RESPIRATORY AND HEMODYNAMIC EFFECTS OF DIMINISHED EXPIRATORY FLOW DURING ARTIFICIAL VENTILATION

THESIS

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THE PUBLIC DEFENCE WILL TAKE PLACE ON
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BY

WILLEM VAN ROOYEN

BORN IN BANDUNG

krips repro meppel

PROMOTIECOMMISSIE

PROMOTOR:	PROF. DR. A. VERSPRILLE
OVERIGE LEDEN:	PROF. DR. C. HILVERING
	PROF. DR. L.G. THIJS
	PROF. DR. D.L. WESTBROEK
CO-PROMOTOR:	DR. H.A. BRUINING

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Druk: Krips Repro Meppel

To Magali, Willem-Arnoud,
Milou and my parents

Contents

List of abreviations frequently used:

IPPV : intermittent positive pressure ventilation

DEF : diminished expiratory flow

PEEP : positive end-expiratory pressure

P_T : tracheal pressure

P_aO_2 : partial pressure of arterial oxygen

P_aCO_2 : partial pressure of arterial carbon dioxide

$P_{\bar{v}}CO_2$: partial pressure of mixed venous carbon dioxide

P_ECO_2 : partial pressure of carbon dioxide in the expiratory air

$P_ECO_{2,e}$: partial pressure of carbon dioxide in the end-expiratory air

P_{ao} : systemic arterial pressure

P_{pa} : pulmonary arterial pressure

P_{ra} : right atrial pressure

Substituting $\bar{P}$ for P gives the mean

$\dot{V}$: ventilatory flow

V_{CO_2} : carbon dioxide output

V_D/V_T : physiological dead space fraction

CO_{Th} : cardiac output estimated by the thermodilution method

CO_{Fick} : cardiac output estimated by the Fick method for oxygen

CHAPTER 1

Introduction and review of the literature

It is a matter of common clinical observation, that many patients with chronic obstructive pulmonary disease (COPD), especially patients with a severe emphysema, perform their expiratory effort through pursed lips, particularly during episodes of dyspnea.
One of the main objectives in the treatment of COPD is to avoid hypoventilation by an increase of tidal volume and to diminish uneven ventilation. The resultant improvement of gas exchange can partly be achieved by breathing exercises using a prolonged expiration, with or without the active use of diaphragmatic muscles (Barach, 1938; Miller, 1958). The mechanism of this improvement obtained by pursed lips breathing has been debated in the literature. Indeed, it does seem conflicting to further increase airway resistance during expiration by pursed lips breathing or an additional external expiratory resistance, since an elevated expiratory airflow resistance is a main problem in patients with COPD. Thus an additional airway resistance will even further increase expiratory effort (Mead et al., 1955). However, in patients with pulmonary emphysema, the expiratory obstruction is mainly caused by a collapse of the airways due to a loss of pulmonary elasticity which is shown to exist in patients with emphysema (Christie, 1934) and which normally support the airways (Hughes et al., 1974). During expiration a rise of intrapleural pressure due to active muscular effort compresses the bronchi in those segments, where intraluminal pressure is lower (Dayman, 1951) resulting in air trapping. Pursed lips breathing may prevent this phenomenon of collapse by causing an extra obstruction downstream from the bronchial level resulting in an increase of the intraluminal airway pressure, and thus reducing the effective transbronchial pressure difference (Miller, 1958). An increased intraluminal airway pressure of 4-8 cm H_2O has been shown to result in less constriction of the bronchi during expiration in asthmatic patients, studied by bronchograms (Barach, 1938). A higher mean airway pressure, either caused by prolonged insufflation during mechanical ventilation or retarded expiration, has been thought to be the main determinant for a

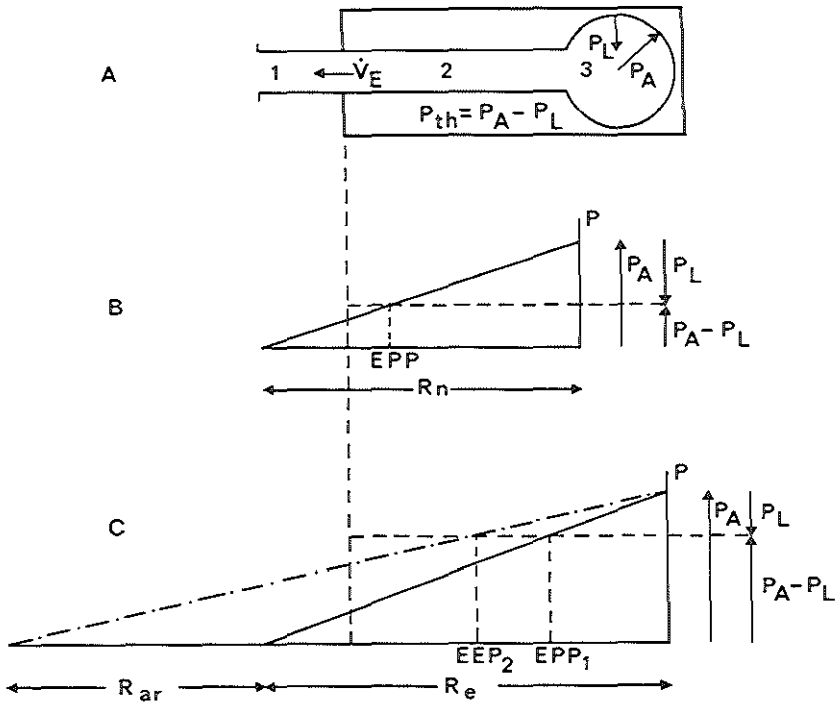

Fig. I-1: Pressure fall during expiration over intra- and extrathoracic airways

A. A schematic conceptual model of extra (1) and intrathoracic (2) airways as a tube of constant resistance between alveoli (3) and mouth of nostrils. This implies a nonlinear projection of anatomical length of the airways on this tube. Parts with a relatively large resistance as the upper airways will take a longer part of the tube than peripheral bronchioli where the resistance is relatively low.
P_A is alveolar pressure during expiration; $\dot{V}_E$ is expiratory flow; P_L is recoil pressure; P_{th} (intrathoracic pressure) = P_A-P_L; P_{th} surrounds the airways.
B. Pressure fall from alveoli to nostrils over a normal airway resistance (R_n). At the site where pressure in the airways is decreased to P_A-P_L, transmural pressure is zero because airway pressure is equal to P_{th}. This is the equal pressure point (EEP). Downstream (in left direction) surrounding pressure is higher than intraluminal pressure causing some compression of the airways.
C. Conceptual diagram for a patient with emphysema. Airway resistance is increased, therefore the abscis is lengthened to the right (R_e) with respect to R_n. Extrathoracic resistance is constant. A higher P_A is needed for expiration. Due to loss of elasticity P_L is decreased. Therefore, P_{th} is higher during expiration than in normal humans. The point of zero transmural pressure is shifted to the periphery with respect to normals (EPP_1). An additional external resistance (P_{ar}) decreases the pressure gradient giving a shift of EPP_1 to proximal airways (EPP_2) and a smaller positive pressure on the airways down-stream of EPP_2.

more uniform distribution of inspired gas and pulmonary blood, producing better gas exchange (Bergman, 1963).

Expiratory flow depends on the pressure drop along the intrathoracic airways. By pursed lips breathing a portion of this pressure drop will be moved to the upmost airway so that the drop occurring along the airways will be decreased by an equivalent amount, resulting in an increased amount of expiratory volume and hence ventilation (Fry and Hyatt, 1960). This mechanism is explained in Fig. I-1.

An additional effect of pursed lips breathing is the induced reduction of the initial respiratory flow rate reducing the Bernouilli effect created by airflow and therefore reducing the tendency for poorly supported airways to collapse (Schmidt et al., 1964), resulting in a longer maintained patency of very compliant airways.

Another effect seen with pursed lips breathing is a reduced respiratory rate after the onset. The reduction of the respiratory rate has been favoured by some as the main beneficial effect (Thoman et al., 1966; Abboud et al., 1968; Mueller et al., 1970). This would be in accordance with Motley (1963), who found that slow deep breathing in patients with emphysema resulted in an increase in tidal volume, and a significant improvement in the blood-gas exchange for oxygen and carbon dioxide. However, Paul et al. (1966) did not find an improved effective distribution of ventilation during respiratory rate slowing, although effective ventilation increased and allowed the patients to breathe with a smaller total ventilation. Yet, the patients felt less comfortable during the slowed respiratory rate.

According to Thoman et al. (1966), pursed lips breathing results in a slow expiration and may thus cause a more uniform emptying of different parts of the lung. This results in an increased ventilatory rate of the slow space, representing the more poorly ventilated areas of the lung, as lung regions with a low ventilation to perfusion ratio preferentially empty at low flow rates, whereas regions with a high ventilation to perfusion ratio preferentially empty at high rates of flow (Young et al., 1963). So, by pursed lips breathing ventilation to perfusion relationships seem to improve in different parts of the lung.

Ventilatory and pulmonary changes ascribed to pursed lips breathing or an additional external expiratory resistance will include:

- a higher vital capacity (Schmidt et al., 1964);
- a higher end-expiratory lung volume (Moomjian et al., 1980) which is even more marked in normal subjects (Ingram and Schilder, 1967);
- an increase of the tidal volume (Zechman et al., 1957; Thoman et al., 1966; Mueller et al., 1970);
- a decrease of respiratory rate (Zechman et al., 1957; Thoman et al.,

1966; Abboud et al., 1968; Mueller et al., 1970);
- increase in the ventilation rate of the slow space (Thoman et al., 1966);
- an increase in the partial pressure of oxygen in the systemic arterial blood (Thoman et al., 1966; Mueller et al., 1970);
- a decrease in the partial pressure of carbon dioxide in the systemic arterial blood (Thoman et al., 1966; Mueller et al., 1970);
- a decrease of the physiological dead space (Abboud et al., 1968), and
- a shift of the equal pressure point to the higher airways, and therefore a decrease in collapsibility (Fig. I-1).

The data presented in the literature are incomplete, and some authors are not in accordance with others. Probably, the beneficial effect of pursed lips breathing in patients with COPD is the combination of a decreased airway collapse resulting in less airtrapping and in better emptying of the more compliant alveoli and so a better ventilation to perfusion relationship in them, an enlarged tidal volume and a slowed respiratory rate.
Hemodynamic phenomena were not studied during pursed lips breathing, except for the demonstration of a decrease of cardiac output during expiratory obstruction (Huggett, 1924).

Acute decompensation of chronic respiratory failure in a patient with COPD poses a great problem, with large difficulties to treat. It is emphasized however to delay mechanical ventilation as long as possible (Pontoppidan et al., 1972), because intubation and mechanical ventilation produce a high incidence of complications, e.g. pulmonary barotrauma resulting in subcutaneous and/or mediastinal emphysema or even pneumothorax (Kumar et al., 1973) and a decrease in cardiac output. "Auto-PEEP" (positive alveolar pressure throughout the ventilatory cycle during mechanical ventilation producing an increase in intrathoracic pressure, even without intentional application of PEEP) has been reported as a mechanism for these complications in mechanically ventilated patients with airflow obstruction (Pepe and Marini, 1982). Often high tidal volumes are needed for effective artificial ventilation of COPD patients, which may lead to a fall of cardiac output to very low levels (Hedley-Whyte et al., 1966).
Many studies have been done to investigate the influence of the inspiratory waveform on the efficiency of gas exchange, but experimental and clinical investigations and extensive computer simulation of biophysical modeling have failed to show convincingly that the configuration of the inspiratory pressure flow pattern is of major clinical importance (Pontoppidan et al., 1977; Damman and McAslan, 1977) especially in healthy subjects (Bergman, 1967). However, an inspiratory

hold or end-inspiratory pause was seen to be beneficial to improve gas distribution and efficiency of washout (Damman et al., 1978; Perez-Chada et al., 1983) resulting in a rise of the partial pressure of systemic arterial oxygen and a decrease in the partial pressure of systemic arterial carbon dioxide (Knelson et al., 1970). The effects of an expiratory flow retard during artificial ventilation, simulating pursed lips breathing were thought to be disadvantageous (Fairley, 1976) but have not as yet been investigated. It has been mentioned once that an expiratory flow retard should be distinguished from a positive expiratory pressure plateau (McIntyre et al., 1969), which is the same as PEEP. Expiratory flow impedance was used to generate PEEP but coughing and straining with the creation of dangerously high airway pressures were a hazard with consequently a high incidence of barotrauma resulting in bilateral tension pneumothorax, subcutaneous and mediastinal emphysema (Kumar et al., 1970). There was no evidence of its effectiveness (Pontoppidan et al., 1972) and it was therefore abandoned (Falke et al., 1972).

Objectives of the study

The supposition, that a diminished expiratory flow (DEF) during artificial ventilation will improve blood-gas exchange, especially in obstructive pulmonary disease and that DEF improves blood-gas exchange better than a comparable positive end-expiratory pressure (PEEP, producing the same rise in mean tracheal pressure) was explored in experiments using Yorkshire piglets, without altering respiratory rate, tidal volume, inspiratory time, inspiratory hold or expiratory time.
During mechanical ventilation the effects of DEF and a comparable PEEP on hemodynamics, gas exchange and pulmonary mechanics were studied.
These effects were compared to each other and to intermittent positive pressure ventilation (IPPV) in health and disease induced by histamine, acetylcholine or oleic acid in order to evaluate hypothetic mechanisms of the effects of DEF.
Additionally the validity of cardiac output estimation by the thermodilution method and the cyclic modulation of these estimates during the three modes of mechanical ventilation were analysed in order to find the most appropriate way of calculating mean cardiac output from the smallest number of estimates.

Outlines of this thesis

In chapter II the experimental model and the methods are described.
In chapter III cardiac output estimations by the thermodilution method are evaluated.
The results of hemodynamic and respiratory effects (pulmonary mechanics and gas exchange) of DEF and PEEP are presented in chapter IV and discussed in chapter V.
In chapter VI the effects of the expiratory flow on the exchange of carbon dioxide during mechanical ventilation are studied using single breath analyses.

CHAPTER II

METHODS

II-1 MATERIAL

Yorkshire piglets with a mean age of 40 days (range 29-49) and with a mean weight of 9.4 kg (range 8.2-11.3) were used for the experiments. All piglets came from the same breeding farm (Rijpwetering, Holland) and were used for the experiments upon arrival at the laboratory.

II-2 EXPERIMENTAL CONDITIONS

Anesthesia was induced by intraperitoneal administration of 30 $mg \cdot kg^{-1}$ pentobarbital sodium. After completion of the surgical procedures anesthesia was maintained by a continuous intravenous infusion of 7.5 $mg \cdot kg^{-1} \cdot h^{-1}$. The piglets were paralysed with d-tubocurarine hydrochloride. Initially 1 mg was administered intravenously as a loading dose over a period of three minutes, followed by a continuous infusion of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ throughout the experiments.
Body temperature was maintained between 37°C and 39°C by placing the animals on a thermo-controlled operating table.
Heparin-sodium was administered every hour in a dosage of 200 $IU \cdot kg^{-1}$ to prevent clotting.

II-3 SURGICAL PROCEDURES

Induction of anesthesia was followed by the application of subcutaneous ECG electrodes. Expiratory CO_2-concentration was monitored throughout the surgical procedures. A tracheostomy was performed between the fourth and fifth cartilage ring, a metal Y-shaped tracheal canula was inserted and the trachea was ligated around the canula. Connection of one of the Y

branches to a Fleisch pneumotachograph head (type 0, Godart) followed. The other branch was sealed off and used for occasional bronchial suctioning.

Two polyethylene catheters, manufactured on the laboratory, were inserted into the right common carotid artery. One, a double-walled injection catheter, was placed with its tip about 2.5 cm beyond the aortic valve within the left ventricle under the guidance of pressure-curve monitoring. The outer diameter was 1.9 mm and the inner diameter 0.86 mm. The length of the intracorporeal part of the catheter varied from 10-14 cm, dependent on the size of the individual animal. The other catheter, with a thermistor at its tip, was positioned in the aortic arch near the origin of the brachiocephalic artery. The outer diameter was 1.57 mm. The lumen was used for measurement and continuous monitoring of the systemic arterial pressure and for sampling systemic arterial blood.
A four-lumen catheter, modified from a Swan-Ganz catheter (Edwards Laboratories, type 93A-131, 7 French) was placed with its tip at the level of the right atrium through the right internal jugular vein. One lumen was used for monitoring the central venous pressure, the other lumina for intravenous infusions of pentobarbital sodium and d-tubocurarine hydrochloride and injections of heparin (II-2).
A Swan-Ganz catheter (Edwards Laboratories, type 93-110, 5 French) was inserted via the external jugular vein into the pulmonary artery under the guidance of pressure-curve monitoring. It was used for monitoring the pulmonary arterial pressure, and for sampling mixed venous blood.

II-4 VENTILATION

During the surgical procedures the pigs breathed spontaneously with intermittent sighs. After the surgical procedures total paralysis was induced (see II-2) and intermittent positive pressure ventilation (IPPV) with room air was started using a Servo-ventilator (type 900A, Siemens Elema-Schönander, Sweden) at a rate of 10 per minute. The inflation time was 25%, the inspiratory pause was 10% and the expiratory time 65% of the ventilatory cycle. The tidal volume was adjusted to obtain a systemic arterial PCO_2 between 41 mmHg and 45 mmHg under steady state circumstances. On average the ventilatory volume was 15 $ml \cdot kg^{-1}$ (range 13.5-18.5), measured by an oil-filled volumeter (type 5L, Meterfabriek, Dordrecht).

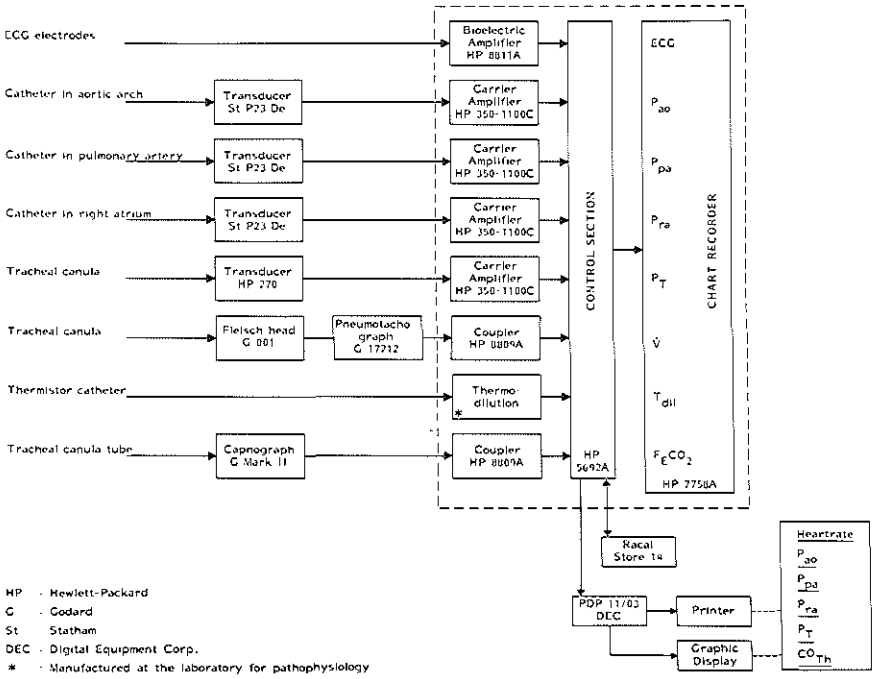

Fig. II-1. SCHEMATIC REPRESENTATION OF THE DATA FLOW AND CONTINUOUS MONITORING

II-5 DATA AQUISITION AND ANALYSIS

II-5-1 *Measured signals*

By continuous monitoring on a Hewlett-Packard 7758A chart recorder (fig. II-1) the following data were simultaneously obtained throughout the experiments:

- electrocardiogram (ECG) with subcutanous needles midsternally and in the right leg;
- aortic pressure (P_{ao}), pulmonary arterial pressure (P_{pa}), and central venous pressure in the right atrium (P_{ra}) by means of fluid pressure transducers (Statham medical instruments, type P23De);
- blood temperature in the aortic arch or thermodilution signals as

described later;

- tracheal pressure (P_T) with a gaspressure transducer (Hewlett-Packard, type 270);
- ventilatory flow ($\dot{V}$) by means of a pneumotachograph (Godart, type 17212), and
- CO_2-concentration in the expiratory air as a function of time (capnogram) with a capnograph (Godart mark II).

Sampled air was returned into the expiratory tube of the ventilatory system.

The site of the measurements of the last three data is shown in Fig. II-2.

The signals were also recorded on a Racal thermionic store 14 electromagnetic tape recorder during a series of measurements. Moreover they were analysed on-line with a digital computer PDP 11/03, except for the capnogram and ventilatory flow (Fig. II-1). The sample frequency was 200 Hz for ECG and bloodpressures and 50 Hz for the ventilatory flow, tracheal pressure and thermodilution curves.

