) De methode moet eenvoudig toe te passen zijn aan het bed van een intensive care patient en mag de patiëntenzorg niet verstoren; 4) Het beademingspatroon mag niet verstoord worden door de uitwas tests

(bijvoorbeeld door verandering van eind-expiratoire druk of slagvolume of het tijdelijk onderbreken van het beademings circuit); 5) Het moet mogelijk zijn om met twee gassen met verschillende diffusie coëfficiënten tegelijkertijd uitwas tests te doen. Hierdoor is het mogelijk om diffusiegerelateerde problemen in het gastransport te onderkennen; 5) De uitwas tests moeten computergestuurd kunnen plaatsvinden.

Het instrument bestaat uit een stelsel debiet-regulateurs en kleppen en mengt een stroom indicator gas met constant debiet met een grotere stroom zuurstof-lucht mengsel die ook een constant debiet heeft. De resulterende gas-stroom heeft een constante fractie van het indicator gas en is geschikt om een Servo ventilator (Siemens-Elema, Solna, Zweden) via de lage-druk ingang van beademingsgas te voorzien. De uitwas wordt gestart door de stroom van het indicator gas af te sluiten of te vervangen door een stroom van een ander indicator gas, zodat de uitwas van een indicator gas gecombineerd wordt met de inwas van een ander indicator gas, hetgeen bepaalde voordelen heeft. De voordelen van deze opzet zijn, dat het instrument opgebouwd is uit standaard debiet regulateurs en electromagnetische kleppen, en dat het een constante indicator gas-fractie tijdens de inwas garandeert. De voornaamste nadelen zijn, dat het instrument meer gas verbruikt dan nodig is voor de beademing van de patiënt (het overtollige gas wordt door een in de ventilator aanwezige afblaasklep geloosd), dat de indicator gas-fractie verandering aan het begin van de uitwas niet zuiver stapvormig is omdat er een balg in de Servo ventilator moet worden doorgespoeld en dat het instrument niet aan ventilatoren kan worden aangesloten die een hoge ingangs-druk (meer dan 3 Bar) nodig hebben.

Om de werking van het instrument te testen zijn uitwas tests gedaan aan een dummy long bestaande uit een stelsel van twee balgen, aan 7 vrijwilligers die zich door de ventilator passief lieten beademen (zonder trachea canule) en aan 12 kunstmatig beademde intensive care patienten. Met de uitwas tests aan de balg kon het volume ervan zeer nauwkeurig berekend worden. Uit de uitwas test werd een volume van $3,04 \pm 0,01$ l berekend, terwijl het werkelijke volume $3,05 \pm 0,01$ l was. Bij de proefpersonen werden 4 inwas tests en 4 uitwas tests gedaan. Uit de uitwas tests waarbij de expiratoire slagvolumina een kleinere standaard deviatie hadden dan 100 ml werd het long volume berekend. Dit werd vergeleken met het longvolume dat met een gesloten helium verdunningsmethode bepaald werd in het longfunctie laboratorium. De intra-individuele standaard deviatie van de berekende longvolumina was gemiddeld 5%. Bij één van de proefpersonen was de intra-individuele standaard deviatie 10%. Het verschil van de longvolume-berekening met de open en de gesloten methode was gemiddeld $3 \pm 6\%$ en was statistisch niet significant.

Uit de resultaten van de uitwas tests aan de beademde patienten bleek dat het long volume van deze patienten met een reproduceerbaarheid van gemiddeld 3% bepaald kon worden. De maximale intra-individuele standaard-deviatie die wij vonden was 6%. Figuur 2.4 laat het effect zien van het niet zuiver stapvormig zijn van de verandering van de indicator gas-fractie aan het begin van de uitwas. Het blijkt dat na 3-4 ademcycli de inspiratoire indicator gas-fractie constant is. Deze tijd is kort genoeg om niet storend te zijn bij een visuele beoordeling van het verloop van de expiratoire gas-fractie tijdens de uitwas test. Het is wel nodig om met de niet-stapvormigheid van de inspiratoire gas-fractie rekening te houden bij het berekenen van het longvolume. Geconcludeerd wordt dat de ontwikkelde indicator gas injector voldoet aan de 6 ontwerp eisen.

Hoofdstuk 3 beschrijft een computer programma waarmee de signalen van een uitwas test kunnen worden geregistreerd en off-line geanalyseerd. Bij de analyse wordt gebruik gemaakt van het in-en expiratoire debiet signaal, de fracties van een of meer inerte indicator gassen die inwassen of uitwassen en de fracties van de metabole gassen zuurstof en CO_2. Het programma maakt gebruik van de mogelijkheden van een massaspectrometer om de fracties van verschillende gassen op een uniforme manier en met korte respons tijd te meten. Een vergelijking van het gedrag van de indicator gassen, die tijdens de uitwas een overgangsproces doormaken en de metabole gassen, die een stabiele toestand representeren, levert gegevens over ventilatie inhomogeniteit en ventilatie-perfusie inhomogeniteit op die niet te verkrijgen zijn door afzonderlijke analyse van de metabole gassen of de indicator gassen. Met de verkregen gegevens kunnen verschillende modellen van ventilatie inhomogeniteit worden onderscheiden. Figuur A.1 geeft verschillende van deze mechanismen weer. De linker kolom van deze figuur laat een gestyleerd en geïdealiseerd beeld van de longen zien met een bepaalde vorm van ventilatie inhomogeniteit. De middelste kolom laat zien hoe tijdens een uitwas expiratie de indicator gasfractie aan de mond verandert als functie van het in de expiratie uitgeademde volume gas (expirogram), aannemende dat de inspiratoire indicator gas-fractie tijdens de uitwas gelijk is aan 0. Een expirogram wordt doorgaans genormaliseerd door op de x-as het quotient van het uitgeademde gasvolume en het teugvolume uit te zetten en op de y-as het quotient van de gasfractie aan de mond en de eind-expiratoire gasfractie aan de mond uit te zetten. In dit coördinatensysteem is het expirogram een curve die zich in het gebied tussen $x = 0$ en $x = 1$ en tussen $y = 0$ en $y = 1$ bevindt (in uitzonderlijke gevallen kan de expiratoire fractie groter worden dan de eind-expiratoire fractie, zodat het expirogram de lijn $y = 1$ overschrijdt). Het oppervlak in dit gebied is gelijk aan 1. Het op-