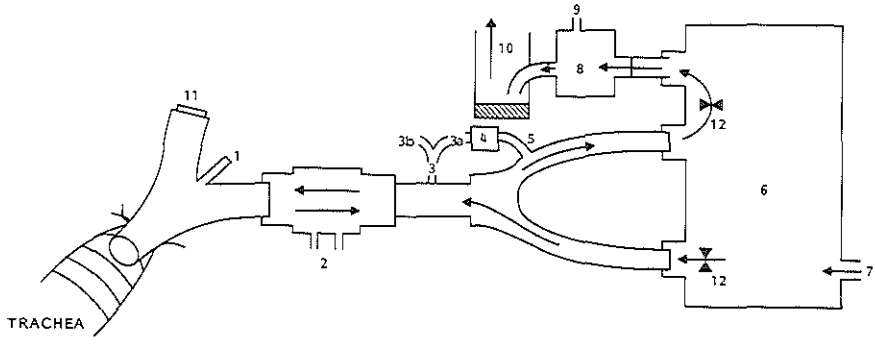

Fig. II-2. SCHEMATIC DIAGRAM OF VENTILATORY CONNECTIONS

1. outlet of tracheal canula for measuring tracheal pressure
2. outlets of Fleisch-head for connection to pneumotachograph
3. outlet for CO_2 analysis of the ventilatory air
   3a. to capnograph
   3b. to mass-spectrometer
4. Capnograph Godard Mark II
5. inlet for return of sampled air by capnograph
6. Servo-ventilator
7. inlet ventilator for connection to compressed air
8. mixing box for expired air
9. outlet mixing box for measurement of mixed expired O_2 and CO_2 fractions
10. water seal, used for Positive End Expiratory Pressure
11. sealed off access for bronchial suctioning
12. one way valve

Arrows indicate direction of airflow.

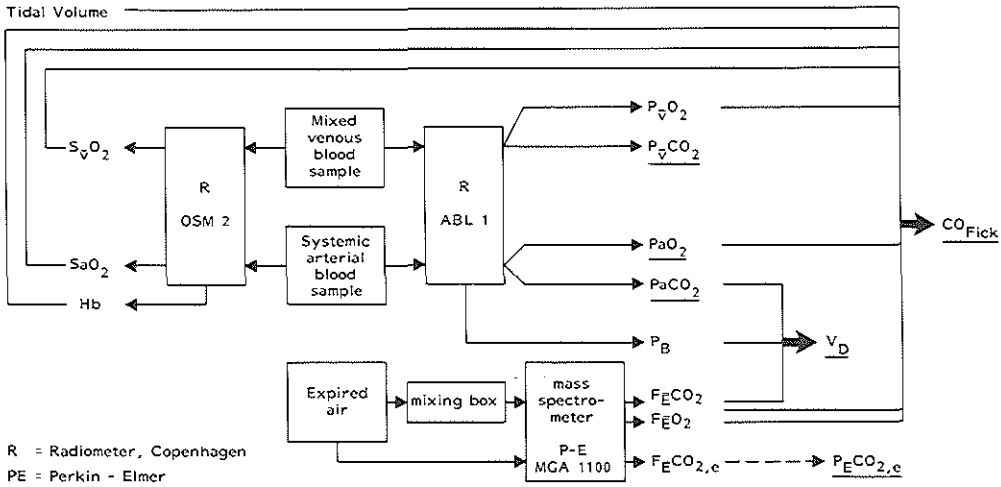

Fig. II-3. SCHEMATIC REPRESENTATION OF THE ADDITIONAL MEASUREMENTS AND CALCULATIONS

II-5-2 *Off line measurements*

The following additional measurements and calculations were performed (Fig. II-3):

- systemic arterial and mixed venous bloodgas analysis, i.e. partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) in mm Hg and acid-base values (ABL 1, Radiometer, Copenhagen) at 37°C;
- the partial pressure of CO_2 in the end expiratory air ($P_ECO_{2,e}$) in mmHg $P_ECO_{2,e}$ was calculated according to:

$$P_ECO_{2,e} = F_ECO_{2,e} (P_B - P_sH_2O),$$

where:

$F_ECO_{2,e}$ = fraction of CO_2 in the end-expiratory air
P_B = atmospheric pressure in mm Hg
P_sH_2O = water vapour pressure at the central temperature of the animal and at full saturation

Cardiac output was estimated using two methods:

1. the thermodilution method

   The thermodilution measurements of cardiac output (CO_{Th}) were automatically performed by injections of 0.5 ml saline (0.9% NaCl) at room temperature into the left ventricle through the double walled catheter (Fig. II-4), as described by Jansen et al. (1981). To obtain complete mixing of indicator with blood three small sideholes were made in the last centimeter of the catheter on the circumference, about 120° apart. The tip of this catheter was sealed off.

   Volume reproducibility of the syringe was checked by weighing the volume after multiple ejections, which were performed by a pneumatic cylinder driven by compressed air. Injections of indicator into the ventricle were initiated by an electric signal derived from a delay

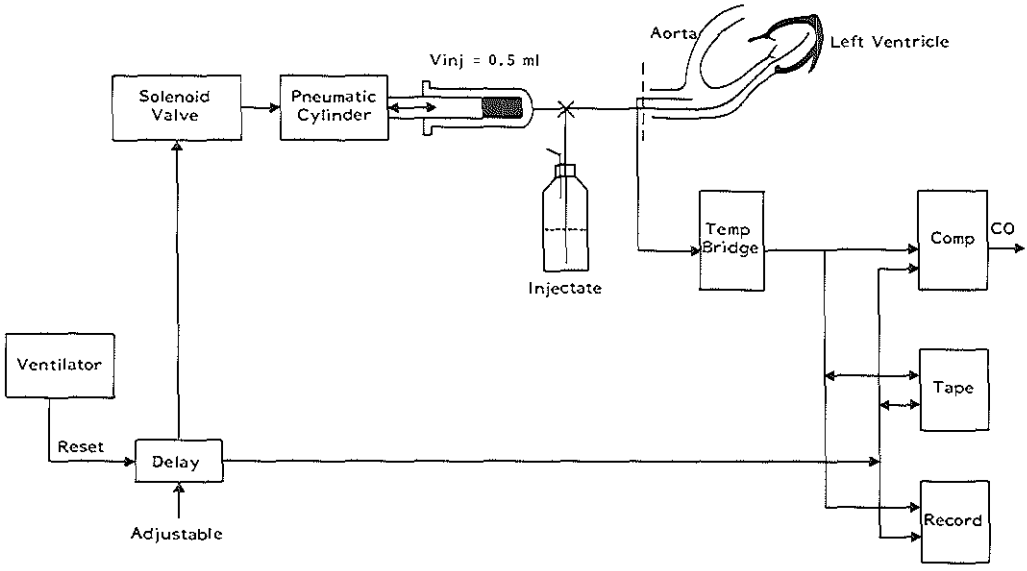

Fig. II-4. SCHEMATIC DIAGRAM OF THE THERMODILUTION TECHNIQUE USED

Vinj = syringe giving an injection volume of 0.5 ml
Comp = digital computer PDP 11/03
Tape = Racal thermionic tape recorder
Record = Hewlett Packard 7758 A chart recorder

unit. After each measurement the syringe was automatically refilled. At least five ventilatory cycles (i.e. 30 seconds) were taken between two injections, as the 99% thermal response time of the double walled injection catheter was about 26 seconds.

The moment of injection of the indicator depended on two factors:

a. a manual starting signal in the middle of the ventilatory cycle cycle in which CO_{Th} was to be determined,
b. the moment within the ventilatory cycle. This actual moment of automatic injection was derived from the ventilator signal of the cycle and preset before the manual starting signal was given (Delay, Fig. II-4).

The thermistor in the aortic arch for the detection of the temperature-time curve had the following characteristics: diameter 0.5 mm, resistance at 37°C 5000 Ω. It had a 90% thermal response time of approximately 0.2 seconds. To avoid influences caused by changes in the velocity of blood, the voltage across the thermistor was kept low. The thermistor, measuring blood temperature (T_b) had been calibrated against a mercury thermometer, by which the temperature of the injectate (T_i) was measured. T_b and T_i were determined before and after each series of measurements.

The delay unit controlled the start of the digital integration of the temperature-time curve, detected with the thermistor catheter and derived from the temperature bridge. The voltage temperature characteristic of the temperature bridge gave a satisfactory linearity within the range of the measurements (37-39°C). CO_{Th} was calculated according to the following equation:

$$CO = {}^{m_i}\!/_{\rho_b S_b \left\{ \int_{t_1}^{t_2} [T_b(t) - T_{b1}]dt - A \right\}}$$

where:

$$m_i = \rho_i S_i Q_i (T_{b1} - T_i) - C_k (T_{b1} - T_i)$$

$$A = {}^{(T_{b2} - T_{b1})(t_2 - t_1)}\!/_{2}$$

$$T_{b1} = \int_{t_1}^{t_1+\Delta t} T_b(t)dt/\Delta t$$

and:

$$T_{b2} = \int_{t_2}^{t_2+\Delta t} T_b(t)dt/\Delta t$$

m_i is the effective amount of indicator in calories;

ρ_i and ρ_b are specific gravity of injectate (1.005) and blood (1.045) respectively in $g \cdot ml^{-1}$;

S_i and S_b are specific heat of injectate (0.097) and blood (0.870) respectively in $cal \cdot g^{-1} \cdot {}^{o}C^{-1}$;

T_b is the temperature of blood at the detection site in ^{o}C;

T_i is the temperature of injectate in ^{o}C;

A is leakage of cold through the wall of the injection catheter in $^{o}C \cdot sec$;

Q_i is the injectate volume in ml;

C_k is the caloric value of injection catheter plus remaining injectate in $cal \cdot cm^{-1} \cdot {}^{o}C^{-1}$;

l is the length of the intracorporeal part of the injection catheter in cm;

t_1-t_2 is the integration interval;

Δt is the heart interval.

The cyclic temperature fluctuations concomitant with the ventilatory cycle were corrected for by integration of the area of these fluctuations over an equal period of time within the phase of the cycle after the dilutioncurve.

Transfer of cold through the wall of the injection catheter, negligable during the short injection period and slow in the measuring period, was corrected for by subtracting the area produced by this phenomenon in the temperature-time curve from the total area.

The sequence of the measurements was either every half second from 0.0 to 5.5 seconds or reversedly from 5.5 to 0.0 seconds, reckoned from the beginning of insufflation (in total 12 measurements in one ventilatory cycle), because of the cyclic modulation of the CO_{Th} value with the respiratory cycle (Jansen et al., 1981).

Furthermore this series was carried out to investigate the effects of a slackened fall in airway pressure on the CO_{Th} estimates during a diminished expiratory flow, as described in II-6. Finally this series was done to find an appropriate way of calculating mean cardiac output with the smallest number of estimates. For this purpose the average of two estimations, a half cycle apart from each other, was calculated, as well as the average of three and four estimations, one third and one quarter cycle apart respectively. These averages were compared with the mean cardiac output.

Mean individual CO_{Th} was determined as the mean of the 12 measurements equally spread over the ventilatory cycle.

2: <u>The direct Fick method for oxygen</u> (Stow, 1954).

A measurement of cardiac output by the direct Fick method for oxygen (CO_{Fick}) was performed immediately before and after each series of 12 thermodilution measurements. Systemic arterial and mixed venous blood

was sampled for bloodgas analyses (Fig. II-3). The duration of the sampling lasted at least a few ventilatory cycles.
Cardiac output was calculated according to:

$$\dot{Q} = \frac{\dot{V}_I \cdot F_IO_2 - \dot{V}_E \cdot F_{\bar{E}}O_2}{(C_aO_2 - C_{\bar{v}}O_2)} \quad ml \cdot sec^{-1}$$

where:

$$\dot{V}_I = V_T \cdot k \cdot RR/60 \quad ml \cdot sec^{-1}$$

$$k = \frac{273}{273 + T_r} \times \frac{P_B - H_r \cdot P_sH_2O\,(T_r)}{760}$$

$$\dot{V}_E = \dot{V}_I \times \frac{(1 - F_IO_2)}{(1 - F_{\bar{E}}O_2 - F_{\bar{E}}CO_2)} \quad ml \cdot sec^{-1}$$

$$C_aO_2 = S_aO_2 \cdot Hb \cdot 1.39 + 0.003 \cdot P_aO_2$$

and

$$C_{\bar{v}}O_2 = S_{\bar{v}}O_2 \cdot Hb \cdot 1.39 + 0.003 \cdot P_{\bar{v}}O_2$$

$\dot{V}_I$ = inspiratory flow ($ml \cdot sec^{-1}$) of dry air;
$\dot{V}_E$ = expiratory flow ($ml \cdot sec^{-1}$) of dry air;
F_IO_2 = oxygen-fraction in the inspiratory air;
$F_{\bar{E}}O_2$ = oxygen-fraction in the mixed expiratory air;
$F_{\bar{E}}CO_2$ = carbon dioxide fraction in the mixed expiratory air;
C_aO_2, $C_{\bar{v}}O_2$ = oxygen content of systemic arterial, a, and mixed venous, $\bar{v}$, blood;
V_T = tidal volume, delivered by the respirator (ml);
RR = respiratory rate per minute;
T_r = room temperature in ^oC;
P_B = atmospheric pressure in mmHg;
H_r = relative humidity of room air as a fraction of full saturation;
$P_sH_2O(T_r)$ = water vapour pressure, at T_r and full saturation;
S_aO_2, $S_{\bar{v}}O_2$ = oxygen saturation of systemic arterial, a, and mixed venous, $\bar{v}$, blood;
P_aO_2, $P_{\bar{v}}O_2$ = partial pressure of oxygen in systemic arterial, a, and mixed venous, $\bar{v}$, blood in mmHg.

A value of 1.39 ml $O_2 \cdot g^{-1}$ Hb (STPB) was used as the oxygen binding capacity (International Committee for Standardization in Hematology, 1965).

Expiratory air, sampled from the gas mixing box (Fig. II-2) over a period of 3 minutes, was analyzed concerning oxygen (O_2) and carbon dioxide using a mass-spectrometer (Perkin-Elmer MGA 1100). The oxygen uptake, VO_2 ($ml \cdot s^{-1}$, STPD), was corrected for differences between inspired and expired volumes, assuming that no volume change of nitrogen took place (Otis, 1964).

Physiological dead space fraction (V_D/V_T) was derived (Fig. II-4) according to:

$$V_D/V_T = 1 - F_{\bar{E}}CO_2 \, (P_B - P_sH_2O)/P_aCO_2$$

where

P_aCO_2 = partial pressure of carbon dioxide (CO_2) in the systemic arterial blood in mmHg;

$F_{\bar{E}}CO_2$ = CO_2 fraction in the dry mixed expiratory air;

P_B = atmospheric pressure in mmHg;

P_sH_2O = saturated water vapor pressure at body temperature in mmHg.

In summary, a series of measurements and calculations consisted of:

- CO_{Th} and CO_{Fick}
- Heart rate
- P_{ao}, P_{pa}, P_{ra}
- $P_{T,p}$
- P_aO_2, P_aCO_2, $P_{\bar{v}}CO_2$, $P_ECO_{2,e}$
- V_D/V_T

II-6 EXPERIMENTAL PROTOCOL

During each experiment the effects of three different modes of artificial ventilation were examined and compared. Measurements and calculations were carried out when stationary circumstances were achieved. An interval of 15 minutes after changing the ventilatory mode appeared to be sufficient.

The first mode was intermittent positive pressure ventilation ($IPPV_I$) as a

control series (Fig. II-5A).
In the second mode the spontaneous expiratory flow was changed into a diminished expiratory flow (DEF), which was accomplished by means of the variable expiratory flow rate control of the Servo-ventilator. The degree of DEF was chosen in such a manner, that the tracheal pressure returned to zero at a point in the expiratory phase, when 66% of the available expiration time had passed (DEF 66%, Fig. II-5B).
The third mode consisted of a positive end-expiratory pressure (PEEP, Fig. II-5C), chosen in such a manner that the same rise of mean airway pressure was obtained, compared to the previous condition of DEF 66%. To realize this similar rise in mean airway pressure a device was developed, which integrated on line each tracheal pressure-time curve after resetting at the beginning of insufflation. The areas of the pressure-time curve C in Fig. II-5 was chosen equal to that of B. PEEP was produced by submerging the tube from the expiratory port of the ventilator under a water column. The three modes were investigated in the sequence mentioned above and followed again by the first mode in order to check the return of the measured and calculated variables to the basic values. This second control phase was called $IPPV_{II}$.
In a second protocol of experiments the same order of ventilatory modes was followed, but DEF was prolonged to 100% of the available expiratory time (DEF 100%) and PEEP was correspondingly chosen (Fig. II-5D and E). Thus under these conditions airway pressure during expiration was more slackened than during DEF 66%, causing a higher mean airway pressure.
In summary, the two experimental protocols were as follow:

Protocol I (DEF 66% series)
1: $IPPV_I$, first control observations
2: DEF 66%
3: PEEP, comparable to DEF 66% with respect to the mean airway pressure (PEEP ~ DEF 66%)
4: $IPPV_{II}$, second control observations.

and

Protocol II (DEF 100% series)
1: $IPPV_I$
2: DEF 100%
3: PEEP, comparable to DEF 100% with respect to the mean airway pressure (PEEP ~ DEF 100%)
4: $IPPV_{II}$.

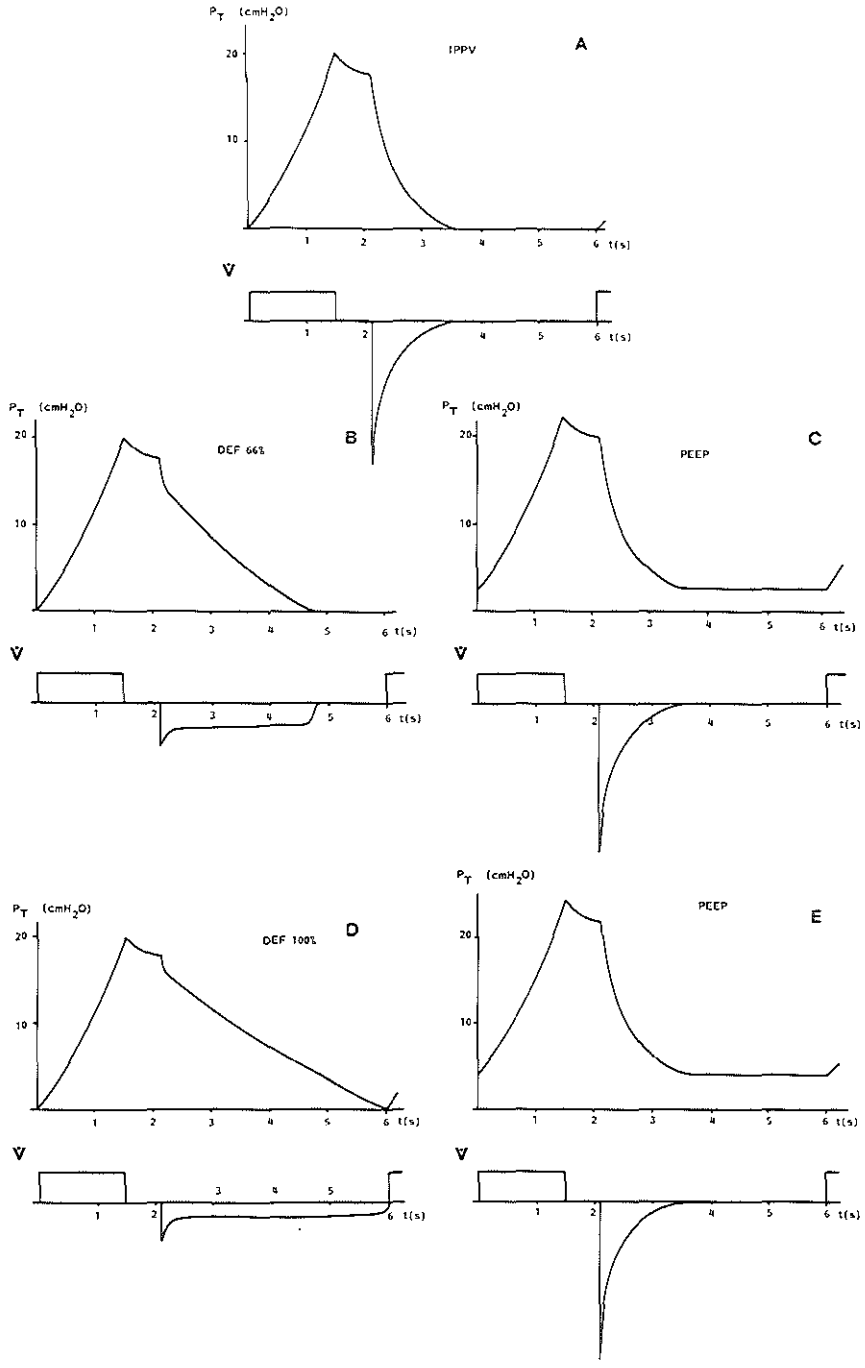
P_T (cmH$_2$O)
IPPV
A
20
10
1 2 3 4 5 6 t(s)
$\dot{V}$
B
DEF 66%
C
PEEP
D
DEF 100%
E

Fig. II-5:

Course of tracheal pressure (P_T) and airflow ($\dot{V}$) during a ventilatory cycle. A: Intermittent positive pressure ventilation (IPPV). B: IPPV with a diminished expiratory flow retarded to 66% of the total expiratory time (DEF 66%). C: IPPV with a positive end-expiratory pressure (PEEP) producing the same increase in mean tracheal pressure as DEF 66%. D: IPPV with a diminished expiratory flow retarded to 100% of the total expiratory time (DEF). E: IPPV with a positive end-expiratory pressure (PEEP) producing the same increase in mean tracheal pressure as DEF 100%.