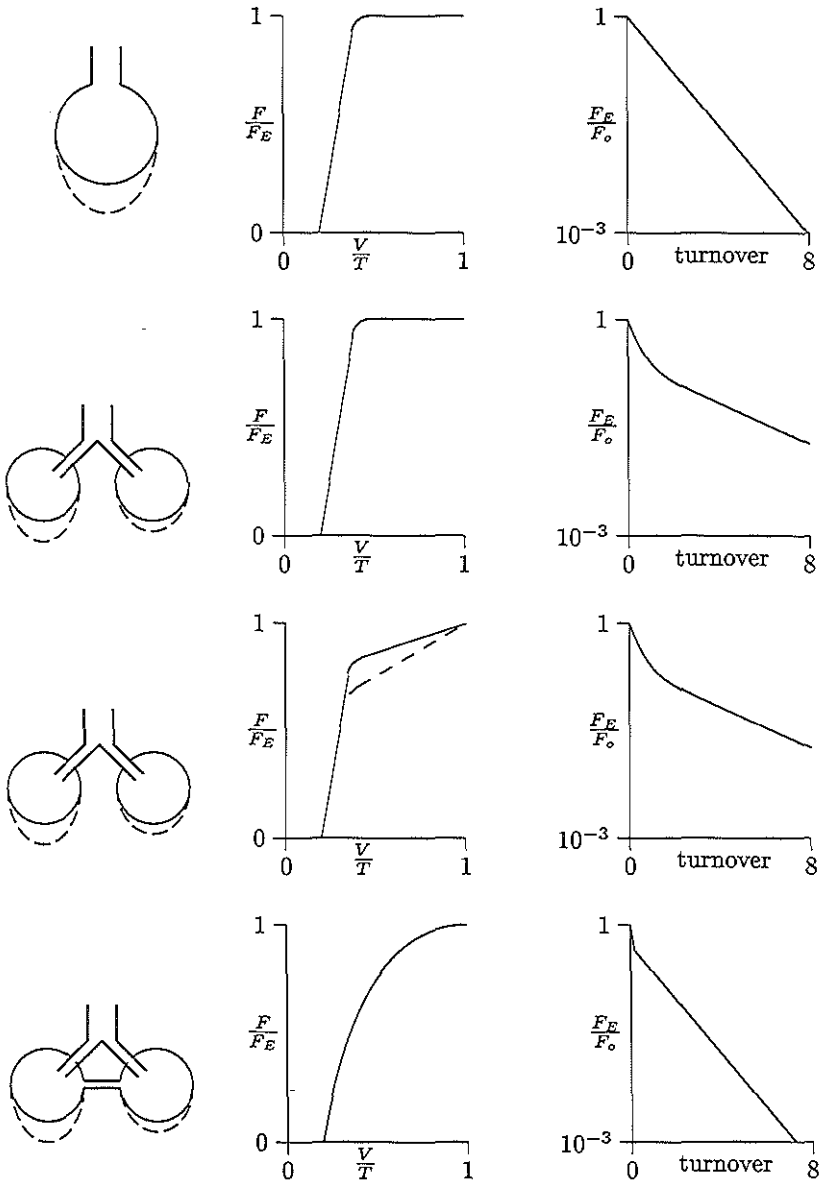

FIGURE A.1: Verschillende typen ventilatie inhomogeniteit. Zie tekst.

pervlak tussen het expirogram en de lijn $y = 1$ wordt Bohr dode ruimte genoemd.

De rechter kolom van figuurA.1 laat het verloop van de eind-expiratoire indicator gas-fractie zien als functie van de sinds het begin van de uitwas uitgeademde hoeveelheid lucht. Op de y-as is het quotient van de eind-expiratoire gas-fractie en inspiratoire gas-fractie sinds het begin van de uitwas logarithmisch uitgezet en op de x-as het quotient van de sinds het begin van de uitwas uitgeademde hoeveelheid gas en het longvolume (turnover). Deze curve heet *uitwas curve*.

Bovenaan is een homogeen geventileerde long afgebeeld. Buitenlucht wordt via de trachea en de hogere bronchiën de alveoli ingezogen en mengt zich daar met het aanwezige gas. Bij het uitademen passeert aan de mond eerst het gas dat in de hogere luchtwegen zat en dus dezelfde samenstelling had als het ingeademde gasmengsel. Als een volume van ongeveer 125 ml is uitgeademd passeert er ook gas uit de alveolaire ruimte, en spoedig is al het gas aan de mond afkomstig uit de alveoli. Omdat de ventilatie in de alveolaire ruimte homogeen is, blijft de samenstelling van het gas aan de mond in deze fase van de ademhaling constant, onafhankelijk van het uitgeademde volume. Het horizontale deel van het expirogram dat daardoor ontstaat wordt *alveolair plateau* genoemd. In de homogene long kan de verdunning van het indicator gas als functie van de luchtverversing mathematisch beschreven worden met een enkele exponentiële functie. Daardoor is de uitwas curve een rechte lijn.

De twee volgende modellen stellen ventilatie inhomogeniteit voor doordat parallelle gebieden in de long verschillende luchtverversingssnelheid hebben. Dit kan ontstaan door locale verschillen in stijfheid van het longweefsel of door locale verschillend van de mechanische weerstand van de luchtwegen. In ieder gebied zal de verdunning van het indicator gas in de loop van de uitwas een mono-exponentieel proces zijn. De eind-expiratoire gasfractie aan de mond zal een gewogen gemiddelde zijn van de gasfracties in de verschillende parallelle gebieden, en daardoor een multi-exponentiële functie zijn van de turnover. De parallelle gebieden kunnen in een expiratie *synchroon* of *asynchroon* ledigen. In het eerste geval blijft de verhouding van het debiet uit de verschillende gebieden constant en in het tweede geval verandert zij in de loop van de uitademing. De eind-expiratoire gas-fractie is een debiet-gewogen gemiddelde van de gasfracties in de verschillende gebieden. Bij synchrone lediging blijft, nadat het gas uit de dode ruimte is uitgeademd, de samenstelling van het uitgeademde gas constant, zodat het alveolair plateau een horizontale lijn is. Bij synchrone lediging verandert de eind-expiratoire gas-fractie in de loop van de expiratie. Doorgaans ledigen de beter ven-

tilerende gebieden voornamelijk aan het begin van de uitademing, en de slechter ventilerende gebieden voornamelijk aan het eind van de uitademing. Omdat in de beter ventilerende gebieden het indicator gas sterker verdund is dan in de slechter ventilerende gebieden zal de indicator gasfractie in de loop van de uitademing stijgen, zodat het alveolaire plateau een positieve helling heeft. Deze helling zal in de loop van de uitwas geprononceerder worden omdat de verhouding van de indicator gas-fracties in de slecht geventileerde gebieden en in de beter geventileerde gebieden toeneemt in de loop van de uitwas.

Het laatste model stelt ventilatie inhomogeniteit door een longitudinale gradiënt voor. Zo een gradiënt kan ontstaan doordat luchtwegen zijn afgesloten en de achterliggende gebieden alleen indirect via andere gebieden kunnen ventileren (collaterale ventilatie), of doordat er verschillen in vertakkingsdiepte zijn in de lunchtwegen, waardoor er vanaf de grens tussen het dode ruimte gas en het alveolaire gas (het *diffusie front*) via een ingewikkeld samenspel van convectie en diffusie een gradiënt ontstaat. Bij seriële ventilatie inhomogeniteit kan in korte tijd een constante verdeling van het indicator gas in de long ontstaan waarbij de verhouding van de indicator gasfractie in de verschillende gebieden van de long onderling niet meer veranderen. De gradiënt uit zich in een stijgend alveolair plateau. Deze helling van het alveolair plateau zal echter na een beperkt aantal ademcycli niet meer groeien. De eindexpiratoire gasfractie zal, nadat de constante verdeling van het indicator gas in de long is ontstaan, een mono-exponentiële functie zijn van het uitgeademde volume.

Het beschreven computer-programma produceert grafieken van expirogrammen en uitwas curves en van het verloop van de Bohr dode ruimte in de loop van de uitwas. In de grafieken wordt telkens het gedrag van het uitwassende indicator gas vergeleken met het gedrag van CO_2. Hierdoor worden veranderingen van het gedrag van het indicator gas geäccentueerd en wordt de invloed van variabele teugvolumina op de vorm van de grafieken verminderd. Tenslotte kan in het geval van parallelle inhomogeniteit met sequentiële lediging onderzocht worden of de ongelijkmatige ventilatie gecompenseerd wordt door de perfusie, zodat de ventilatie-perfusie verhouding gelijk blijft.

Hoofdstuk 4 is een analyse van de nauwkeurigheid waarmee het long volume bepaald kan worden door middel van uitwas tests. De invloed van de volgende artefacten werd bepaald: 1) Stochastische factoren (constante ruis en constante signaal-ruis verhouding in het debiet-signaal en het gas-fractie signaal; 2) Variaties in de vertraging van de meting van het gas-fractie signaal door variaties in de tijd die nodig is voor het

transport van het gasmengsel naar de meetkamer; 3) Beperkte respons van het gas-fractie meetinstrument; 4) Effect van de metabole gaswisseling als die niet kan worden gecorrigeerd; 5) Effect van de oplosbaarheid van het indicator gas in bloed en organen.

De nauwkeurigheid van de gebruikte instrumenten is eerst bepaald. De signaal-ruis verhouding van de massaspectrometer blijkt voor de gebruikte indicator gassen beter te zijn dan 50. De 10-90% respons tijd op een stapvormige gas-fractie verandering is kleiner dan 40 msec voor helium en kleiner dan 50 msec voor SF_6, en de vertragingstijd bedraagt 228 msec. Overdruk aan de inlaat van het bemonsterings capillair veroorzaakt variaties in de vertraging van -0,28 msec/hPa. Viscositeitsvariaties van het te bemonsteren gas veroorzaken looptijdvariaties van 1,3 msec/μP. De signaal-ruis verhouding van het debiet signaal was groter dan 100.