II-7 PHYSIOLOGICAL AND EXPERIMENTAL PATHOLOGICAL CONDITIONS

Experimental series were carried out under four different pulmonary conditions:

a. *Normal lungs*

In 12 piglets both protocols were performed; in 6 animals protocol I and in the other 6 protocol II was performed firstly. In these series $IPPV_{II}$ of the first protocol served as $IPPV_I$ of the second. In 6 other animals only protocol I and in 9 animals only protocol II was done. This means, that in total protocol I was performed as a first series in 12 piglets and as a second series in 6, whereas protocol II was done as a first series in 15 and as a second series in 6 animals.

b. *Histamine induced bronchoconstriction*

To simulate bronchocontriction, histamine in a dose of 1.1 $mg \cdot kg^{-1} \cdot h^{-1}$ was continuously infused into the pulmonary artery. On average a stable situation was reached 75 minutes (range 40-126) after the beginning of infusion. Then the protocols could commence.

In six piglets both protocols I and II were succesfully carried out, four times protocol I and two times protocol II first. In one animal only protocol I could be included and in another only protocol II.

c. *Acetylcholine induced bronchoconstriction*

To simulate bronchoconstriction, acetylcholine in a dose of 0.56 $mg \cdot kg^{-1} \cdot h^{-1}$ was continuously infused into the pulmonary artery. The protocols started on average 59 minutes (range 46-79) after the onset of infusion.

In six piglets both protocols I and II were performed, four times protocol I first, and two times protocol II first. In one piglet only protocol II could be included.

d. *Oleic acid and alloxan induced pulmonary edema*

These lungs served as a model for the respiratory distress syndrome by the administration of Alloxan in a dose of $75 \cdot mg \cdot kg^{-1}$ and 1 ml of a mixture consisting of 50% ethanol and 50% oleic acid, both into the pulmonary artery, as a slow bolus injection over a period of about 30 seconds. To compensate for the expected deterioration of the hemodynamic condition, $10\ mg \cdot kg^{-1}$ Dextran (10%, mean molecular weight 40.000) was infused simultaneously. The hypoxia was compensated for by increasing the inspiratory oxygen fraction (F_IO_2) to 0.40.
In four animals only protocol II was performed, on average 61 minutes (range 55-69) after the injections when the situation had stabilized.

II-8 POSTMORTEM EXAMINATION

After each experiment the piglet was sacrificed and at autopsy the position of all catheters was verified. The lungs were examined, and sections were taken for histopathological investigation when histamine, acetylcholine or oleic acid had been administered.

II-9 STATISTICAL ANALYSIS

The data were analysed by the method of paired comparison using the student's t-test. Significance was determined at the 95 percent confidence level. In both protocols DEF was compared with $IPPV_I$, $IPPV_{II}$ and PEEP of the corresponding DEF (PEEP ~ DEF). PEEP was also compared with both IPPV's and $IPPV_{II}$ was compared with $IPPV_I$.
Both protocols were devided into two parts:

1: protocol performed as a first series in the individual animal
2: protocol performed as a second series in the individual animal.
These two parts were separately compiled for statistical analysis.
Also the two parts were totalled and statistically analysed.

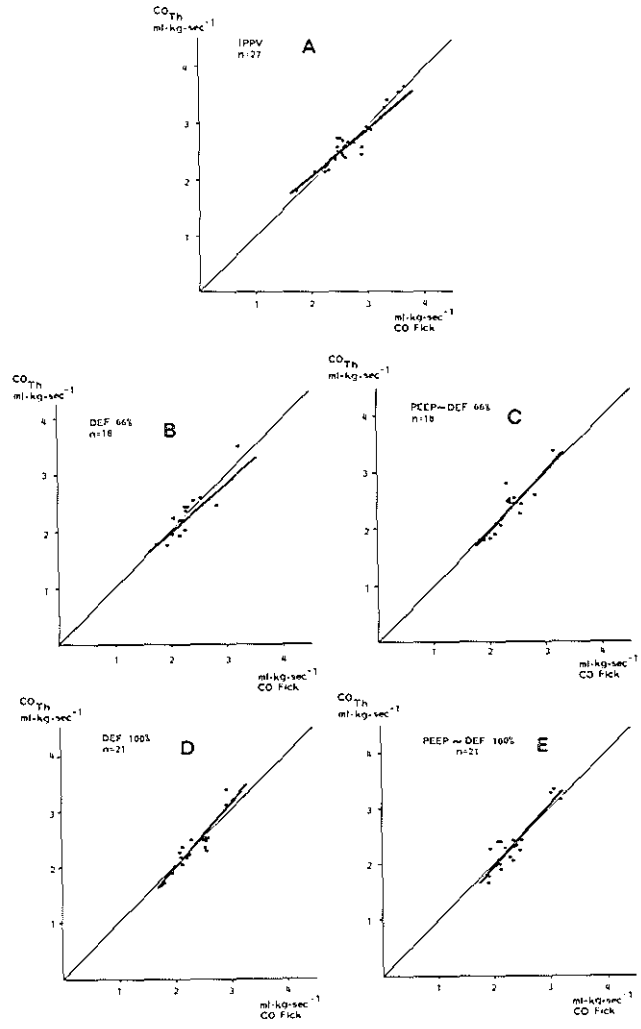

Fig. III-1:

Correlation between cardiac output estimated by the thermodilution technique (CO_{Th}) and the direct Fick method for oxygen (CO_{Fick}) during the different ventilatory modes.

Thin line is the identity line
Thick line is the regression line
n is the number of animals

CHAPTER III

CARDIAC OUTPUT MEASUREMENT BY THE THERMODILUTION METHOD

RESULTS

Three aspects of cardiac output measurement will be presented:

1. the correlation between cardiac output measurements by the thermodilution method and those by the direct Fick method for oxygen
2. the cyclic variation in cardiac output estimates with the thermodilution method during the five different patterns of artificial ventilation
3. reduction of the deviation of these individual estimates from the mean.

Thermodilution versus Fick method

The mean value of all 12 cardiac output estimates equally spread over the ventilatory cycle using the thermodilution method (CO_{Th}) was plotted against the mean of both cardiac output values, measured by the direct Fick method for oxygen (CO_{Fick}) before and after each series of thermodilution measurements (Fig. III-1). The equations of the regression lines and the correlation coefficients for the different modes of ventilation are depicted in Table A-1, showing a good agreement between the two methods within the range of cardiac output measurements.

Cyclic variation of cardiac output

The mean of 12 CO_{Th} estimates with the moment of injection equally spread over the ventilatory cycle was taken as the 100% value for each series. Individual measurements of each series were expressed as a percentage of the corresponding mean. All results at similar phases in the ventilatory

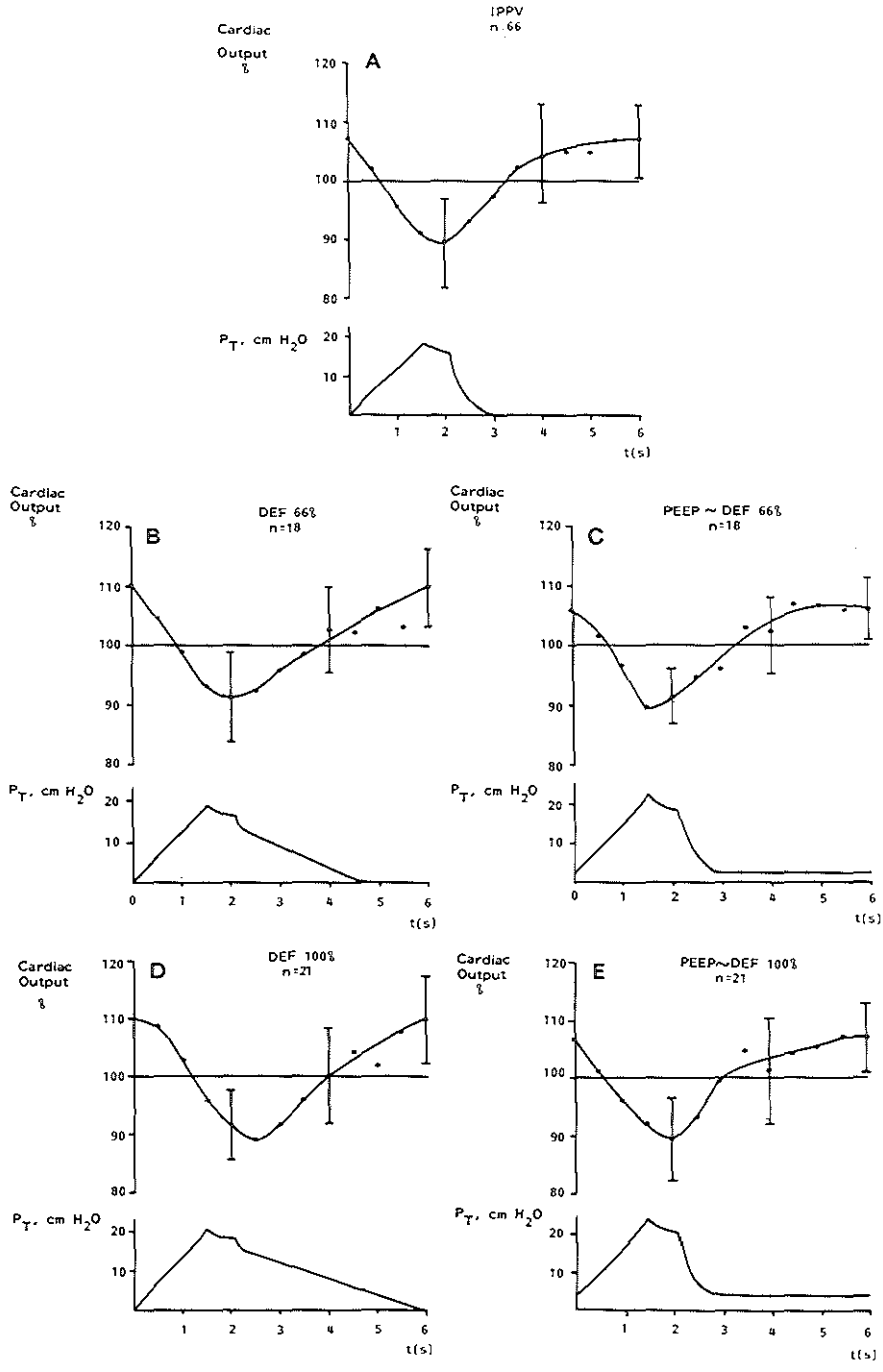
IPPV
n=66
Cardiac Output %
A
120
110
100
90
80
P_T, cm H_2O
20
10
1 2 3 4 5 6
t(s)
Cardiac Output %
DEF 66%
n=18
B
120
110
100
90
80
P_T, cm H_2O
20
10
0 1 2 3 4 5 6
t(s)
Cardiac Output %
PEEP ~ DEF 66%
n=18
C
120
110
100
90
80
P_T, cm H_2O
20
10
0 1 2 3 4 5 6
t(s)
Cardiac Output %
DEF 100%
n=21
D
120
110
100
90
80
P_T, cm H_2O
20
10
1 2 3 4 5 6
t(s)
Cardiac Output %
PEEP~DEF 100%
n=21
E
120
110
100
90
80
P_T, cm H_2O
20
10
1 2 3 4 5 6
t(s)

Fig. III-2:

Cardiac output estimated by the thermodilution technique in % of the mean (=100%) as a function of the time of injection during the different ventilatory modes. Vertical bars represent standard deviation from the mean. The tracheal pressure-time (P_T) of each ventilatory mode is given as a reference. n is number of series.

cycle of the same pattern of ventilation were averaged and plotted as a function of the corresponding cycle-time. A cyclic modulation of CO_{Th}-estimates became apparent. The highest and the lowest value in the series with maximal disparity were 135% and 58% of the mean respectively. In the averaged series this was 125% and 72% (Table A-2). To compare the cyclic modulation between the different modes, the tracheal pressure-time curve of each mode is given as a reference (Fig. III-2).

The pattern of cyclic modulation during IPPV (Fig. III-2A) did not change when PEEP was added (Figs. III-2C and III-2E). A decrease of cardiac output was observed during the increase of airway pressure at insufflation, which ceased at the end of the inspiratory plateau, and cardiac output subsequently increased during the spontaneous expiration. In the expiratory pause cardiac output values approached the starting point values. At 52-54% of the ventilatory cycle time from the beginning of insufflation the estimates of cardiac output corresponded to the mean of all the 12 thermodilution measurements. At the end-expiratory phase an overestimation of cardiac output of 6% regarding the mean became apparent with a standard deviation of about 9%, when a plateau in the estimates is obvious.

When artificial ventilation took place with DEF 66% (Fig. III-2B) a change in the pattern of modulation of CO_{Th} estimates was observed. A slackened increase in the estimates was seen during the delayed expiratory flow between 2.5 sec. and 4.5 sec. after the beginning of the ventilatory cycle associated with the gradual decrease in tracheal pressure (P_T). In this period the cardiac output reached the mean at a later point in the ventilatory cycle (circa 0.5 sec. later at 63% of the respiratory cycle), compared to IPPV. In the period 0.0 sec. to 2.0 sec. no difference in the degree of modulation was observed with respect to the modulation during either IPPV or PEEP.

Application of DEF 100% (Fig. III-2D) showed the same changes in the pattern of cardiac output modulation as DEF 66% with respect to IPPV. However, in comparison to DEF 66%, the pattern slightly shifted about 0.5 sec. to a later phase in the ventilatory cycle. The overestimation at

the end of expiration with respect to the mean was the same for DEF 66% and DEF 100% as during IPPV and PEEP, but during DEF (either 66% or 100%) no expiratory plateau is present.

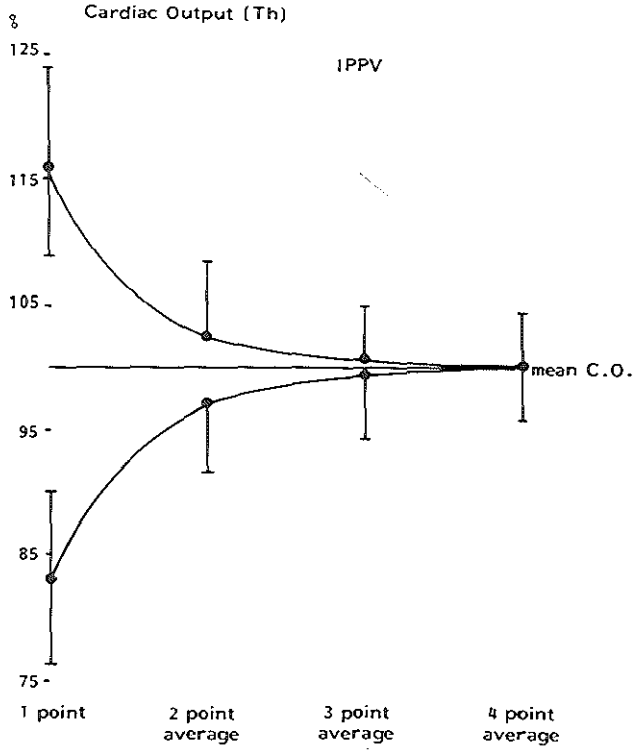

Fig. III-3:

Averaging stratagem for estimation of cardiac output by the thermodilution (Th) technique, reducing the deviation from the mean (=100%) to between 0.1% and 0.7% in the fourpoint average. IPPV is shown here, but the configuration is valid for all ventilatory modes studied (Table A-2). Vertical bars represent standard deviations from the mean.

Reduction of the deviation from the mean cardiac output, as seen with individual measurements with the thermodilution method

As described in the preceding paragraph an appreciable deviation from the mean cardiac output can exist in the individual estimates by the thermodilution method due to the cyclic modulation of cardiac output by artificial ventilation. To reduce this deviation, the average was calculated of two, three and four estimates in each series evenly spread over the ventilatory cycle. So, in these series the respective measurements were 50%, 33.3% and 25% apart from each other in the ventilatory cycle. Thus, three new series were produced with 6, 4 and 3 averaged estimates. This averaging technique reduced the deviation from the mean from the range between 72% and 125% in the mean of the individual measurements to a range between 84% and 114% in the mean of two point averages, between 89% and 110% in the mean of three point averages and an even smaller range in the mean of four point averages (Fig. III-3 and Table A-2).

DISCUSSION

The thermodilution method

Cardiac output was measured by the thermodilution technique (CO_{Th}) as well as by the direct Fick method for oxygen (CO_{Fick}). In the experiments automatic injections with a very short injection time (0.3 seconds), using a pneumatic cylinder driven by compressed air (Jansen et al., 1981), were carried out for measuring CO_{Th}. This provides a highly reproducible amount of indicator injected (Saadjian et al., 1976) and a steadiness of injectate flow rate (Nelson and Houtchens, 1982) compared to manual injections.

Three important conditions have to be fulfilled for reliable accuracy of CO_{Th}-measurements:

1. Complete mixing of diluent
2. No loss of indicator
3. Constant blood flow during the measurements.

Complete mixing of the indicator fluid with the blood was assumed to be

achieved by the mechanical actions of the heart resulting in turbulence, and a high injection speed through multiple side holes at the tip of the injection catheter (Saadjian et al., 1976; Jansen et al., 1981).
Loss of indicator theoretically can occur during injection through the wall of the catheter and between injection and detection sites to the surrounding tissues. The heat loss through the wall of the catheter during the period of injection could be neglected due to a high degree of insulation of the catheter (double-walled with air in between the walls) producing a very low thermal conductivity and due to the short time and high speed of injection. Evenso, heat loss to the endothelial structures of the left ventricle and aorta after injection of thermal indicator is negligible in piglets (von Reth et al., 1978) and could not be demonstrated when cardiac output measurements by thermal and dye-dilution were compared (Wessel et al., 1971).
The third condition, a constant blood flow during the measurements is not fulfilled during positive pressure ventilation. The concomitant modulation of flow causes a distortion of the shape of the dilution curve. This was not corrected for, but it may well be possible to realize this in future time (Jansen et al., 1983).
Indicator volume (0.5 ml NaCl 0.9%) sufficed, as together with corrections (as mentioned) a good correlation between the mean of 12 CO_{Th}-measurements equally spread over the ventilatory cycle and CO_{Fick} was demonstrated (Fig. III-1, Tables A-1, A-3 and A-4).
To simplify the practice of correction of the effective amount of indicator the temperature of the indicator was chosen to be room temperature, as otherwise the temperature of the amount of indicator in the extracorporeal part of the injection catheter would continuously change (Wessel et al., 1971; Vliers et al., 1973). The amount of indicator in the intracorporeal part of the injection catheter had to be deducted from the total amount of indicator as this rises to body temperature between two consecutive injections. After the injections residual indicator is "injected" unintentionally, producing an enlargement of the thermodilution curve which has to be corrected for (Jansen et al., 1981). Artificial ventilation produces cyclic fluctuations in aortic blood temperature with small pulsations due to heart actions superimposed on it (Pavek et al., 1970; Vliers et al., 1973; Saadjian et al., 1976). The actual dilution curves were corrected for these base line fluctuations.

CO_{Th} estimates spread throughout the ventilatory cycle show a cyclic modulation when the estimates are plotted against the moment of indicator-injection in the ventilatory cycle, as was described by Jansen et al. (1981). Although the maximal disparity between single CO_{Th} estimates in the individual series was 130% - 58% of the mean CO_{Th} and in the averaged series 115% - 81% of the mean CO_{Th}, the mean of the twelve CO_{Th} estimates correlated well with the mean cardiac output as expressed by CO_{Fick} (Fig. III-1). During IPPV the mean CO_{Th} is reached in the curve, producing by plotting CO_{Th} against the moment of indicator injection in the ventilatory cycle at 10% and 54% of the ventilatory cycle, during DEF 66% at 14% and 63%, during DEF 100% at 19% and 67%, during PEEP ~ DEF 66% at 12% and 54% and during PEEP ~ DEF 100% at 11% and 53%. This indicates that for IPPV and PEEP ideal injection times are 10-12% or 53-54% of the ventilatory cycle, and that during DEF 66% and 100% these ideal moments of injection shift to a later phase in the ventilatory cycle. Such a shift was also seen by Jansen and Versprille (1986) in experiments with a diversity of other patterns of ventilation. It must be stressed that these results are valid for artificial ventilation with an inspiration-expiration ratio of 25-65% and an inspiratory hold of 10%, and may well be different when other ratio's are instituted.