De analyse van de invloed van de foutenbronnen op de nauwkeurigheid van de berekening was gedaan met behulp van de resultaten van uitwas tests aan patienten en proefpersonen. Het effect dat foutenbronnen op deze metingen zouden hebben gehad werd gesimuleerd door eenzelfde storing toe te voegen aan de signalen van de metingen. De grootste invloed op het berekende longvolume had het varieren van de vertraging van het gas-fractie signaal ten opzichte van het debiet signaal. Een extra vertraging van 10 ms kon een overschatting van het longvolume van 7% tot gevolg hebben. Zo een vertraging kan gemakkelijk ontstaan door variatie van de inspiratoire zuurstof-fractie of door verhoging van de gemiddelde druk in het ademcircuit. Bij onze opstelling is de invloed van de stap respons snelheid van de massaspectrometer op de long volume berekening veel kleiner. Als het gas-fractie signaal geconvolueerd wordt met een gaussische functie met $\sigma = 50$ msec, wat overeenkomt met een 0,1–0,9 respons tijd van 125 msec, dan verandert het berekende longvolume minder dan 3%. Meetruis heeft ook maar een beperkt effect op de nauwkeurigheid van de resultaten. Bij toevoeging van een signaal-ruis verhouding van 50 aan het gas-fractie signaal ontstonden longvolume variaties van minder dan 5%.

Om de invloed van het effect van oplosbaarheid van het indicator gas in het bloed te analyseren is een mathematisch model gemaakt van een geïdealiseerde long en het transport van het indicator gas door het bloed naar verschillende organen. De resultaten van de simulaties werden vergeleken met uitwas tests waarbij de uitwas van argon (bloed-gas partitie coëfficiënt λ: 0,023) werd gecombineerd met de inwas van SF_6 ($\lambda = 0,006$). Zowel bij de mathematische simulatie als bij de echte uitwas tests werd het longvolume 4% overschat bij de Argon uitwas test. Als bij de inwas van SF_6 het effect van de metabole gasuitwisseling werd

verwaarloosd, dan werd het longvolume met gemiddeld 6% onderschat.

Concluderend: bij uitwas tests moet er in de eerste plaats voor gezorgd worden dat de vertraging van het gas-fractie signaal ten opzichte van het debiet signaal binnen 10 ms nauwkeurig bekend is. In onze opstelling is de gas-fractie ruis de op één na grootste bron van onnauwkeurigheid.

Hoofdstuk 5 introduceert een nieuwe methode om een uitwas test te analyseren. De nieuwe analyse levert een nauwkeurige berekening van het longvolume op en een nieuwe index voor ventilatie inhomogeniteit. De methode is gebaseerd op een grafiek waarin voor iedere ademcyclus tijdens de uitwas het geschatte longvolume is uitgezet als functie van het quotient van de hoeveelheid tot dusver uitgewassen indicator gas en de hoeveelheid indicator gas die oorspronkelijk in de long aanwezig was. De curve door de meetpunten heet *volumes estimation curve*. Het longvolume wordt berekend als het quotient van de hoeveelheid sinds het begin van de uitwas uitgewassen indicator gas en de verdunning van het indicator gas die hier het gevolg van is. Omdat de verdunning niet meetbaar is wordt deze benaderd met de verdunning van het eind-expiratoire gas. Als er een verschil is tussen de eind-expiratoire indicator gas-fractie en de gemiddelde indicator gas-fractie in de longen (gemiddelde alveolaire gas-fractie), dan zal het geschatte longvolume daardoor afwijken van het werkelijke longvolume. In de loop van de uitwas neemt het verschil tussen de eind-expiratoire en de gemiddelde alveolaire gas-fractie af en worden de long volume schattingen steeds nauwkeuriger. In uitwas tests aan gezonde proefpersonen en beademde patienten bleek dat de eind-expiratoire gas-fractie lager is dan de gemiddelde alveolaire gas-fractie, en dat de volumes estimation curve goed benaderd kon worden door een rechte lijn. Extrapolatie van deze lijn levert een nauwkeurige waarde op van het long volume, en het quotient van de richtingscoëfficient van de lijn en het longvolume kan beschouwd worden als index voor ventilatie inhomogeniteit. Deze index is *volumes regression index* (S) genoemd.

Om de index te valideren zijn uitwas tests verricht bij een homogeen geventileerde dummy long, bij 9 gezonde proefpersonen en bij 37 beademde post-operatieve intensive care patienten, die aan de hand van de pré-operatief bepaalde waarde van de Tiffeneau index (een maat voor bronchiale obstructie) verdeeld waren in een CARA en een non-CARA groep. Het volume van de dummy long kon zeer nauwkeurig bepaald worden met de volumes regression methode. De gemeten volumes regression index was $0,02 \pm 0,04$. Bij de gezonde proefpersonen was de intra-individuele variatie coëfficiënt van de longvolume metingen gemiddeld 5% en maximaal 10%. Het verschil tussen het longvolume, gemeten

met de gesloten dilutie methode en het longvolume gemeten met de volumes regression methode was in deze groep gemiddeld 2%. Bij de gezonde proefpersonen werd een volumes regression index van $0,37 \pm 0,08$ gemeten. In de niet-obstructieve beademde patienten was S gelijk aan $0,6 \pm 0,2$, en in de obstructieve patienten was S gelijk aan $1,1 \pm 0,3$.

Om de gevoeligheid van de volumes regression index te vergelijken met die van conventionele ventilatie inhomogeniteits indices zijn van de beademde patienten ook de Becklake index en de moment ratio index bepaald. De moment ratio index kon niet bij alle patienten bepaald worden omdat in sommige patienten de benodigde turnover van 8 niet werd gehaald. Alle drie de indices waren hoger in de obstructieve patienten dan in de niet-obstructieve patienten. Het verschil was echter significanter voor de volumes regression index dan voor de andere twee indices ($p < 0,01$ voor volumes regression index en $p < 0,05$ voor de andere twee indices). Ook de correlatie van de volumes regression index was sterker dan de correlatie van de andere twee ventilatie inhomogeniteit indices met de Tiffeneau index. Bij de totale groep patienten was de correlatie coëfficiënt tussen volumes regression index en Tiffeneau index gelijk aan -0,68, terwijl de correlatie coëfficiënt tussen de Becklake index en de Tiffeneau index gelijk was aan -0,34. In de patiëntengroep waarin de turnover ratio groter was dan 8, was de correlatie coëfficiënt tussen de volumes regression index en de Tiffeneau index gelijk aan -0,61 en de correlatie coëfficiënt tussen de moment ratio index en de Tiffeneau index gelijk aan -0,41. In de beademde patienten was de intra-individuele reproduceerbaarheid van de longvolume metingen groter dan bij de proefpersonen ($\sigma = 3$ % voor de patienten en $\sigma = 5$ % voor de proefpersonen).

De conclusie is dat analyse van de volumes estimation curve een nauwkeurige schatting van het long volume oplevert en een ventilatie inhomogeniteits index die gebaseerd is op het verschil tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie, en die bij de beademde patiënten een goede correlatie heeft met chronische pulmonale obstructie.

Hoofdstuk 6 is een analyse van de vorm van de volumes estimation curve die in hoofdstuk 5 is geïntroduceerd. Als er geen ventilatie inhomogeniteit aanwezig is dan is deze curve een horizontale lijn omdat de schattingen van het long volume het werkelijke longvolume opleveren, onafhankelijk van de ademcyclus waarin deze schattingen zijn gedaan. De volumes estimation curve wijkt af van een rechte lijn als er een verschil ontstaat tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie. Het verloop van het verschil tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie is afhankelijk van