The variation of cardiac output is due to the mechanical influence of a varying intrathoracic pressure on venous return (Guyton, 1957; Versprille et al., 1982; Versprille and Jansen, 1985). Insufflation causes a higher intrathoracic pressure with a concomitant fall in venous return to the heart, resulting in a decrease of cardiac output. Therefore lower inflation pressures will produce less variation in cardiac output (Snyder and Powner, 1982). During expiration this is abolished, resulting again in an increase of cardiac output. The shift of the curves (CO_{Th} plotted against the cycle time, Fig. III-2) to the right during DEF 100%, and to a lesser extent during DEF 66% might be explained by the retarded fall in intrathoracic pressure during expiration with respect to IPPV and PEEP, and therefore by a retarded recovery of cardiac output.

Because a difference exists in the ideal injection times for different modes of ventilation, it can be concluded that for estimation of mean cardiac output at least several estimations equally spread in the ventilatory cycle are necessary (Jansen and Versprille, 1986). The end of the expiratory pause could be an easy mark for trend studies to inject indicator fluid with the best stationarity of flow, but an overestimation

will exist regarding mean cardiac output. Moreover, this overestimation will change, when the ventilatory pattern is changed. This implies, that the overestimation is not systematic and therefore not feasible for follow up.

Mean cardiac output estimates by the thermodilution method

The averaging technique showed that mean cardiac output can be reliably calculated by averaging the results of three or four estimates at evenly spaced intervals in the ventilatory cycle and that the averaging technique is dependent of the mode of mechanical ventilation. This confirms the results of Jansen and Versprille (1986).

Conclusion

Cardiac output measurement during mechanical ventilation by the thermodilution technique is reliable and accurate, provided knowledge of the cyclic variations of cardiac output during the respiratory cycle in different modes of artificial ventilation leads to averaging of three to four determinations equally spaced in the ventilatory cycle.

CHAPTER IV

RESULTS OF THE HEMODYNAMIC AND RESPIRATORY EFFECTS OF DEF AND PEEP

The effects of the ventilatory modes on hemodynamics, gas exchange and other pulmonary phenomena under non-pathological circumstances are described in the paragraphs IV-1 and IV-2 respectively. In the paragraphs IV-3, IV-4 and IV-5 the results of the experiments during simulated pathology are presented. The figures represent the results of the totals of protocols I and II. In the tables (Appendix) the results of the protocols done as a first series and as a second series and the totals of these both are presented separately, together with the results of the statistical analysis.

IV-1 HEMODYNAMIC PHENOMENA

IV-1-1 *The effects of DEF and PEEP on mean cardiac output*

Cardiac output measured by both the thermodilution and the Fick method decreased ($p < 0.05$) during ventilation with either DEF 66% and PEEP ~ DEF 66% or with DEF 100% and PEEP ~ DEF 100% (Fig. IV-1) with respect to the mean value measured at IPPV.
The fall of cardiac output was more pronounced during DEF 100% and PEEP ~ DEF 100% compared to DEF 66% and PEEP ~ DEF 66% respectively (Fig. IV-1, Table A-3 and A-4). There was no difference between DEF and the corresponding PEEP in decreasing cardiac output.

IV-1-2 *Systemic arterial pressure*

Aortic pressure averaged over the ventilatory cycle ($\bar{P}_{ao}$, Fig. IV-1 and Table A-5) dropped when artificial ventilation with DEF 66% ($p < 0.025$)

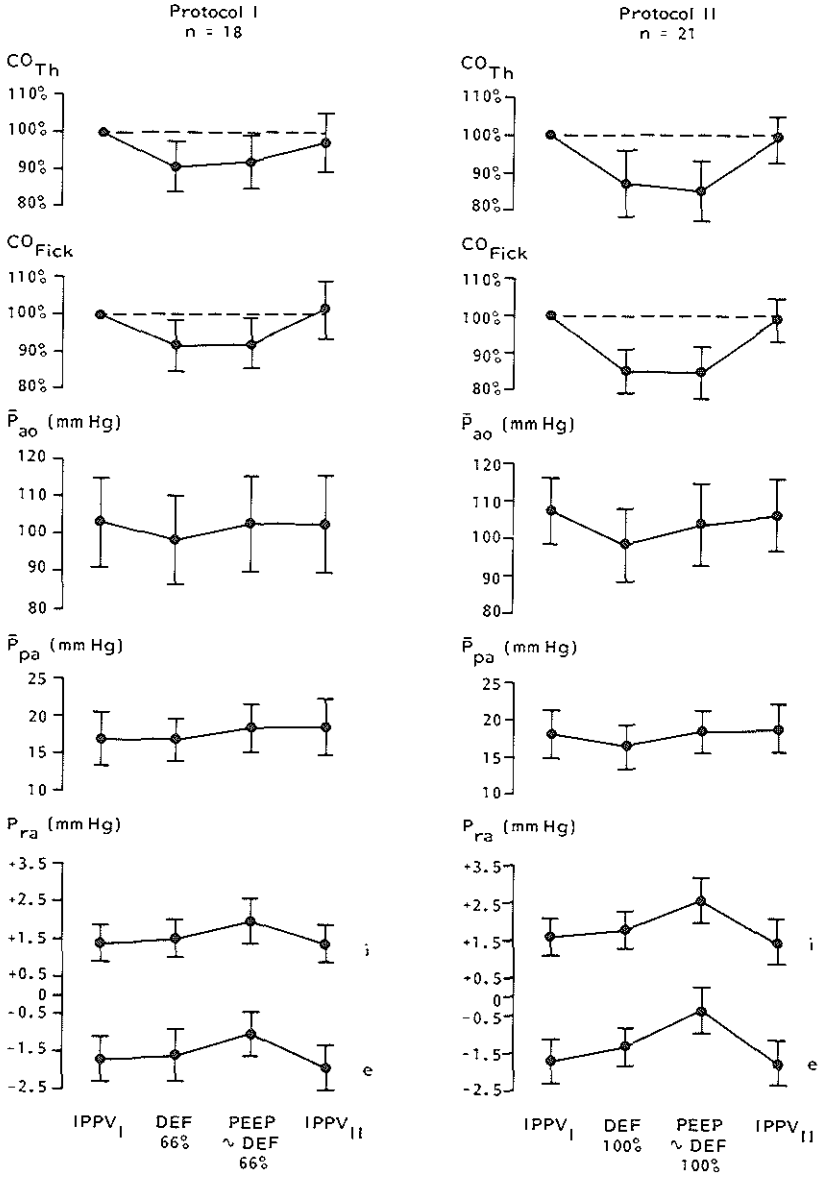
Protocol I
n = 18
Protocol II
n = 21
CO Th
CO Fick
110%
100%
90%
80%
P̄ao (mm Hg)
120
110
100
90
80
P̄pa (mm Hg)
25
20
15
10
Pra (mm Hg)
+3.5
+2.5
+1.5
+0.5
0
-0.5
-1.5
-2.5
i
e
IPPV I
DEF 66%
PEEP ∿ DEF 66%
IPPV II
DEF 100%
PEEP ∿ DEF 100%

Fig. IV-1:

Hemodynamic parameters during the different modes of ventilation in protocols I and II (chapter II-6). Cardiac output, estimated by the thermodilution technique (CO_{Th}) and the direct Fick method for oxygen (CO_{Fick}), for DEF, PEEP DEF and $IPPV_{II}$ is given as % of the mean during $IPPV_I$. $\bar{P}_{ao}$ = mean systemic arterial pressure; $\bar{P}_{pa}$ = mean pressure in the pulmonary artery; P_{ra} = right atrial pressure measured at the end of inflation (i) and at the end of expiration (e); Vertical bars represent standard deviations from the mean; n is number of series in healthy piglets.

was applied whether as a first or as a second series, compared to $IPPV_I$, $IPPV_{II}$ and ventilation with the corresponding PEEP value. PEEP had no effect on mean systemic arterial pressure.
Institution of DEF 100% also decreased aortic pressure ($p < 0.001$) compared to $IPPV_I$ and $IPPV_{II}$. This was slightly more than DEF 66% in the respective series. Compared to the value at the corresponding PEEP systemic arterial pressure was lower during DEF 100% ($p < 0.005$) when the protocol was done as a first series.
PEEP ~ DEF 100% decreased aortic pressure slightly but not significantly compared to IPPV.

IV-1-3 *Pulmonary arterial pressure*

Pulmonary arterial pressure averaged over the ventilatory cycle ($\bar{P}_{pa}$) did not change with DEF 66%, compared to $IPPV_I$. When the corresponding PEEP was applicated $\bar{P}_{pa}$ rose and remained at the same level ($p < 0.001$) when PEEP was discontinued (Fig. IV-1 and Table A-6) in protocol I as done as a first series. There was no statistical significance in protocol I done as a second series. In protocol II $\bar{P}_{pa}$ was lower ($p < 0.01$) during DEF 100% compared to $IPPV_I$, $IPPV_{II}$ and the corresponding PEEP, which had no effect on $\bar{P}_{pa}$, with respect to $IPPV_I$ and $IPPV_{II}$.

IV-1-4 *Right atrial pressure*

Right atrial pressure averaged over the cardiac cycle and measured at the end of the inspiratory pause ($P_{ra,i}$) and at the end of the expiratory

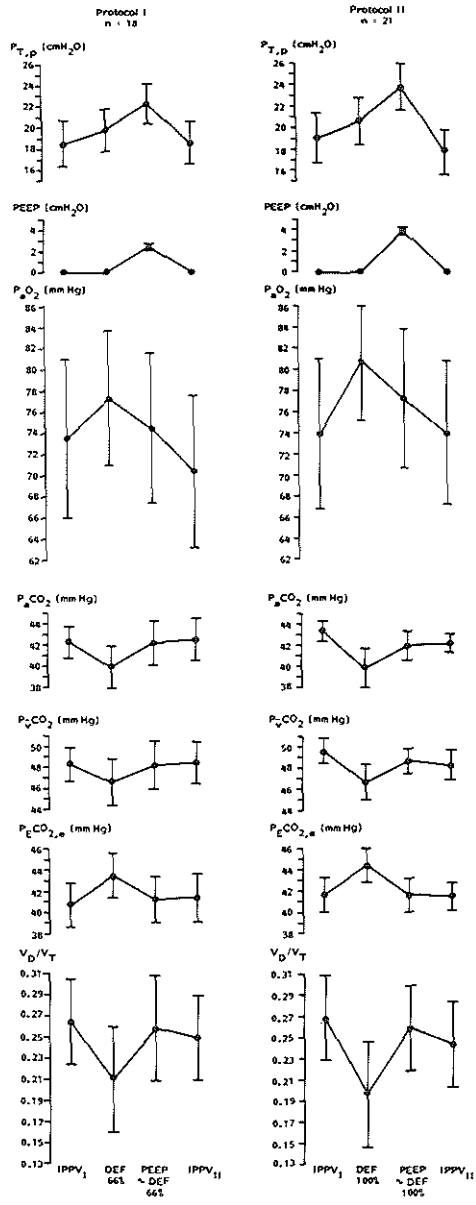

Fig. IV-2:

Peak tracheal pressure ($P_{T,p}$), positive end-expiratory pressure (PEEP), partial pressure of systemic arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and of carbon dioxide in the end-expiratory air ($P_ECO_{2,e}$), and physiological dead space (V_D/V_T) during the different modes of ventilation in protocols I and II (chapter II-6). Vertical bars represents standard deviations from the mean. n is number of series in healthy piglets.

pause ($P_{ra,e}$) changed slightly (Fig. IV-1, Tables A-7 and A-8). At the end of the inspiratory pause during both levels of PEEP a rise ($p < 0.01$) was noted compared to IPPV and DEF in both protocols and both series. During DEF 66% and DEF 100% $P_{ra,i}$ increased ($p < 0.05$) only when the protocols I and II were carried out as a first series. The right atrial pressure at the end of the expiratory phase was higher ($p < 0.025$) during circumstances of DEF and PEEP in both protocols compared to $IPPV_I$ except for DEF 66% compared to $IPPV_I$ in the second series. During both levels of PEEP, $P_{ra,e}$ was higher ($p < 0.001$) than during ventilation with the two levels of DEF.

IV-1-5 *Heart rate*

The heart rate did not change much during the different types of artificial ventilation in the different experimental series (Table A-9).

IV-2 PULMONARY PHENOMENA AND BLOODGASSES

IV-2-1 *Airway pressure*

PEEP, producing a similar rise in mean tracheal pressure as DEF 66% or DEF 100% in the protocols I and II, amounted to a mean of 2.4 $\pm$ 0.3 cm H_2O and 3.9 $\pm$ 0.4 cm H_2O respectively (fig. IV-2).
The peak tracheal pressure ($P_{T,p}$) was higher at $p < 0.001$ during ventilation with DEF (either 66% or 100%) than during IPPV (Fig. IV-5 and Table A-10) but not different between DEF 66% and $IPPV_{II}$ in protocol I done as a second series. During DEF 66% or 100% $P_{T,p}$ was lower at $p < 0.001$ compared to the $P_{T,p}$ values during ventilation with the corresponding PEEP values. These $P_{T,p}$ values during PEEP were higher at $p < 0.001$ than those during IPPV. In protocol I, $P_{T,p}$ during $IPPV_{II}$ was lower at $p < 0.05$ than the value of $IPPV_I$ when the protocol was carried out as a first series, but higher at $p < 0.01$ after a second series. In protocol II, $P_{T,p}$ during $IPPV_{II}$ was lower at $p < 0.01$ compared to the value of $IPPV_I$, whether the protocol was performed as a first or as a

second series.

IV-2-2 *Partial pressure of arterial oxygen (P_aO_2)*

Artificial ventilation with DEF (both 66% and 100%) raised P_aO_2 (Fig. IV-2) compared to IPPV and ventilation with PEEP ~ DEF 66% as well as PEEP ~ DEF 100% respectively ($p < 0.05$). The increase of P_aO_2 was more pronounced during DEF 100% than during DEF 66%. During PEEP ~ DEF 66%, the P_aO_2 did not increase compared to $IPPV_I$, but was higher at $p < 0.005$ than the value measured during $IPPV_{II}$. This latter value was at $p < 0.005$ lower than the initial P_aO_2 ($IPPV_I$). With a higher PEEP (~ DEF 100%) the P_aO_2 was raised regarding $IPPV_I$ and $IPPV_{II}$ ($p < 0.025$), except regarding $IPPV_{II}$ in the second series.

IV-2-3 *Partial pressure of arterial carbon dioxide (P_aCO_2)*

Artificial ventilation with DEF (66% as well as 100%) brought down P_aCO_2 ($p < 0.025$), regarding other types of ventilation (Fig. IV-2 and Table A-12). The effect of DEF 100% in this respect was slightly better than the effect of DEF 66%. PEEP ~ DEF 66% had no effect on P_aCO_2.
PEEP ~ DEF 100% produced a lower P_aCO_2 compared to $IPPV_I$ ($p < 0.01$), but not with respect to $IPPV_{II}$.

IV-2-4 *Partial pressure of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$)*

DEF in both protocols had the same effect on $P_{\bar{v}}CO_2$ as regarding P_aCO_2, i.e. $P_{\bar{v}}CO_2$ dropped ($p < 0.025$) compared to the other modes of artificial ventilation (Fig. IV-2 and Table A-13).
PEEP ~ DEF 66% had no effect on $P_{\bar{v}}CO_2$, and PEEP ~ DEF 100% lowered $P_{\bar{v}}CO_2$ only compared to $IPPV_I$ when the protocol was carried out as a first series.

IV-2-5 *Partial pressure of carbon dioxide in the end expiratory air ($P_ECO_{2,e}$)*

$P_ECO_{2,e}$ was higher at $p < 0.025$ (Fig. IV-2 and Table A-14) during artificial ventilation with both DEF 66% as well as with DEF 100%, compared to IPPV and PEEP (~ DEF 66% or 100% in the respective series). PEEP had no influence on $P_ECO_{2,e}$.
The value of $P_ECO_{2,e}$ approximated the value of $P_{\bar{v}}CO_2$ under DEF circumstances, i.e. $P_ECO_{2,e}$ was higher at $p < 0.001$ than P_aCO_2 (Fig. IV-2). During IPPV and PEEP the $P_ECO_{2,e}$ values were below the P_aCO_2 values ($p < 0.001$).

IV-2-6 *Physiological dead space fraction (V_D/V_T)*

V_D/V_T appeared to be lower ($p < 0.01$) during DEF 66% as well as DEF 100% compared to the other modes of ventilation (Fig. IV-2 and Table A-15). V_D/V_T did not change during PEEP ~ DEF 66% compared to $IPPV_I$ and $IPPV_{II}$. During $IPPV_{II}$, V_D/V_T was lower than $IPPV_I$ ($p < 0.05$) if protocol I was done as a first series. PEEP ~ DEF 100% did not change V_D/V_T compared to $IPPV_I$, but during $IPPV_{II}$ V_D/V_T was lower than during PEEP ~ DEF 100% and $IPPV_I$ ($p < 0.01$) if the protocol was carried out as a first series. The effect of DEF 100% compared to DEF 66% in lowering V_D/V_T was better in all series.

IV-3 HISTAMINE INDUCED PULMONARY PATHOLOGY SIMULATING OBSTRUCTIVE LUNG DISEASE

The effect of histamine, continuously infused into the pulmonary artery (see paragraph II-7) on hemodynamic, ventilatory and respiratory variables compared to those under normal circumstances during IPPV are listed in Table IV-1. Cardiac output and mean pulmonary arterial pressure increased, while mean systemic arterial pressure decreased. Peak tracheal pressure increased. P_aO_2 decreased considerably, while P_aCO_2 and $P_{\bar{v}}CO_2$ were higher after histamine administration. On auscultation a definite wheezing with basal crepitation could be heard over the lungs.

	Normal lungs	Histamine induced pulmonary pathology	% change	Statistical analysis
CO_{Th} ($ml \cdot kg^{-1} \cdot s^{-1}$)	2.63 ± 0.56	3.24 ± 0.66	+24	$p < 0.001$
$\bar{P}_{ao}$ (mm Hg)	100.9 ± 8.7	79.7 ± 7.9	-21	$p < 0.001$
$\bar{P}_{pa}$ (mm Hg)	16.8 ± 1.8	22.6 ± 2.3	+36	$p < 0.001$
$P_{ra,e}$ (mm Hg)	- 2.0 ± 0.4	- 2.2 ± 0.5	-	NS
$P_{ra,i}$ (mm Hg)	+ 1.2 ± 0.4	+ 1.2 ± 0.4	-	NS
Heartrate ($1 \cdot min^{-1}$)	150 ± 21	182 ± 16	+23	$p < 0.005$
$P_{T,p}$ (cm H_2O)	17.6 ± 1.4	23.3 ± 1.7	+33	$p < 0.001$
P_aO_2 (mm Hg)	75.8 ± 6.4	58.4 ± 5.2	-23	$p < 0.001$
P_aCO_2 (mm Hg)	42.8 ± 1.4	47.1 ± 1.9	+10	$p < 0.005$
$P_{\bar{v}}CO_2$ (mm Hg)	49.1 ± 0.9	54.2 ± 3.1	+10	$p < 0.005$
$P_ECO_{2,e}$ (mm Hg)	42.2 ± 1.7	48.6 ± 2.5	+14	$p < 0.001$
V_D/V_T	0.25 ± 0.03	0.25 ± 0.03	-	NS

Table IV-1:

Mean absolute values and standard deviations from the mean of hemodynamic and pulmonary parameters before and after infusion of histamine ($1.1\ mg \cdot kg^{-1} \cdot h^{-1}$) into the pulmonary artery.

IV-3-1 *Hemodynamic phenomena*

The effects of the different modes of artificial ventilation on the hemodynamic variables were not substantially different from those, as described for the experiments under non-pathological circumstances (see paragraph IV-1 and Tables A-16 to A-21). Therefore only the respiratory phenomena of the experiments with histamine induced pulmonary pathology

will be described in the same order as those under baseline conditions (III-2).

IV-3-2 *Pulmonary phenomena and bloodgasses*

IV-3-2-1 Airway pressure

PEEP, producing a similar rise in mean tracheal pressure as DEF 66% and DEF 100% amounted to a mean of 2.9 $\pm$ 0.2 cm H_2O and 4.4 $\pm$ 0.2 cm H_2O respectively (Fig. IV-3 and table A-22). These values are on average 0.5 cm higher than in the series under non-pathological circumstances (see paragraph IV-2-1).
The peak tracheal pressure did not change with DEF 66% or DEF 100% compared to $IPPV_I$. After the DEF 100% series the peak tracheal pressure at $IPPV_{II}$ was lower ($p < 0.001$) compared to $IPPV_I$ and DEF (Table A-22).