de aard van de ventilatie inhomogeniteit. In dit hoofdstuk is onderzocht hoe de volumes estimations curves van verschillende geïdealiseerde typen ventilatie inhomogeniteit er uit zouden zien. Bij een zuivere longitudinale gradiënt stelt zich aan het begin van de uitwas een stabiele verdeling van de gas-fractie over de verschillende gebieden van de long in, waardoor de verhouding tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie constant wordt. Onder deze omstandigheden heeft de volumes estimation curve een negatieve tweede afgeleide. Bij een zuivere parallelle ventilatie inhomogeniteit neemt de verhouding van de gas-fractie in de verschillende compartimenten toe in de loop van de uitwas. Daardoor neemt de verhouding tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie ook toe in de loop van de uitwas. Als gevolg hiervan heeft de volumes estimation curve een positieve tweede afgeleide. Staan de parallelle compartimenten echter in verbinding met de buitenlucht via een gezamelijke dode ruimte dan zullen aanvankelijk de gas-fracties in de verschillende compartimenten steeds sterker van elkaar gaan verschillen. Er vindt echter gasuitwisseling tussen de parallelle compartimenten plaats via de gezamelijke dode ruimte. Hierdoor ontstaat op den duur een stabiele situatie waarbij de verhouding tussen de gas-fracties in de verschillende compartimenten, en dus ook tussen de gemiddelde alveolaire gas-fractie en de eind-expiratoire gas-fractie, niet meer toeneemt. Daardoor zal de helling van de volumes estimation curve aanvankelijk toenemen, maar uiteindelijk weer afnemen.

Om te onderzoeken of de vorm van de volumes estimations curve verklaard kan worden door eenvoudige modellen van ventilatie inhomogeniteit zijn uitwas tests gedaan aan 9 gezonde proefpersonen en aan 6 CARA patienten van wie er drie alle tekenen van emphyseem vertonen. De eind-expiratoire en gemiddelde expiratoire gas-fracties van de uitwas tests zijn gefit aan een mathematisch model van een drie-compartiments long-model waarin twee parallelle compartimenten via een gezamelijke dode ruimte verbonden zijn met de buitenwereld. Het blijkt dat de volumes estimations curves van het model aanmerkelijk sterker gekromd zijn dan die van de proefpersonen en de patienten. Dit betekent dat er nog andere mechanismen een rol moeten spelen die niet gemodelleerd zijn.

Het bleek dat de volumes estimation curves van de patienten een sterkere kromming hadden dan de volumes estimations curves van de gezonde proefpersonen en die van de beademde patienten die gerapporteerd waren in hoofdstuk 5. Daarom werd de volumes regression index niet berekend in het interval waarbinnen tussen 70% en 90% van het indicator gas was uitgewassen, maar in het interval waarbinnen 80–95% was uitgewassen. De zo berekende volumes regression index was in de

gezonde proefpersonen $0,34 \pm 0,16$, bij de CARA patienten met aanwijzingen voor emphyseem $2,3 \pm 0,3$ en bij de overige patienten $1,1 \pm 0,0$. De volumes regression indices waren significant verschillend in de drie groepen ($p < 0,05$, berekend met Wilcoxon test). Ten slotte werd onderzocht of er aanwijzingen waren voor sequentiële lediging van de parallelle compartimenten. De model fit kon hierover geen uitsluitsel geven omdat hij niet gevoelig was voor de invloed van sequentiële lediging. Het verloop van de Bohr dode ruimte gedurende de uitwas gaf echter bij alle CARA patienten en bij 2 van de gezonde proefpersonen aan dat er sequentiële lediging plaatsvond.

Hoofdstuk 7 Is een epiloog waarin mogelijke toepassingen van de geïntroduceerde uitwas techniek voor het optimaliseren van de beademing van IC patienten wordt aangegeven, en waarin wordt aangegeven welke verbeteringen kunnen worden aangebracht om de methode te automatiseren en zo min mogelijk te laten interfereren met de patiëntenzorg.

Appendix B

Dankwoord

Op deze plaats wil ik graag iedereen bedanken die mij heeft geholpen met het voltooien van dit proefschrift.