IV-3-2-2 Partial pressure of arterial oxygen (P_aO_2)

DEF, either 66% or 100%, raised P_aO_2 (Fig. IV-3 and Table A-23) compared to IPPV ($p < 0.001$). The rise in P_aO_2 during DEF was higher on average than in both protocols under non-pathological circumstances (11% more in the DEF 100% series).
DEF 66% and PEEP $\sim$ DEF 66% were not different in raising P_aO_2. DEF 100% produced a higher P_aO_2 than PEEP $\sim$ DEF 100% ($p < 0.01$). PEEP (both $\sim$ DEF 66% and $\sim$ 100%) also gave a higher P_aO_2 compared to IPPV ($p < 0.025$ and $p < 0.001$ respectively). P_aO_2 during $IPPV_I$ and $IPPV_{II}$ was not different.

IV-3-2-3 Partial pressure of arterial carbon dioxide (P_aCO_2)

Both DEF 66% and DEF 100% reduced P_aCO_2 ($p < 0.01$) regarding other patterns of ventilation (Fig. IV-3 and Table A-24). Only in the DEF 100%

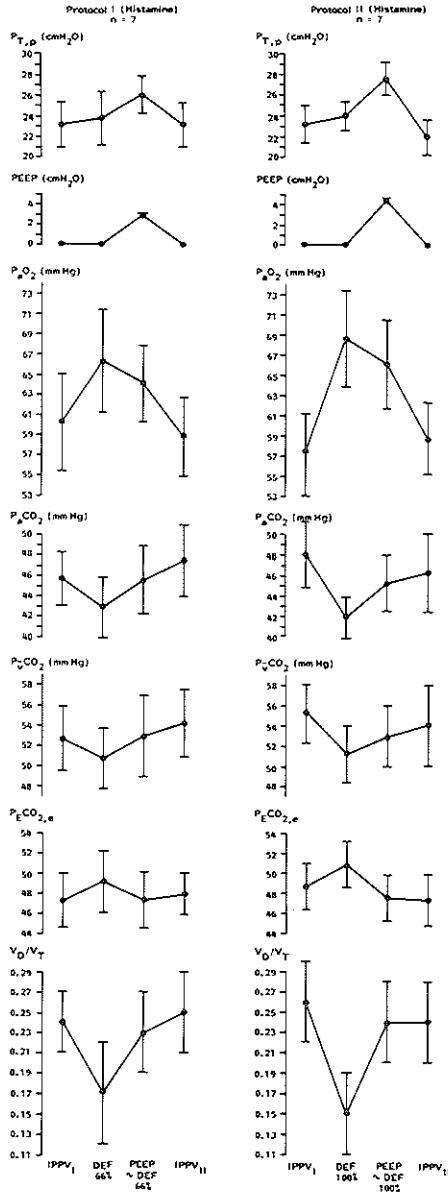

Fig. IV-3:

Peak tracheal pressure ($P_{T,p}$), positive end-expiratory pressure (PEEP), partial pressures of systemic arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and of carbon dioxide in the end-expiratory air ($P_ECO_{2,e}$), and physiological dead space (V_D/V_T) during the different modes of ventilation in protocols I and II (chapter II-6). Vertical bars represent standard deviations from the mean. n is number of series in histamine induced pulmonary disease.

series P_aCO_2 on average was more markedly reduced than in the comparable series under non-pathological circumstances. There was no difference between P_aCO_2 during $IPPV_I$ and $IPPV_{II}$. PEEP in the DEF 66% series did not affect P_aCO_2 regarding $IPPV_I$, but during $IPPV_{II}$, P_aCO_2 increased with respect to PEEP ~ DEF 66% ($p < 0.005$). In the DEF 100% series P_aCO_2 was lower during PEEP compared to $IPPV_I$ ($p < 0.005$), but was not significantly different from the value during $IPPV_{II}$.

IV-3-2-4 Partial pressure of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$)

DEF 66% as well as DEF 100% produced a lower $P_{\bar{v}}CO_2$ (Fig. IV-3 and Table A-25) compared to both IPPV and PEEP ($p < 0.01$). This was hardly different from the results seen during non-pathological circumstances.

IV-3-2-5 Partial pressure of carbon dioxide in the end expiratory air ($P_ECO_{2,e}$)

$P_ECO_{2,e}$ was higher (Fig. IV-3 and Table A-26) with DEF 66% as well as DEF 100% compared to the other modes of ventilation ($p < 0.025$). The values of $P_ECO_{2,e}$ were about the same as in the comparable series under non pathological circumstances.

IV-3-2-6 Physiological dead space fraction (V_D/V_T)

V_D/V_T was lower with both DEF 66% and DEF 100%, compared to IPPV and PEEP in the respective series ($p < 0.01$ and $p < 0.001$). The decrease in V_D/V_T was markedly more in the DEF 66% and in the DEF 100% series compared to the values seen under non-pathological circumstances (71% versus 80% and 58% versus 72% respectively). PEEP had no effect on V_D/V_T compared to IPPV (fig. IV-3 and Table A-27).

IV-3-3 *Histological examinations*

In the lung biopsies, taken after postmortem examination, a vasodilatation was seen with a capillary overhydration. Locally a protein-like substance was present in the alveolar spaces. Septal edema was encountered and in four piglets perivascular edema was present.

	Normal conditions	Acetylcholine induced pulmonary pathology	% change	Statistical analysis
CO_{Th} ($ml \cdot kg^{-1} \cdot s^{-1}$)	2.38 ± 0.36	2.84 ± 0.53	+20	$p < 0.05$
$\bar{P}_{ao}$ (mm Hg)	94.7 ± 13.7	72.5 ± 7.6	-23	$p < 0.001$
$\bar{P}_{pa}$ (mm Hg)	17.7 ± 4.4	24.5 ± 2.5	+44	$p < 0.005$
$P_{ra,e}$ (mm Hg)	- 1.28 ± 0.47	- 0.47 ± 0.67		$p < 0.05$
$P_{ra,i}$ (mm Hg)	1.86 ± 0.69	2.79 ± 0.62		$p < 0.05$
Heartrate ($\cdot min^{-1}$)	147 ± 16	182 ± 17	+26	$p < 0.025$
$P_{T,p}$ (cm H_2O)	19.4 ± 2.8	24.8 ± 1.4	+29	$p < 0.005$
P_aO_2 (mm Hg)	75.9 ± 6.2	66.5 ± 6.2	-12	$p < 0.005$
P_aCO_2 (mm Hg)	43.7 ± 1.3	45.8 ± 1.6	+ 5	$p < 0.005$
$P_{\bar{v}}CO_2$ (mm Hg)	49.9 ± 1.3	50.8 ± 2		NS
$P_ECO_{2,e}$ (mm Hg)	41.3 ± 1.8	44.3 ± 1.5	+ 7	$p < 0.005$
V_D/V_T	0.30 ± 0.05	0.30 ± 0.03		NS

Table IV-2:

Mean absolute values and standard deviations from the mean of hemodynamic and pulmonary parameters before and after infusion of acetylcholine (0.56 $mg \cdot kg^{-1} \cdot h^{-1}$) into the pulmonary artery.

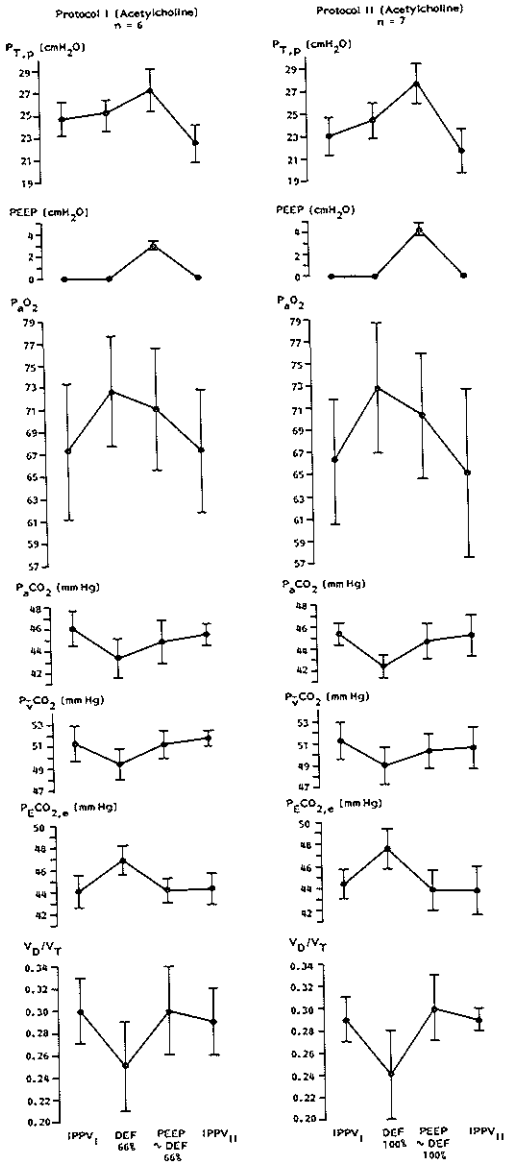

Fig. IV-4:

Peak tracheal pressure ($P_{T,p}$), positive end-expiratory pressure (PEEP), partial pressures of systemic arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and of carbon dioxide in the end-expiratory air ($P_ECO_{2,e}$), and physiological dead space (V_D/V_T) during the different modes of ventilation in protocols I and II (chapter II-6). Vertical bars represent standard deviations from the mean. n is number of series in acetylcholine induced pulmonary disease.

IV-4 ACETYLCHOLINE INDUCED PULMONARY PATHOLOGY SIMULATING OBSTRUCTIVE LUNG DISEASE

Acetylcholine, continuously infused into the pulmonary artery (II-7) had the effects on hemodynamic and respiratory parameters compared to those under normal pulmonary circumstances as listed in Table IV-2. The hemodynamic effects were about the same as in the histamine series (Tables A-16 to A-21). P_aO_2 decreased and P_aCO_2 increased less than in the histamine series.

The effects of DEF and PEEP on pulmonary phenomena and gas exchange compared mutually and to IPPV during acetylcholine induced pulmonary pathology (Fig. IV-4) were less marked than the results seen with histamine (Tables A-22 to A-27), and were about the same as the results seen during non-pathological circumstances. PEEP amounted to 3 $\pm$ 0.4 cm H_2O and 4.3 $\pm$ 0.5 cm H_2O in protocol I and II respectively (Fig. IV-4 and Table A-22), which is comparable to the PEEP values in the histamine series.

In the lung biopsies after postmortem examination a marked vasodilatation was seen with focal hemorrhages in the alveolar septa. Sometimes the septa were very pronounced with a polymorphonuclear infiltrate. Edema was present, but not in all specimens, together with a intra-alveolar protein-like substance.

IV-5 PULMONARY PATHOLOGY INDUCED BY ALLOXAN AND OLEIC ACID

The conditions of the animals after injection of alloxan and oleic acid into the pulmonary artery and after compensatory Dextran infusion (II-7) are listed in Table IV-3. Cardiac output decreased in spite of compensatory infusions of Dextran. Peak tracheal pressure and physiological dead space increased markedly (48% and 56% respectively). P_aO_2 levels were good with an F_IO_2 of 0.40. P_aCO_2 increased by 15%. With respect to the condition of the animals only a DEF 100% series was carried out.

PEEP amounted to 5.4 $\pm$ 0.7 cm H_2O (Fig. IV-5). Cardiac output was not altered by DEF or PEEP (Table A-28)

DEF 100% and PEEP $\sim$ DEF 100% increased P_aO_2 ($p < 0.025$) compared with IPPV, but PEEP $\sim$ DEF 100% elevated P_aO_2 to a much higher level (Fig. IV-5 and Table A-30).

	Normal conditions	Alloxan and oleic acid induced pulmonary pathology*	% change	Statistical analysis
CO_{Th} ($ml \cdot kg^{-1} \cdot s^{-1}$)	2.59 ± 0.2	2.22 ± 0.1	-14	$p < 0.025$
$\bar{P}_{ao}$ (mm Hg)	98.8 ± 9.9	117.2 ± 14.5	+15	$p < 0.050$
$\bar{P}_{pa}$ (mm Hg)	22.4 ± 3.8	25.7 ± 2.6	+16	$p < 0.01$
$P_{ra,e}$ (mm Hg)	- 0.94 ± 0.6	+ 0.72 ± 0.6		$p < 0.025$
$P_{ra,i}$ (mm Hg)	2.3 ± 0.7	3.65 ± 0.7		$p < 0.025$
Heartrate ($\cdot min^{-1}$)	188 ± 29	133 ± 16	-26	$p < 0.01$
$P_{T,p}$ (cm H_2O)	18.7 ± 3.1	27.4 ± 2.5	+48	$p < 0.001$
P_aO_2 (mm Hg)	68.8 ± 10.1	95.1 ± 13.9**	+39	**
P_aCO_2 (mm Hg)	42.6 ± 1.3	49 ± 4.4	+15	$p < 0.025$
$P_{\bar{v}}CO_2$ (mm Hg)	48.5 ± 2.5	58.6 ± 5	+21	$p < 0.005$
$P_ECO_{2,e}$ (mm Hg)	42.1 ± 1.7	40.1 ± 0.9	+ 5	$p < 0.05$
V_D/V_T	0.28 ± 0.04	0.38 ± 0.06	+36	$p < 0.001$

* After infusion of Dextran (10 $ml.kg^{-1}$)

** $F_IO_2 = 0.40$

Table IV-3:

Mean absolute values and standard deviations from the mean of hemodynamic and pulmonary parameters before and after injection of alloxan (75 $mg \cdot kg^{-1}$) and oleic acid (0.5 ml) into the pulmonary artery and after infusion of Dextran (10 $ml \cdot kg^{-1}$).

Both DEF and PEEP diminished P_aCO_2 ($p < 0.025$) and $P_{\bar{v}}CO_2$ ($p < 0.05$) to the same extent (Fig. IV-5 and Table A-30). DEF caused a rise in $P_ECO_{2,e}$ ($p < 0.01$), on which PEEP had no effect (Fig. IV-5 and Table A-31). Both DEF and PEEP decreased the physiological dead space (V_D/V_T, Fig. III-8 and Table A-32) compared to IPPV ($p < 0.01$).

Histological examination of the postmortem lung biopsies showed a peribronchial and peri-arteriolar edema with a capillary congestion and a protein-like substance in the alveolar spaces. The arterial endothelium was swollen and the alveolar septa were focally thickened. Also hemorrhages were seen in the alveolar septa.

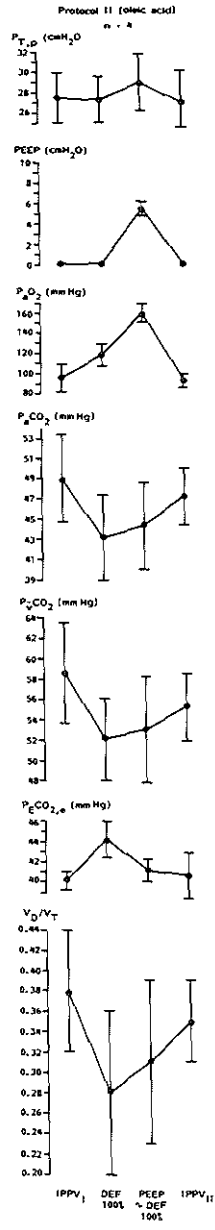

Fig. IV-5:

Peak tracheal pressure ($P_{T,p}$), positive end-expiratory pressure (PEEP), partial pressures of systemic arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and of carbon dioxide in the end-expiratory air ($P_ECO_{2,e}$), and physiological dead space (V_D/V_T) during the different modes of ventilation in protocol II (chapter II-6). Vertical bars represent standard deviations from the mean. n is number of series in oleic acid induced pulmonary disease.

CHAPTER V

DISCUSSION

THE EXPERIMENTAL CONDITIONS

Stability

Piglets, 4-7 weeks old, constitute an adequate animal model, resembling adult swine regarding cardiovascular control (Buckley et al., 1979,a) and the geometric relations of the heart (Versprille et al., 1976). The dose of pentobarbital sodium (II-2) injected intraperitoneally provided sufficient surgical anesthesia (Buckley et al., 1979,b and present experience). During the surgical procedures the pigs breathed spontaneously in a regular pattern with intermittent sighs. This was terminated by the infusion of d-tubocurarine during the experimental procedures when mechanical ventilation was started. Schreuder et al. (1982) have demonstrated that continuous infusion of pentobarbital sodium sufficient for anesthesia as used for the experiments in this study (II-2), produced stable plasma-concentrations over hours. Together with continuous infusion of d-tubocurarine hemodynamic and respiratory parameters were constant and comparable in the different animals throughout the experimental procedures. Pentobarbital has been said to depress the cardiovascular functions (Strobel and Wollman, 1969; Effendi, 1972; Effendi et al., 1974). Sawyer et al. (1971) found a decrease of 41% in cardiac output compared to pre-anesthesia control values with slightly higher plasma-concentrations of pentobarbital sodium as Schreuder et al. (1982) described. However Buckley et al. (1979,b) did not find significantly different values for systemic arterial pressure under pentobarbital anesthesia, compared to those obtained in piglets and swine under local (Evans et al., 1963; Hörnicke, 1966), halothane (Buckley et al., 1976) or ketamine (Rowe and Arango, 1977) anesthesia. This leads to the conclusion that pentobarbital anesthesia produces reliable experimental circumstances for studying the effects of several modes of mechanical ventilation on hemodynamic variables during baseline conditions

and experimental pathology. The hemodynamic values before and after the DEF 66% and the DEF 100% series were not significantly different (III-1) indicating a stable animal model throughout the observation period. The baseline values were in accordance with those described by Hörnicke (1966), Rowe and Arango (1977), Buckley et al. (1979,b) and Schreuder et al. (1982).
PEEP was produced by submerging the tube from the expiratory port of the ventilator under a water column because it was noted, that the PEEP-valve of the Servo ventilator had a marked expiratory resistance producing an increase in expiration time, as described later by Link (1983).

Histamine

Obstructive lung disease was simulated by infusion of histamine or acetylcholine into the pulmonary artery. Histamine has definite effects on the respiratory and cardiovascular systems. The drug is known to constrict bronchial and alveolar duct smooth muscle, the magnitude of which is qualitatively related to the amount of smooth muscle in alveolar ducts (Colebatch and Engel, 1974). The resultant effect is an increase in predominantly peripheral resistance of the lung (Drazen et al., 1976) and a decrease of the dynamic compliance. A higher airway pressure at volume-constant inflation is seen with histamine, due to constriction of alveolar duct muscle in series with the pulmonary fibre network and thus regulating the distensibility of respiratory units (Colebatch and Mitchell, 1971). In accordance, a rise in peak tracheal pressure was observed in this study after histamine infusion (Table A-16). It has however been extremely difficult to reproduce the typical increase in functional residual capacity seen in humans after bronchial provocation (Hutchison et al., 1982). There is a wide range of responsiveness to aerosol challenge among individual animals (Snapper et al., 1978). However, a correlation was found to exist between responsiveness to aerosol histamine and parenterally administered histamine, suggesting that airway responsiveness is an inherent physiologic property (Hutchison et al., 1982). Histamine infused into the left atrium or into the pulmonary artery produced similar afore mentioned changes in pulmonary mechanics (Hutchison et al., 1982), but according to Colebatch et al. (1966) a 12-30 times greater minimal dose is needed for left sided injections to decrease lung compliance and increase lung resistance compared to right sided injections. Infusion into the pulmonary artery was highly

reproducible. Histamine has no effect on dead space (Folkow and Pappenheimer, 1955; Colebatch et al., 1966; Drazen et al., 1979) which was confirmed in this study (Table A-16). According to Douglas (1980) the effects of histamine on cardiovascular systems are the following: the most characteristic action on the vascular tree is a vasodilatation, which can produce an impressive fall in systemic blood pressure. The second classic effect of histamine on the fine vessels is an increased capillary permeability resulting in edema, as was seen histopathologically in the post mortem lung biopsies (see chapter IV-5) and was made likely in this study, because the hemoglobin concentration increased by 0.7 $mmol \cdot L^{-1}$ (range 0.2 - 1.5) during histamine infusion (unpublished data). Heart rate and cardiac output tend to be augmented by histamine, evenso the pulmonary artery blood pressure. This was also confirmed in the experiments (Table A-16). The dose used (1.1 $mg \cdot kg^{-1} \cdot h^{-1}$) was empirically found to obtain a good reproducible response and is somewhat higher than used in the literature. This may account for the pulmonary edema seen at post mortem investigation.
Because both $P_{T,p}$ and P_aCO_2 increased during histamine infusion and wheezing was heard over the lungs, it may be concluded, that bronchospasm was present.

Acetylcholine

Acetylcholine has a diffuseness of action (Taylor, 1980). The effects on the respiratory system include increased tracheobronchial secretion and bronchoconstriction, which may precipitate an asthmatic attack. Acetylcholine produces a smaller decrease in lung compliance, but a greater increase in pulmonary resistance compared to histamine. It reduces dead space and decreases arterial tension (Colebatch et al., 1966). Reduction of dead space was not encountered in this study, but the decrease in arterial oxygen tension was highly significant, evenso the rise in peak tracheal pressure.
The reported cardiovascular effects after the dose used (0.56 $mg \cdot kg^{-1} \cdot h^{-1}$) were a generalized vasodilatation (Taylor, 1980), producing an evanescent fall in systemic arterial pressure, accompanied usually by reflex tachycardia. These indeed were features in this study together with an augmented cardiac output and a remarkable increase in pulmonary arterial pressure (Table A-29). The systemic arterial pressure though did not return to pre-infusion values after the initial fall (Table A-29) due to

the continuous infusion of acetylcholine.
Acetylcholine is rapidly hydrolyzed enzymatically and thus removed from the circulation, accounting for the rapid recovery after single dose injection (Colebatch et al., 1966).
It is concluded, that during infusion of acetylcholine bronchospasm was present, because $P_{T,p}$ and P_aCO_2 increased and wheezing was heard over the lungs.

Alloxan and oleic acid

The respiratory distress syndrome (RDS) was simulated by the infusion of alloxan and oleic acid into the pulmonary artery.
Alloxan infusion produces electron microscopically a disruption of both endothelial and epithelial cells (Cottrell et al., 1967) in contrast to hemodynamic edema. This may account for the increased permeability of the fluid exchanging vessels in the lung (Hopewell, 1979) and for the differences seen when alloxan edema is compared to hemodynamic (high pressure) edema (Staub et al., 1967):
- a pulmonary capillary pressure below edemogenic level;
- a decreased pulmonary capillary volume;
- congested alveolar capillaries only in the lower zone;
- edema fluid containing a high amount of protein resulting in a lot of foam in the airways, and
- no red cells in the edema fluid.

Fluid filling of the alveoli is individual and occurs independently of their neighbours.

Oleic acid was found to produce a massive hemorrhagic edema of the lungs, probably due to toxic effects on the capillaries of the lung. Fat embolism does not seem to be the mechanism, as olive oil injected intravenously produces a more pronounced massive fat embolism without any toxic effects (Jefferson and Necheles, 1948). The dosage of oleic acid above 0.1 $ml \cdot kg^{-1}$ bodyweight injected into the pulmonary artery of the dog is rapidly lethal without artificial ventilatory support, whereas a dose of 0.075 $ml \cdot kg^{-1}$ bodyweight caused a characteristic pattern of illness: respiratory failure with tachypnea, hypoxemia and cyanosis, pulmonary edema, increase of inspiratory effort, a grunting type of expiration and eventually death (Ashbaugh and Uzawa, 1968). These observations in the dog were remarkably similar to the respiratory distress syndrome seen in

humans (Ashbaugh et al., 1967).
After intravenous injection of oleic acid (0.045 and 0.09 $ml \cdot kg^{-1}$, differing only in the extent of the diseased zones) pulmonary edema, capillary congestion, perivascular infiltrates and hemorrhage are seen microscopically (Derks and Jacobovits-Derks, 1977). Grossman et al. (1980) found that the loss of lung volume after oleic acid injury (0.043 $ml \cdot kg^{-1}$) secondary to alveolar flooding was the most important reason for the decrease of lung compliance. Increase in extravascular lung water content and sequential flooding of the alveoli with edema fluid is related to an increase in the alveolo-arterial oxygen gradient, and a decrease in compliance and functional residual capacity (Hofman et al., 1985). This increase in extravascular lung water may be much more an index for the degree of lung injury than the decrease of P_aO_2 (Schuster and Trulock, 1984). In the oleic acid model for pulmonary edema intravascular coagulation occurs as a secondary phenomenon (King et al., 1971).

The effects produced by ***alloxan*** and ***oleic acid*** as described in chapter IV-5 in the doses described in chapter II-7 were in accordance with the results of other workers (Ashbaugh and Uzawa, 1968; Schuster and Trulock, 1984; Hofman et al., 1985; Johnston et al., 1985). As the hemodynamic and gasexchange conditions were stable throughout the experiments, and the effects of oleic acid and alloxan infusion were well reproducible, it can therefore be concluded that a useful respiratory distress model was achieved for studying the effects of DEF and PEEP on hemodynamic and pulmonary phenomena.

HEMODYNAMIC PHENOMENA

Mean cardiac output decreased to the same extent compared to IPPV when DEF or PEEP ~ DEF were instituted. This can be explained primarily by the same rise in mean tracheal pressure. If the tracheal pressure is substituted as an indicator of intrathoracic pressure (especially in the experiments on animals with non-diseased pulmonary conditons and within the same animals), this rise will impede venous return to the heart, causing less right ventricular filling (Humphreys et al., 1938; Cournand et al., 1948; Versprille and Jansen, 1985). Indeed, with a higher mean tracheal pressure during DEF 100% and PEEP ~ DEF 100% the decrease in cardiac output was more pronounced than during a lower mean tracheal pressure as during DEF 66% and PEEP ~ DEF 66% (Fig. IV-1, Table A-3, A-4,

A-17).

Although right atrial pressure averaged over the cardiac cycle (P_{ra}), measured at the moments of end expiration and peak insufflation, was significantly higher during PEEP compared to the values of the same moments in the other modes of ventilation, no differences in the mean value of P_{ra} averaged over the ventilatory cycle were observed because in the phase of prolonged expiration by DEF (between the end-inspiration and end-expiration measuring moments) a higher and gradually diminishing P_{ra} existed as seen on the recording (Fig. V-1). This behaviour of P_{ra} might explain the same fall in cardiac output during DEF or PEEP circumstances. Mean pulmonary arterial pressure ($\bar{P}_{pa}$) only dropped during DEF 100% compared to the other ventilatory patterns, whereas PEEP ~ DEF 66% caused an increase.

However, transmural P_{ra} and P_{pa} may well drop (Versprille, 1983) both due to a decrease in venous return i.e. preload of the ventricle and thus producing a fall in cardiac output.

Mean aortic pressure dropped during DEF (either 66% of 100%) compared to the other modes of ventilation probably due to a lower value of systemic arterial carbondioxide (chapter IV-2-3).

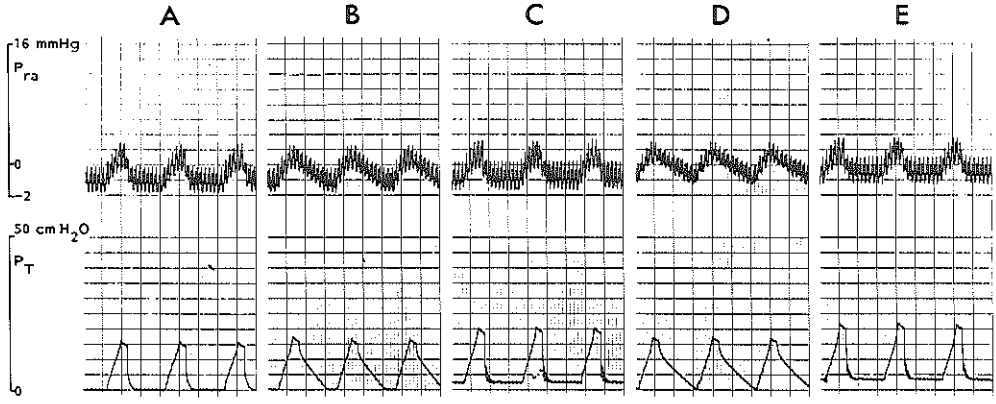

Fig. V-1:

Tracing of right atrial pressure (P_{ra}) and tracheal pressure (P_T) during IPPV (A), DEF 66% (B), PEEP ~ DEF 66% (C), DEF 100% (D) and PEEP ~ DEF 100% (E). P_{ra} and P_T show a slackening fall during expiration with DEF 66% and DEF 100%.

Airway pressure

During artificial ventilation with DEF a rise in peak tracheal pressure ($P_{T,p}$) compared to the first control series ($IPPV_I$) was only seen in the piglets with normal lungs (Fig. IV-5, Table A-10) and not under pathological circumstances. This phenomenon, without a change of tidal volume, could be explained by an increase in functional residual capacity (FRC) as seen during expiration with a resistance (Buhain et al., 1972; Moomjiam et al., 1980) and during pursed lips breathing producing a more pronounced rise in end-expiratory lung volume in healthy controls (Ingram and Schilder, 1967). Also, a small rise was seen in FRC during mechanical ventilation with a maximum inspiratory hold and shortest expiration to produce zero end-expiratory flow (Perez-Chada et al., 1983). This was also the impression, when Helium wash-in and wash-out procedures were performed on three occasions (unpublished data).
At higher $P_{T,p}$, as seen after induced pulmonary pathology (Tables A-16, A-29 and A-30) DEF did not result in a significantly higher $P_{T,p}$ compared to $IPPV_I$, probably due to less or absent increase of FRC (Ingram and Schilder, 1967). Whether opening of units with airtrapping due to airway collapse is a mechanism remains speculative.
The $P_{T,p}$ during the second control series ($IPPV_{II}$) was lower than during $IPPV_I$, presumably due to "adaptation" (Bernstein, 1957) after the period of higher inflation pressures during the previous positive end-expiratory pressure (PEEP) period in the experimental series (see chapter II-6), and due to influence of stress relaxation (Sharp et al., 1967). Elastic hysteresis related to surface phenomena may also contribute (Mead et al., 1957).
Further, PEEP will dissolve atelectasis in the dependent regions of the lung during artificial ventilation and anesthesia (Strandberg, 1985) and PEEP causes a release of surfactant, resulting in a lower surface tension of the alveoli and lower peak tracheal pressures after PEEP is discontinued. There is gradual recovery from the adapted state (Bernstein, 1957) and probably, after PEEP, atelactasis in the dependent regions may reoccur, which may account for the one exception in this study, i.e. $P_{T,p}$ during $IPPV_{II}$ was higher than the value during $IPPV_I$, if the DEF 66% series was performed after a DEF 100% series (Table A-10). The highest $P_{T,p}$ evidently was found during PEEP ~ DEF 100% and this part

of the series was done just before the DEF 66% series started meaning the $IPPV_{II}$ of the DEF 100% series was the $IPPV_{I}$ of the DEF 100% series. The gradual recovery from the adapted state took place during the whole of the DEF 66% series so $P_{T,p}$ rose to a higher level during $IPPV_{II}$ compared to $IPPV_{I}$

CO_2 elimination and O_2 uptake

In this study the respiratory rate, tidal volume, inspiratory flow rate and time and inspiratory hold were maintained constant to rule out any possible change in blood gas exchange by altering these settings. Mechanical ventilation with a diminished expiratory flow (DEF) always ended in a zero end-expiratory pressure (ZEEP) and flow and resulted in an increase in mean airway pressure by the slower pressure fall from peak airway pressure to ZEEP. During intermittent positive pressure ventilation (IPPV) with a positive end-expiratory pressure (PEEP) mean airway pressure was adjusted to the same level in order to approximate similar effects on cardiac output.

In summary DEF, in piglets with normal lungs, was found to have the following effects on CO_2 elimination and O_2 uptake when compared to IPPV (fig. III-5).:

- an increase in P_aO_2 (6% $\pm$ 4 at DEF 66%; 10% $\pm$ 4 at DEF 100%);
- a decrease in P_aCO_2 (6% $\pm$ 3 at DEF 66%; 8% $\pm$ 3 at DEF 100%);
- a decrease in $P_{\bar{v}}CO_2$ (3% $\pm$ 3 at DEF 66%; 6% $\pm$ 3 at DEF 100%), and
- a decrease in V_D/V_T (20% $\pm$ 13 at DEF 66%; 28% $\pm$ 15 at DEF 100%).

The effects of PEEP on P_aO_2 were less marked, whereas the effect of PEEP on P_aCO_2 and V_D/V_T were slight, if present at all. This leads to the conclusion that both CO_2 elimination and O_2 uptake are better during DEF than during comparable PEEP especially as cardiac output is the same.

However, as oxygen saturation is only slightly higher during DEF compared to IPPV (about 1-2% for DEF 66% and DEF 100% respectively), oxygen transport will decrease as cardiac output falls. Oxygen transport is slightly better during DEF than during PEEP, as cardiac output is the same and oxygen saturation is higher (about 1% for both DEF 66% and DEF 100%). In the clinical situation, oxygen transport may be elevated by raising the preload of the right ventricle through infusion of fluids (Ashbaugh and Petty, 1973; Qvist et al., 1975).

The better CO_2 elimination and O_2 uptake can be explained by a better effective alveolar ventilation ($V_{A,eff}$), which can be deducted from the

equation:

$$V_{CO_2} = F_{\bar{A}}CO_2 \times V_{A,eff}, \text{ where}$$

V_{CO_2} = carbon dioxide production, and
$F_{\bar{A}}CO_2$ = mean alveolar carbon dioxide fraction.

As V_{CO_2} remained the same during the three ventilatory modes (CO_2 fraction in the mixed expiratory air did not change at steady state conditions during the three ventilatory modes in one protocol, unpublished data) and as P_aCO_2 represents $F_{\bar{A}}CO_2$, meaning $F_{\bar{A}}CO_2$ decreased during DEF, $V_{A,eff}$ must have increased leading to a decrease of V_D/V_T, because tidal volume did not change. There are several possible explanations for the increased efficiency of alveolar ventilation during DEF compared to PEEP and IPPV and probably all contribute.

First, the longer presence of a larger amount of inspired gas in the lung will result in a greater amount of CO_2 expired (Nye, 1970), as a larger volume provides a greater area for blood gas diffusion with a lower resistance for diffusion due to a thinner membrane (Stam et al., 1983).

Second, a longer increased lung volume will increase the surface area of the diffusion interface between gas in the alveoli and gas in the airways and thus provides a longer period for diffusion to occur (Cumming et al., 1967; Bowes et al., 1985).

Third, during retarded expiration redistribution of gas from overventilated, low resistance alveoli to underventilated high resistance alveoli can occur (Otis et al., 1956), which may be improved by the sustained increase in the pressure of the main airways as with DEF (Sykes and Lumley, 1969).

Also, DEF will result in more complete emptying of the alveoli, especially the alveoli with high airflow resistance, resulting in movement of more air into these alveoli during inspiration, producing a more even distribution of ventilation and therefore an improved ventilation/perfusion matching (Connors et al., 1981). Thus, a larger fraction of the inspired volume will effectively mix with the alveolar air (Luijendijk et al., 1980).

The prolonged actual expiration during DEF may allow better homogenisation of the intra-acinar gas concentration by diffusion (Feenstra et al., 1985), resulting in a redistribution of O_2 from alveoli with high ventilation/perfusion ratio's to alveoli with low ventilation/perfusion ratio's and vice versa for CO_2, reducing the part of the physiological dead space determined by inhomogeneity.

A fourth mechanism could be an increased FRC-level during ventilation with DEF. During spontaneous expiration with a relatively high initial flow, FRC-level is reached within 30% of the available expiratory time in this study. During anesthesia and paralysis spontaneous atelectasis is to be expected even with healthy lungs (Finley et al., 1960; Bynum et al., 1976; Strandberg, 1985). The reason for atelectasis to occur is a reduced FRC during mechanical ventilation (Hedenstierna et al., 1976) with a closing capacity that exceeds FRC in the supine position (Rehder et al., 1977; Hedenstierna et al., 1981). If airway closure occurs, the closed spaces are essentially atelectatic and the resulting reduced pulmonary compliance can be reversed immediately by forced inflation of the lung (Mead and Collier, 1959). DEF by means of prolonged positive pressure during expiration may inhibit airway closure (Rodarte et al., 1975), as was demonstrated, however not significantly, by Hedenstierna et al. (1976). PEEP will also prevent airway closure (Craig and McCarthy, 1972), so this mechanism does not explain the differences between DEF and PEEP. The small effect of PEEP on P_aO_2 in this study can probably be ascribed to the recruitment of atelectatic alveoli which produced a right to left shunt, for ventilation, as the main effect of reducing a frank shunt is seen on P_aO_2 and not on P_aCO_2 (Zwart, 1983). The increase of FRC induced by PEEP (McIntyre et al., 1969; Powers et al., 1973) may be the reason for the slight decrease of P_aCO_2 during PEEP in this study. Also, P_aO_2 may increase and P_aCO_2 may decrease due to an increase in ventilation and improvement of ventilation to perfusion ratio in the dependent regions seen with levels of PEEP to 5 cm H_2O (Hammon et al., 1976).

These beneficial effects of DEF on CO_2 elimination and V_D/V_T are grossly similar to the studies with a long inspiratory hold compared to IPPV (Frumin et al., 1959; Bergman, 1963; Knelson et al., 1970; Nye, 1970) and in accordance with suggestions that also an inspiratory hold improves ventilatory homogeneity (Kjellmer et al., 1959). However, whether DEF or a long inspiratory hold is more effective in CO_2 elimination and O_2 uptake remains a subject for further investigation.

Evidence on mean airway pressure being the main determinant of blood gas exchange has been reported (Bergman, 1963; Gallagher and Banner, 1980; Berman et al., 1981; Pesenti et al., 1985) but may be rejected by this study. Different expiratory wave forms appear to be of great importance in blood gas exchange.

In the series with simulated bronchoconstriction by administration of histamine and acetylcholine the beneficial effects of DEF especially compared to PEEP on CO_2 elimination and O_2 uptake are even more marked. Alveolar emptying could be a major factor in the improvement of the distribution of ventilation. Prolonging actual expiration will allow more

complete emptying of respiratory units with large time constants for volume changes, resulting in more air movement from and into these alveoli producing a more even distribution of ventilation and an improved matching of ventilation to perfusion by this type of ventilation.
PEEP mainly improved O_2 uptake, which may be due to the dissolvement of atelectasis caused by formation of pulmonary edema during histamine and acetylcholine infusion. PEEP again had hardly beneficial effects on V_D/V_T, if any, and therefore on P_aCO_2.
In oleic acid lung injury, both DEF and PEEP reduced P_aCO_2 and V_D/V_T to non significantly different levels, but PEEP produced a greater increase in P_aO_2. The cause for this is probably the great increase in FRC by the recruitment and splinting of previously collapsed alveoli produced by this pattern of ventilation especially in this form of pulmonary disease.
These results are in accordance with the experimental work of Perez-Chada et al. (1983) comparing an inspiratory hold to PEEP with respect to the same rise in mean airway pressure in oleic acid induced pulmonary injury in goats. This also suggests that the more beneficial effects of either DEF or an inspiratory hold remain to be investigated.

Partial pressure of CO_2 in the expiratory air (P_ECO_2)

During DEF the partial pressure of CO_2 in the end expiratory air ($P_ECO_{2,e}$) was always higher than this value during the other modes of ventilation studied in health and simulated disease (Fig. IV-2, IV-3, IV-4 and IV-5). Also, during DEF $P_ECO_{2,e}$ was higher than the partial pressure of systemic arterial CO_2 (P_aCO_2) but lower than the values of the partial pressure of CO_2 in the mixed venous blood ($P_{\bar{v}}CO_2$, Table A-12, A-13, A-14, A-24, A-25, A-26, A-30 and A-31). A negative arterial to alveolar CO_2 gradient ((a-A) PCO_2) has been described during rebreathing studies in dogs (Jennings and Chen, 1975) and in man with pulmonary disease (Field et al., 1971), and even a negative mixed venous to alveolar carbon dioxide pressure gradient was found (Gurtner et al., 1969; Guyatt et al., 1973). Possible explanations for this phenomenon include a charged membrane hypothesis (Gurtner et al., 1969) and a delayed equilibration hypothesis (Hill et al., 1973) but these were disputed (Forster, 1977) and rejected in a critical review, which concluded that PCO_2 equality is attained between gas and blood when CO_2 is at equilibrium (Scheid and Piiper, 1980).
Nevertheless, in exercise a negative arterial to end-tidal CO_2 gradient ((a-ET) PCO_2) was calculated (Zwart et al., 1983) and seen to be inversely

related to the frequency of breathing and directly related to tidal volume (Jones et al., 1979).

Another explanation might be valid. Fluctuations in alveolar CO_2 (P_ACO_2) occur, due to the respiratory cycle, as was examined theoretically by DuBois et al. (1952). Different patterns of airflow effect this modulation (Nye, 1970; Damokosh-Giordano et al., 1975). Alveolar PCO_2 increases during expiration, as CO_2 is being transferred from the blood into a decreasing lung volume. It even increases still during early inspiration (DuBois et al., 1952). Actual expiratory air flow during IPPV with or without PEEP in this study, ceased however after approximately 25-30% of the available expiratory time, and in the continuous recording of the fraction of CO_2 in the expired air a sloping plateau is seen. $P_ECO_{2,e}$ is reached relatively early and remains below P_aCO_2 (Zwart et al., 1983). During DEF, a longer span of the expiratory time is used for airflow to occur, meaning a higher $P_ECO_{2,e}$ will be seen as the time of measurement is further on the increasing slope of P_ACO_2 and may be well above the mean P_ACO_2 over the cycle. As the value of P_aCO_2 measured is a time-weighted mean, this may be the primary reason for the observed negative (a-ET) PCO_2 during DEF, i.e. $P_ECO_{2,e}$ is measured above mean P_ACO_2 and P_aCO_2 as the mean.
This may also be the explanation for the inversed relation between (a-ET)PCO_2 and frequency of breathing reported by Jones et al. (1979) as during a lower frequency more time is left for the expiration which can be performed slower, meaning during the slower expiration (seen in athletes after exercise) CO_2 is washed out more efficiently and P_aCO_2 is a mean value, whereas $P_ECO_{2,e}$ is probably measured above the mean.
By measuring a higher $P_ECO_{2,e}$ and a decreased P_aCO_2 during DEF whilst P_ECO_2 remains constant the reasons for a higher Bohr dead space than physiological dead space are explained, and it can be stated, that values found for the Bohr dead space depend on the rate of flow during expiration when measuring $P_ECO_{2,e}$, and may at least partly explain the classic dispute between Haldane and Krogh.