In de eerste plaats wil ik mijn promotor Prof. Dr H.A. Bruining, co-promotor Prof.Dr Ir C. Ince en Dr Ir B.W.A. Feenstra bedanken. Zij waren de eerste begeleiders van het onderzoek, en ik heb veel van hen geleerd.

Ik bedank Ir W.P.J. Holland, die mij geholpen heeft op het gebied van de meet techniek, en altijd klaar stond met nuttige adviezen. Verder heb ik veel steun gehad van Dr J.M. Bogaard en Dr Ing. J.R.C. Jansen. Op C. Jabaaij kon ik altijd een beroep doen bij technische en organisatorische problemen. Ook heb ik veel hulp gehad van J. Bovenlander en R. Binkhorst van de Computer Ondersteuning Hoboken, en van J. Schulpen van de Centrale Instrumentatie Dienst. Ing. E. Hoorn heeft de basis gelegd voor het computerprogramma dat in hoofdstuk 3 is beschreven.

In de tijd dat ik dit dankwoord schreef kregen wij het ontstellende bericht dat Dr A. Zwart plotseling overleden was. Voor een groot deel bouwt dit proefschrift voort op ideën van Aart. Ik mis Aart erg als een hartelijk mens en als een gedreven, creatieve en onconventionele onderzoeker. Het spijt mij heel erg dat Aart niet bij mijn promotie kan zijn.

I am grateful to Dr J. Arnold who read the manuscripts and corrected my (mediocre) english style.

De verpleegkundigen van de Intensive Care Unit 10 zuid bedank ik voor hun medewerking en geduld tijdens de metingen aan de patiënten. Erick Branderhorst, Ismail Gültuna, Joke Hendrikx, Ellie Oostveen, Gini Peters, Jan Pompe en Jan Weststraten dank ik voor hun prettige samenwerking. Monique Norel, Anneke Loenen en de paranimfen Bob Kooi en Jan-Pieter Pijn hebben mij bijgestaan bij het verzorgen van het proefschrift en de promotie. De leden van de promotiecommissie bedank ik

voor het grondige en vlotte doorlezen van het manuscript. Theo en Stijn Jordans bedank ik voor het beschikbaar stellen van de tekening op de omslag.

For the processing of the data used in this thesis and for the preparation of the thesis itself extensive use has been made of *public domain* software, i.e. software that can be picked up from the Internet and used freely. It is great that people or institutions are willing to put efford in writing excellent software and offering it freely to community. Therefore I would like to thank the Free Software Foundation (Cambridge, Mass.) for the GNU Emacs editor, the gnuplot plotting program and the GNU AWK interpreter. I thank Russ Nelson for creating the Freemacs editor. Donald E. Knuth (Stanford University) created the wonderful TEX typesetting system that is not only used to typeset this booklet, but also to print and plot the results of calculations on wash-out signals. Leslie Lamport created the macro package LATEX for TEX. The layout of this thesis is based on a style file created by Victor Eijkhout, Nico Poppelier, Johannes Braams, members of the *Nederlands* TEX *genootschap* (however, blame me for style errors).

Tenslotte wil ik Tiemke, Onno en Tamar, die ook veel voor dit proefschrift over moesten hebben, bedanken.

Appendix C

Curriculum Vitae

Paul Huygen is in 1952 geboren in Maastricht. In 1972 begon hij, na het behalen van het HBS-B diploma met de studie experimentele natuurkunde aan de Rijks Universiteit Groningen. In 1978 haalde hij het kandidaatsexamen en in 1983 het doctoraal examen. Tevens werd het diploma stralingveiligheid C behaald. In 1984 werkte hij als fysicus aan de afdeling Thorax-Hart-Vaat chirurgie van het Radboud Ziekenhuis aan een instrument om tijdens coronaire bypass-operaties de capaciteit van de "bypass graft" te meten. Vanaf 1985 werkt hij als klinisch fysicus in de chirurgische Intensive Care van het academisch ziekenhuis/Dijkzigt te Rotterdam aan longfunctie onderzoek van kunstmatig beademde patienten. De Nederlandse Vereniging voor Klinische Fysica (NVKF) registreerde hem in 1989 als klinisch fysicus met registratie functie onderzoek.