Conclusion

A controlled diminished expiratory flow during mechanical ventilation improves gas exchange, especially in obstructive lung disease in comparison to IPPV and PEEP (with the same mean airway pressure as DEF)

and without changing the inspiratory-expiratory time ratio due to a combination of:

- a larger gas volume in the lung for period of the total expiratory time and a better effective mixing of the inspired air with the alveolar air, leading to a better equilibration in the intra-acinar inhomogeneity due to the longer actual expiration;
- a better distribution of ventilation between alveolar units with short and long time constants due to a higher airway pressure during expiration;
- a more complete emptying of the alveoli especially those with a high resistance, and
- a prevention of alveolar collapse during expiration due to the sustained but slackening positive expiratory pressure.

However, in view of the possible side-effects (barotrauma during coughing or fighting the respirator, as has been described by Kumar et al., 1970) patients treated with a controlled diminished expiratory flow should be monitored carefully and at least be sedated, and rather paralysed, as when incomplete emptying of the lung during expiration happens, the patient can be virtually "blown up".

Further, the partial pressure of end-expiratory CO_2 depends on the mode of expiration, and may lead to higher values than the arterial values, which correspond with the average values of alveolar PCO_2.

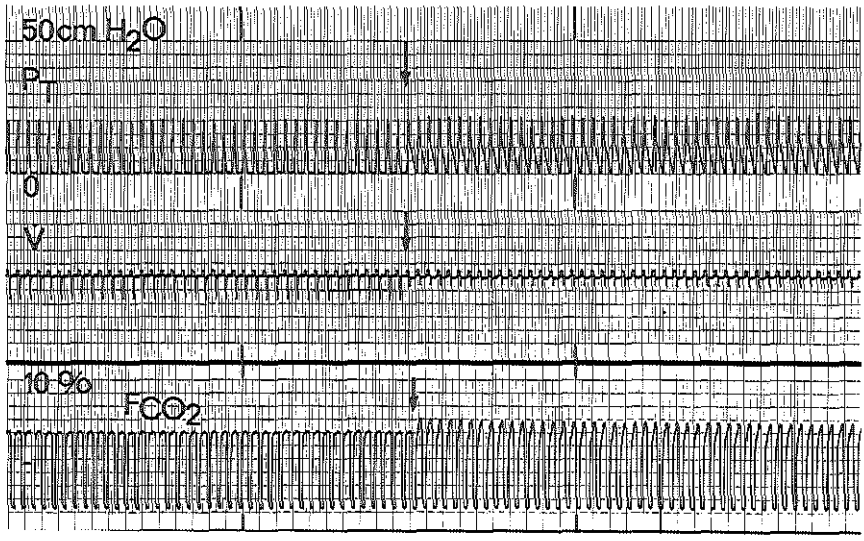

Fig. VI-1:

Slow tracing of tracheal pressure (P_T), airflow ($\dot{V}$) and the fraction of carbon dioxide in the ventilatory air (FCO_2) at IPPV and after the change to IPPV with a maximally retarded expiration (DEF 100%) (arrow). Note the higher FCO_2 at the end of the expirium, which gradually becomes a little less during stabilization.

CHAPTER VI

CO_2 EXCHANGE DEPENDENT ON THE DURATION OF SPONTANEOUS EXPIRATION DURING ARTIFICIAL VENTILATION

Introduction

During spontaneous breathing alveolar CO_2-concentration fluctuates with each respiratory cycle according to a typical pattern (DuBois et al., 1952; Rahn, 1954 and Otis, 1964). Different patterns of airflow effect this pattern of fluctuation (Nye, 1970) and may also show differences in the transferred amount of CO_2 during the respiratory cycle (Nye, 1970; Damokosh-Giordano et al., 1975).

Mechanical ventilation with a diminished expiratory flow (DEF, resulting in a lengthening of the duration of exhalation) and without changing tidal volume, inspiratory flow wave form or inspiratory hold, resulted compared to intermittent positive pressure ventilation in a new steady state, characterized by an increased partial pressure of systemic arterial oxygen (P_aO_2) and a decreased partial pressure of systemic arterial carbon dioxide (P_aCO_2, Fig. IV-2), suggesting very strongly an improvement of gas exchange using a retard during expiration.

During the experiments immediately after the change from IPPV to DEF a rise of end tidal PCO_2 in the expiratory air ($P_ECO_{2,e}$) was seen, which slightly diminished but remained at a higher level than during IPPV (Fig. VI-1). After a gradual stabilization from the sudden changes by DEF the PCO_2 in the mixed expiratory air ($P_{\bar{E}}CO_2$) was similar to the value during IPPV (unpublished data). This implies that in both steady states CO_2 output was also similar but at a lower P_aCO_2 when DEF was used. Thus, during the initial stabilization period after changing the ventilatory mode from IPPV to DEF more CO_2 was transferred from the blood to the pulmonary air, indicating a more effective ventilation (Chapter IV). This leaded to the hypothesis, that the output of CO_2 will be positively dependent on the duration of expiration at constant P_aCO_2 and tidal volume. In order to test this hypothesis, the relationship between the exchange of CO_2 and the duration of expiration was studied in single breath analyses, where retarded expirations of various degrees were inserted at intervals of about two minutes in steady state ventilation.

Five Yorkshire piglets with a mean weight of 7.4 kg (± 9 kg, SD) were used under pentobarbital sodium anesthesia (7.5 $mg \cdot kg^{-1} \cdot h^{-1}$, i.v. infusion). Surgical procedures, experimental conditions and data-acquisition were the same as described in Chapter II except for the CO_2 measurement in the ventilatory air. This signal was directly obtained from the tracheal canula using a Hewlett Packard capnometer, model 47210A. A delay time of 160 msec with respect to the airflow signal was compensated for in order to plot the partial pressure of expiratory carbon dioxide (P_ECO_2) versus expiratory volume (V_E).

CPPV was used at a slight PEEP of 2.5 cm H_2O in steady state conditions. Ventilation was performed with a computer controlled piston ventilator. The ratio of insufflation, inspiratory pause and expiration was 35:5:60. At intervals of two minutes a ventilatory cycle with a diminished expiratory flow (DEF-procedure) was inserted. During these DEF-procedures expiration was lengthened between 30% and 100% of the available expiratory time ($t_{E,max}$, which is the 100% value). Intervals of 2 minutes appeared to be sufficient for maintainance of steady state conditions.

During ventilatory rates of about 10 and 6 per minute a double series of observations was performed with 8 different t_E values between 30% and 100% of $t_{E,max}$, with one exception (exp.501), in which the observations were done only once. The order of observations was randomly chosen, with one exception (exp.502), where the expiratory time was systematically lengthened from 30% to 100% of $t_{E,max}$ and back again. The observations with the same expiratory time were averaged. The expiratory rates were not exactly 6 and 10 per minute in all experiments, due to technical problems in the timing of the control unit of the ventilator. This was of minor importance for the data analyses.

During each DEF-procedure alveolar air went into the piston pump which controlled expiratory flow and t_E. This implied a rebreathing of expiratory air during the next ventilation. During each DEF-procedure expiratory volume (V_E) was made equal to insufflation volume, and expiratory flow ($\dot{V}_E$) was constant. Therefore, $\dot{V}_E$ decreased proportionally with an increase of t_E in percentage of $t_{E,max}$.

Arterial bloodgas analyses were done before and after each series of observations. The partial pressure of arterial carbon dioxide (P_aCO_2) of both measurements was averaged, when used for comparison with the partial pressure of end-expiratory carbon dioxide ($P_ECO_{2,e}$) and for calculation of physiological dead space ($V_{D,phys}$). Recordings were made of ECG, and arterial, pulmonary artery and central venous pressures to check

hemodynamic stability during the series of observations. Furthermore, the ventilatory variables airflow ($\dot{V}$), in- and expiratory volume (V), tracheal pressure (P_T) and PCO_2 were monitored.

Data analysis

$\dot{V}_E$ and P_ECO_2 were the main signals (Fig. VI-2) used for off-line data analysis by means of a computer PDP 11/03, after storage on an electromagnetic tape (Racal termionic store 14). Sampling rate of analog data by the computer was 50 Hz.
Expiratory volume (V_E) at each moment of t_E was calculated from $\dot{V}_E$ by integration and expressed as a percentage of total V_E. P_ECO_2 was plotted against this percentage of V_E.
P_ECO_2 during a DEF-procedure was averaged over the total V_E ($P_{\bar{E}}CO_2$). CO_2-output was calculated according to

$$V_{CO_2} = 273 \; P_{\bar{E}}CO_2 \; V_E \; / \; 760 \; T_{pig}$$

where T_{pig} is the core temperature of the pig. This equation was simplified to

$$V_{CO_2} = 0.1155 \; P_{\bar{E}}CO_2 \; V_E$$

because T_{pig} was found as 38°C with a maximal interindividual range of 1°C resulting in a maximal error of 0.6% in V_{CO_2}. V_{CO_2} and $P_ECO_{2,e}$ were studied as functions of t_E in percentage of $t_{E,max}$.
Physiological dead space was derived during each DEF-procedure.
Physiological dead space ($V_{D,phys}$) was calculated according to

$$V_{D,phys} = V_E \; (P_aCO_2 - P_{\bar{E}}CO_2) \; / \; P_aCO_2$$

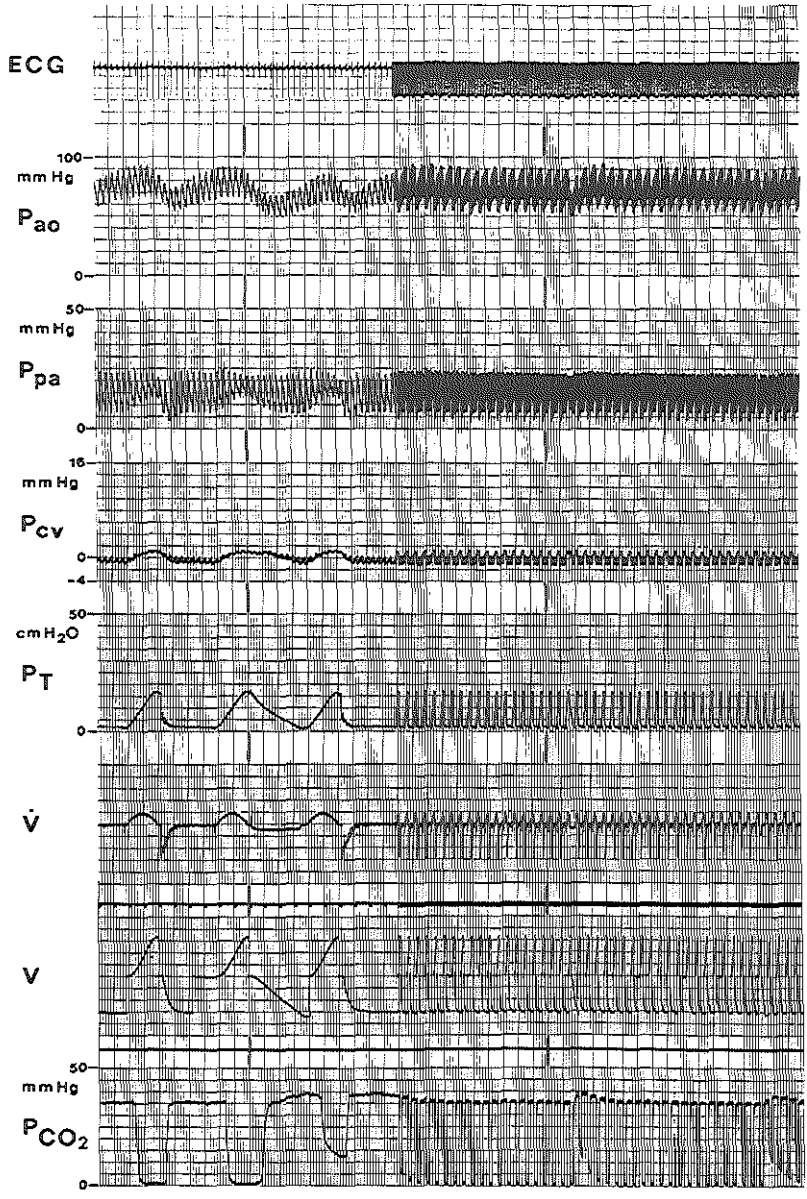
ECG
100
mm Hg
P_{ao}
0
50
mm Hg
P_{pa}
0
16
mm Hg
P_{cv}
0
-4
50
$cm H_2O$
P_T
0
$\dot{V}$
V
50
mm Hg
P_{CO_2}
0

Fig. VI-2:

A recording of three DEF-procedures, obtained from experiment 502, series 1. P_{ao} = aortic pressure measured against ambient air; P_{pa} = pulmonary artery pressure; P_{cv} = central venous pressure; P_T = tracheal pressure; $\dot{V}$ = air flow in arbitrary units, positive deflection indicates insufflation, negative deflection expiration; V = ventilatory volume, obtained by integration of $\dot{V}$. Full negative deflection during these DEF-procedures represents a volume of 155 ml; PCO_2 = partial pressure in ventilatory air of carbon dioxide.

Results

In Fig. VI-2 a recording is shown of three DEF-procedures. The DEF-procedure had no effect on the hemodynamic steady state condition. In the lower traces P_T, $\dot{V}$ and V indicate the constant flow during the DEF-procedures. Only at the beginning and the end of the expiration the flow was temporarily smaller than the applied value of constant flow. During the DEF-procedure P_ECO_2 changed in three phases: first a phase I of zero pressure during expiration of dead space air, followed by a fast rise as phase II and third a plateau of gradual increase as phase III reaching a maximum ($P_ECO_{2,e}$) at the end of expiration. Because the expiratory air of each DEF-procedure was returned into the ventilator the succeeding normal ventilation was characterized by a rebreathing of this expiratory air, causing temporarily an increased value of end tidal PCO_2. After about 5 ventilations baseline values of end tidal PCO_2 were regained. Therefore, 20 normal ventilations in between the DEF-procedures were assumed to be sufficient.

P_ECO_2 was plotted against V_E for all DEF-procedures in order to compare the changes in the relationship between P_ECO_2 and expired volume for different expiratory flow values as a parameter of this relationship. Examples are given in Fig. VI-3. Again a three phasic character of the relationship can be observed, with a maximal-value of P_ECO_2 at total expired volume ($P_ECO_{2,e}$), which coincided with the end of expiration as reported for the CO_2 curves in Fig. VI-2. In general a slight to moderate shift of the steep rise (phase II) to the left was seen, when expiratory time was increased, i.e. when expiratory flow was decreased. In the three plottings of Fig. VI-3 the gradual increase of P_ECO_2 is higher when expiratory flow is smaller and thus t_E longer. This was seen in all experiments.

In order to investigate the parameter function of expiratory time, i.e.

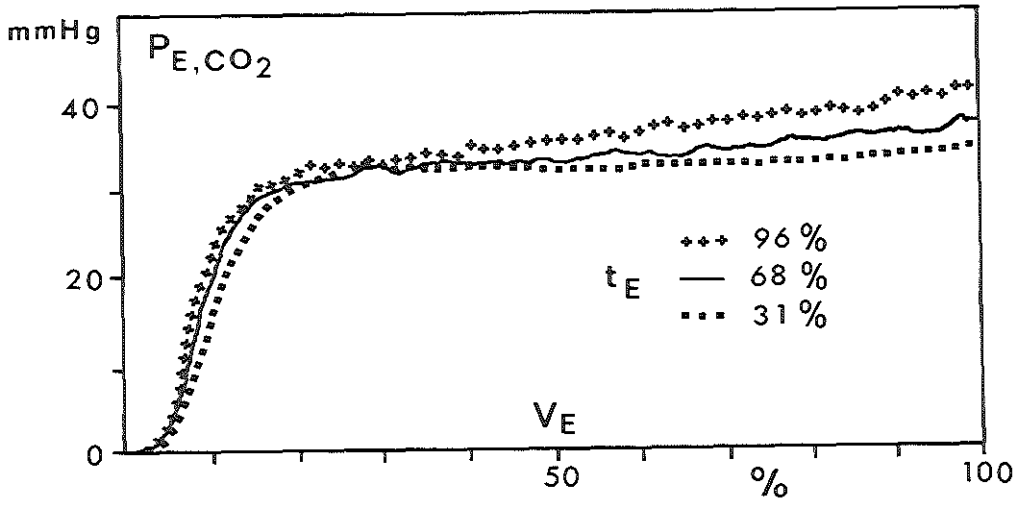

Fig. VI-3:

Expiratory PCO_2 as a function of expired volume (100% = 200ml) at three different DEF values (t_E). Data were obtained from experiment 505, second series. Phase I, II and III are mentioned in the text.

expiratory flow in a reciprocal value, $P_ECO_{2,e}$ was plotted against t_E expressed as a percentage of total available expiration time (Fig. VI-4A). The plottings yield a linear relationship, which was also found in all other experiments (Table VI-1A). Correlation coefficients were high, except for the first series of exp. 503 due to a larger variation of the data.

The area below the CO_2 curve of Fig. VI-3 reflects CO_2 output (V_{CO_2}) during a DEF-procedure. At lower expiratory flow this area was increased. In Fig. VI-4B an example is given of the change in V_{CO_2} as a function of t_E, yielding a linear relationship as the best mathematical description. All regression equations are given in Table VI-1B. Again the results of exp. 503, but now the second series, produced a relatively lower correlation coefficient than the others.

Both regression equations are characterized by a positive slope in all series of observations, implying an increase in $P_ECO_{2,e}$ and V_{CO_2} when expiratory time is lengthened (or expiratory flow is decreased). $P_ECO_{2,e}$ at the end of total available time, i.e. $t_{E,max}$, was calculated from the regression equations and indicated as $P_ECO_{2,max}$. Its value was expressed as a percentage of arterial PCO_2. All values were slightly smaller than 100%, and within all but one experiment not different when using largely

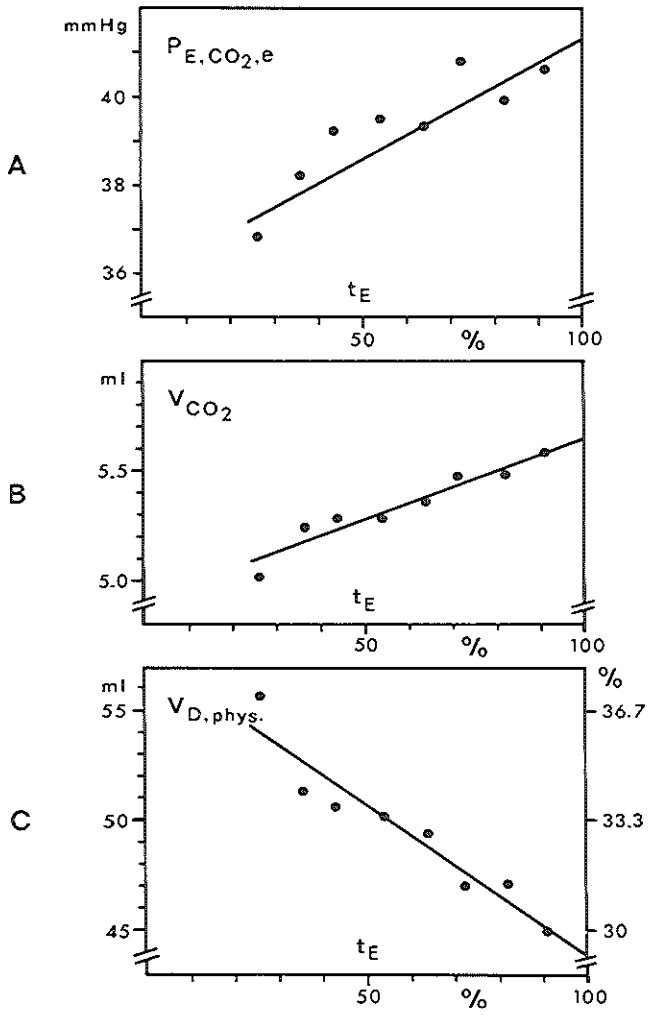

Fig. VI-4:

End tidal PCO_2 (A), CO_2-output during a DEF-procedure (B) and physiological dead space (C) plotted against expiratory time (t_E) in percentage of total available expiratory time. These relationships represent the results of exp. 501, series 1, which was the first series of all observations in order to avoid a selection of the best results. Regression equations and correlation coefficients are given in Tables VI-1A and VI-1B.

different values of $t_{E,max}$. The exception is experiment 503, where r values are relatively low.

TABLE IV-1A

Exp.	series	Vent.Cycle t_c sec	Vent.Cycle V_E ml	$P_{E,CO2,e} = a + bt_E$ a mmHg	b mmHg.%$^{-1}$	r	$P_{E,CO2,max}$ / $P_{a,CO2}$ %
501	1	6.16	150	36.4	.050	.89	90
	2	8.15	199	33.7	.064	.91	90
502	1	5.0	115	35.9	.032	.96	97
	2	8.32	155	33.9	.072	.98	99
503	1	6.0	130	31.3	.047	.84	92
	2	10.0	195	31.5	.049	.90	85
504	1	6.17	115	32.8	.056	.98	99
	2	10.0	200	33.1	.075	.99	98
505	1	6.0	130	30.0	.075	.97	96
	2	10.0	200	31.2	.095	.99	95

$P_{E,CO2,e}$: end expiratory CO_2-pressure, when expiratory flow becomes zero;

t_E : time of expiratory flow as a percentage of total available expiratory time;

$P_{E,CO2,max}$: $P_{E,CO2,e}$ at t_E = 100%;

$P_{a,CO2}$: arterial CO_2-pressure;

t_c : cycle time of ventilation;

V_E : expiratory volume;

a : virtual value of $P_{E,CO2,e}$, when tidal volume should be expired in zero time;

b : increase in $P_{E,CO2,e}$, when diminished expiratory flow lasts a larger part of available expiratory time;

r : correlation coefficient of regression equations.

In Fig. VI-4C physiological dead space is presented as a function of t_E in percentage of $t_{E,max}$, derived from the same series of observations. Physiological dead space decreased linearly, as t_E increased. This phenomenon was observed in all series (Table VI-1B). Correlation coefficients of these linear relationships are high, except for the second series of experiment 503. In all animals physiological dead space

TABLE IV-1B

Exp.	series	$V_{CO2} = c + d.t_E$ c ml	d $ml.\%^{-1}$	r	$V_{D,phys.} = e + f.t_E$ e ml	f $ml.\%^{-1}$	r
501	1	4.91	.0074	.95	57.7	-.138	-.93
	2	6.46	.0097	.93	73.3	-.187	-.93
502	1	3.49	.0043	.95	41.0	-.097	-.96
	2	5.02	.0073	.96	49.6	-.152	-.96
503	1	3.63	.0060	.95	50.4	-.130	-.94
	2	6.14	.0040	.59	72.9	-.087	-.65
504	1	3.61	.0052	.99	34.9	-.117	-.99
	2	6.86	.0091	.94	57.5	-.192	-.94
505	1	3.75	.0058	.96	48.3	-.133	-.95
	2	6.31	.0114	.98	72.9	-.231	-.98

V_{CO2} : CO_2-output during a diminished expiratory flow;
c : virtual value of CO_2-production, when tidal volume should be expired in zero time;
d : increase in CO_2-production, when diminished expiratory flow lasts a larger part of available expiratory time;
$V_{D,phys.}$: physiological dead space;
e : virtual value of $V_{D,phys.}$ for $t_E = 0$;
f : decrease in $V_{D,phys.}$, when t_E increases as percentage of available expiratory time.

expressed in ml increased as V_E increased. This increase is indicated by the value e, which is the extrapolated value of the regression equation for $t_E = 0$. However, when this value is expressed as a fraction of V_E hardly any differences will be observed between the two series within each experiment.

Because the single breath DEF-procedures during a baseline mechanical ventilation at constant rate and tidal volume did not change hemodynamic conditions and the values of the partial pressure of arterial carbon dioxide (P_aCO_2) before and after a series of observations showed differences within $\pm$ 2 mmHg, similar baseline conditions for all DEF-procedures within a series were assumed. Rebreathing of expiratory air after the DEF-procedure only temporarily changed the partial pressure of end tidal carbon dioxide ($P_ECO_{2,e}$) during the following 5 ventilatory cycles. $P_ECO_{2,e}$ recovered to baseline values far before the next DEF-procedure. When expiratory time was lenghtened $P_ECO_{2,e}$ increased (Fig. VI-2), which was obviously demonstrated in Fig. VI-3. The increase in the partial pressure of expiratory carbon dioxide (P_ECO_2) plotted as a function of expiratory volume (Fig. VI-3), is characterized by the same three phases as described by Bouhuys (1964), based on the work of Aitken and Clark-Kennedy (1928). These curves show a steeper rise in phase III when expiratory time (t_E) is increased for the same expiratory volume (V_E), and therefore when expiratory flow is decreased. It is obvious from these results that the area below the CO_2 curve increases with t_E. This area is the product of PCO_2 and expiratory volume, and therefore a measure of CO_2 output.

The increase of $P_ECO_{2,e}$ was linearly related to expiratory time (Fig. VI-4A and Table VI-1A), yielding a value at $t_{E,max}$, which was almost equal to P_aCO_2. Surprisingly, the maximal end tidal PCO_2 (at a t_E of 100%) was about the same for the two different ventilatory rates and thus for largely different $t_{E,max}$ values in seconds. A definite explanation for these similar $P_ECO_{2,max}$ values in spite of different expiratory times was not found. Probably, the larger tidal volume, and thus lung volume, after insufflation needs more time to be loaded with CO_2. Some way or the other a balance exists between tidal volume and the increase of $P_ECO_{2,e}$ leading to the same $P_ECO_{2,max}$ at full expiratory time for different expiratory times, which were concomitantly changed with tidal volume.

A mean value of 0.94 ($\pm$ 0.045, SD) for $P_ECO_{2,max}/P_aCO_2$ implies an approximation of P_aCO_2 by $P_ECO_{2,e}$, when full expiratory time is used. This result is in agreement with those of Tulou and Walsh (1970), Hatle and Rosketh (1974) and Luft et al. (1979).

The increase of P_ECO_2 with time implies a continuous loading of alveolar volume with CO_2 during expiration.

CO_2 output (V_{CO_2}) during the DEF-procedures increased linearly when expiratory time was lengthened (Fig. VI-4B and Table VI-1B). Because all

DEF-procedures were done during steady state conditions the results verify the hypothesis that the output of CO_2 is positively dependent on the duration of expiration at constant P_aCO_2.
When alveolar volume is loaded more with CO_2 at longer expiration time, mean expiratory PCO_2 will increase correspondingly. At constant P_aCO_2 this will decrease the quotient $(P_aCO_2-P_{\bar{E}}CO_2)$ / P_aCO_2, and therefore physiological dead space. This result is shown in Table VI-1B. These results are different from those of Worth et al. (1977), who found no difference of alveolar ventilation with different speeds of expiration.
When physiological dead space decreases, ventilation at constant tidal volume becomes more effective. Thus, the results of the single breath DEF procedures confirm a former conclusion in chapter V, based on steady state ventilation with DEF, implying that DEF improves gas exchange by a more effective ventilation.

CHAPTER VII

SUMMARY

Chapter I

Pursed lips breathing seems beneficial for patients with chronic obstructive pulmonary disease and is tought to them during breathing exercises, if they do not already perform their expiratory effort through pursed lips. The beneficial effects described in the literature are reviewed. Hypotheses about the mechanism of improvement by pursed lips breathing include a decreased airway collapse in the lung (Fig. I-1) resulting in less air trapping and in better emptying of the more compliant lung regions, an improvement of ventilation to perfusion relationships, an enlarged tidal volume and a decreased respiratory rate.

The objectives of this study were to investigate in pigs whether a diminished expiratory flow (DEF) during mechanical ventilation, resembling pursed lips breathing, does improve gas exchange, especially in pulmonary disease and whether this effect is different from intermittent positive pressure ventilation (IPPV) with a positive end-expiratory pressure (PEEP). Further, hemodynamic effects of DEF were explored and the effects of DEF on the measurement of cardiac output by the thermodilution technique were investigated.

Chapter II

Material, experimental conditions, surgical procedures and data acquisition and analysis are described. The thermodilution technique and the direct Fick method for oxygen for the determination of cardiac output are detailed and additional measurements are specified. The respiratory and hemodynamic effects of three different modes of artificial ventilation were examined and compared to each other in healthy pigs: intermittent positive pressure ventilation (IPPV), mechanical ventilation with a

diminished expiratory flow (DEF) and ventilation with a positive end-expiratory pressure (PEEP). IPPV served as a control series. Two degrees of DEF were studied, and DEF was chosen in such a manner, that the tracheal pressure returned to zero at a point in the expiratory phase when 66% (DEF 66%) or 100% (DEF 100%) of the available expiratory time had passed (Fig. II-5). Due to the slackening fall of tracheal pressure a higher mean tracheal pressure ($\bar{P}_T$) was present during DEF, and comparable PEEP values were chosen to produce the same rise in $\bar{P}_T$ as DEF 66% (PEEP ~ DEF 66%) and as DEF 100% (PEEP ~ DEF 100%) in the respective protocols. Thus, the two experimental protocols were:

I, DEF 66% series

1: $IPPV_I$; 2: DEF 66%; 3: PEEP ~ DEF 66%; 4: $IPPV_{II}$

II, DEF 100% series

1: $IPPV_I$; 2: DEF 100%; 3: PEEP ~ DEF 100%; 4: $IPPV_{II}$.

Finally methods for experimental pathology (bronchospasm and pulmonary edema) are delineated. DEF and PEEP studies were repeated under these pathological circumstances.

Chapter III

Under circumstances of mechanical ventilation the thermodilution technique for estimation of mean cardiac output proved to be reliable if the mean of 12 estimates, equally spread over the ventilatory cycle was taken. Compared with the direct Fick method for oxygen, a good correlation between the two methods was seen (Fig. III-1).

However, mechanical ventilation modulates cardiac output within the ventilatory cycle, and the maximal disparity of values in an individual respiratory cycle was from 58% to 135% of the mean, being from 72% to 125% in the average of all series. When plotting the values against the phase in the ventilatory cycle a systemic pattern of modulation appeared, related to airway pressure (Fig. III-2). During IPPV and PEEP an expiratory plateau was present, which was absent with DEF. Furthermore, the curve of cardiac output plotted against ventilatory time seemed to shift to the right.

An averaging stratagem showed, that the averages of 3 to 4 estimations, equally spread over the ventilatory cycle, were approximately 1% ($\pm$ 4%, SD) different from the mean, as calculated by the mean of 12 estimations equally spread over the ventilatory cycle (Fig. III-3).

The following hemodynamic effects of DEF and comparable PEEP, when compared to IPPV, were obtained (Fig. IV-1):

- a decrease of cardiac output to the same extent during DEF and PEEP;
- a decrease of mean systemic arterial pressure during DEF, PEEP having no effect;
- a decrease of mean pressure in the pulmonary artery during DEF, PEEP having no influence, and
- an increase of right atrial pressure during DEF less marked than during PEEP.

The respiratory effects of DEF and PEEP, when compared to IPPV, were as follow (Fig. IV-2):

- a higher peak tracheal pressure during DEF and even higher during PEEP;
- a higher partial pressure of systemic arterial oxygen, during DEF more marked than during comparable PEEP;
- a decrease of the partial pressures of systemic arterial and mixed venous carbon dioxide during DEF, whereas comparable PEEP hardly revealed any influence;
- an increase of the partial pressure of carbon dioxide in the end-expiratory air during DEF, whereas PEEP had no effect, and
- a decrease of the physiological dead space during DEF, not seen during PEEP.

These respiratory effects were more marked during experimental pulmonary pathology induced by infusions of histamine (Fig. IV-3) and acetylcholine (Fig. IV-4) producing bronchospasm, but PEEP did have, although less prominent, some beneficial effects, probably due to pulmonary edema as seen with these infusions.

The beneficial effects of DEF and PEEP during pulmonary edema (Fig. IV-5) induced by alloxan and oleic acid were the same as far as carbon dioxide and physiological dead space were concerned, but PEEP was superior to DEF with regard to oxygenation, probably due to the great increase in functional residual capacity related to this pattern of ventilation.

In conclusion, an improvement of gas exchange by DEF was seen compared to IPPV and IPPV with a PEEP, when a DEF was applied.

Chapter V

The experimental model (chapter II) and actions of histamine, acetylcholine, alloxan and oleic acid (chapter IV) are discussed, showing good correlation with the literature.
The results shown in chapter IV are discussed and interpreted with the literature.
Decrease of cardiac output was thought to be caused by an increase of mean airway pressure producing an increase of mean intrathoracic pressure, and therefore a decrease of venous return to the heart.
The beneficial effects of DEF on gasexchange were thought to be related to several mechanisms:

- a longer presence in the lung of volume of inspired gas and the higer airway pressure produce a greater amount of carbon dioxide expired;
- a better equilibration of the intra-acinar inhomogeneity, and
- a more complete emptying of alveoli resulting in a more even distribution of ventilation and improved ventilation/perfusion relationships.

During DEF partial pressure of carbon dioxide in the end-expiratory air was found to be higher than the arterial value. This was thought to be due to the fact that the arterial PCO_2 was a weighted mean, whilst the value in the end-expiratory air nearly represents the highest alveolar value, i.e. well above the mean.

Chapter VI

During series of single breath procedures of DEF between 30% and 100% at constant P_aCO_2 and $P_{\bar{v}}CO_2$ carbon dioxide output and physiological dead space were found to be linearly related to the expiratory time in % of the maximal available time. CO_2 output during a DEF procedure increased (Fig. VI-4B) and physiological dead space decreased (Fig. VI-4C), when expiratory time was increased. These results verified the hypotheses on the beneficial effects of DEF as stated in chapter V.

CHAPTER VIII

SAMENVATTING

Hoofdstuk I

Langzaam uitademen door samengeperste lippen lijkt nuttig te zijn voor patienten met een chronisch aspecifieke respiratoire aandoening. Deze techniek wordt deze groep patienten aangeleerd tijdens ademhalingsoefeningen, als zij dit niet uit zich zelf al doen. In een literatuur overzicht worden de gunstige invloeden van deze wijze van uitademen besproken. De volgende mechanismen worden verondersteld bij te dragen aan de subjectieve en de objectieve verbetering tijdens het langzaam uitademen door samengeperste lippen:

- verminderde collaps van de luchtwegen, wat resulteert in het minder vasthouden van lucht voor de gecollabeerde luchtwegen en zodoende een verbeterde ontlediging van de longregionen met een hoge compliantie;
- een verbeterde ventilatie-perfusie verhouding;
- een verhoogd ademvolume per teug, en
- een langzame ademfrequentie.

Het doel van deze studie was, met biggen als proefdieren, te onderzoeken, of een vertraagd expirium tijdens beademing (DEF), gelijkend op het uitademen door samengeperste lippen, de gasuitwisseling in de longen verbetert, vooral in de aanwezigheid van longafwijkingen. Tevens werd nagegaan of de effecten van deze vorm van beademing op de gasuitwisseling verschilden van die, veroorzaakt door beademing met een positieve eind-expiratoire druk (PEEP). Ook werd de invloed van DEF of de verschillende bloeddrukken en op het hart-minuutvolume, bepaald met de thermodilutie methode, onderzocht en vergeleken met PEEP.

Hoofdstuk II

Het materiaal, de operatieve handelingen en de proefopstelling worden beschreven. De wijze van het verkrijgen van de data en de analyse ervan

worden uiteengezet. Uitgebreid wordt ingegaan op de bepaling van het hart-minuutvolume door middel van de thermodilutie en de Fick methode, en de overige metingen en berekeningen worden besproken.
De respiratoire en hemodynamische effecten van drie verschillende vormen van beademing werden onderzocht bij gezonde biggen en onderling vergeleken: intermitterende positieve druk beademing (IPPV), beademing met een vertraagd expirium (DEF) en beademing met een positieve eind-expiratoire druk (PEEP). IPPV diende als uitgangspunt. Twee stappen van DEF werden opgelegd, namelijk zo, dat de druk in de trachea kwam op nul, wanneer 66% (DEF 66%) respectievelijk 100% (DEF 100%) van de totaal beschikbare tijd voor uitademing voorbij waren (Fig. II-5). Door het langzame drukverval in de trachea tijdens DEF wordt de gemiddelde intra-tracheale druk (P_T) tijdens een beademingscyclus hoger en een vergelijkbare PEEP werd dusdanig gekozen, dat een zelfde verhoging van $\bar{P}_T$ ontstond tijdens PEEP als tijdens DEF 66% (PEEP $\sim$ DEF 66%) en DEF 100% (PEEP $\sim$ DEF 100%) binnen de experimenten. Aldus ontstonden twee series:
I)1: $IPPV_I$; 2: DEF 66%; 3: PEEP $\sim$ DEF 66%; 4: $IPPV_{II}$, en
II)1: $IPPV_I$; 2: DEF 100%; 3: PEEP $\sim$ DEF 100%; 4: $IPPV_{II}$.
Tenslotte worden methoden vermeld om een bronchospasme (met histamine en acetylcholine) en longoedeem (met alloxan en oliezuur) te veroorzaken. DEF en PEEP werden ook onder deze pathologische omstandigheden bestudeerd.

Hoofdstuk III

Tijdens beademing bleek de bepaling van het hart-minuutvolume met de thermodilutie methode betrouwbaar te zijn op grond van de vergelijking met de Fick methode, als het gemiddelde berekend werd van 12 bepalingen, gelijkelijk verdeeld over de beademingscyclus. Een goede correlatie tussen deze twee methodes werd gevonden (Fig. III-1).
Binnen één beademingscyclus varieert het hart-minuutvolume echter, en de gevonden waarden met de thermodilutie methode in één beademingscyclus lagen tussen 58% en 135% ten opzichte van het gemiddelde. Als de waarden van het hart-minuutvolume uitgezet worden tegen de fase in de beademingscyclus werd een curve verkregen, duidelijk gerelateerd aan de druk in de trachea (Fig. III-2). Tijdens IPPV en PEEP is er een eind-expiratoir plateau, in tegenstelling tot DEF. Verder lijkt deze curve tijdens DEF naar rechts te verschuiven.
Door 3 of 4 bepalingen van het hart-minuutvolume, gelijkelijk verdeeld over de beademingscyclus, te middelen, bleek de gevonden waarde $\pm$ 1% ($\pm$

4%, SD) van het gemiddelde van de bovengenoemde 12 bepalingen, af te liggen (Fig. III-3).

Hoofdstuk IV

De volgende effecten van DEF en van de daarmee vergelijkbare PEEP op de circulatie werden gevonden (Fig. IV-1):
- een daling van het hart-minuutvolume, gelijk voor DEF en PEEP (Fig. IV-4);
- een daling van de gemiddelde druk in de aorta en in de arteria pulmonalis tijdens DEF en niet tijdens PEEP, en
- een verhoging van de centraal veneuze druk tijdens DEF en PEEP.

De respiratoire effecten van DEF en PEEP waren, vergeleken met IPPV, als volgt (Fig. IV-2):
- een hogere piek trachea druk met DEF en nog hoger met PEEP;
- een hogere arteriele zuurstof spanning, die met DEF hoger is dan met de vergelijkbare PEEP;
- een lagere arteriele en gemengd veneuze koolzuur spanning met DEF, terwijl PEEP nauwelijks een beïnvloeding liet zien;
- een hogere koolzuurspanning in de eind-expiratoire lucht met DEF, terwijl PEEP geen effect hierop sorteerde, en
- een vermindering van de physiologische dode ruimte met DEF en niet met PEEP.

De effecten van DEF op de gaswisseling en physiologisch dode ruimte waren versterkt aanwezig bij experimentele longafwijkingen, met name bronchospasme, teweeg gebracht door infusies met histamine (Fig. IV-3) en acetylcholine (Fig. IV-4). PEEP had eveneens, maar in mindere mate, een gunstige invloed op de gaswisseling, waarschijnlijk door het longoedeem, dat door de infusies werd veroorzaakt.
Tijdens longoedeem veroorzaakt door injecties van oliezuur en alloxan, was PEEP superieur ten aanzien van de oxygenatie waarschijnlijk door de verhoging van de functionele residuaal capaciteit. Maar ook DEF liet een verbetering zien. PEEP en DEF hadden eenzelfde gunstige invloed op de uitwas van koolzuur en de verkleining van de physiologische dode ruimte tijdens deze vorm van longoedeem (Fig. IV-5).
Concluderend werd een verbetering van de gasuitwisseling gezien tijdens beademing met DEF onder normale en pathologische (bronchospasme) omstandigheden, vergeleken met IPPV en de PEEP, die dezelfde gemiddelde pulmonale drukverhoging veroorzaakte.

Hoofdstuk V

Het proefdiermodel, zoals omschreven in hoofdstuk II en de effecten van histamine, acetylcholine en alloxan gecombineerd met oliezuur (Hoofdstuk IV) werden besproken. Deze gegevens lieten een goede overeenkomst zien met die in de literatuur.
Vervolgens werden de effecten van DEF en PEEP besproken (Hoofdstuk IV) en vergeleken met de literatuur.
De daling van het hart-minuutvolume werd geweten aan een verhoging van de gemiddelde druk in de luchtwegen, die een verhoging van de gemiddelde intrathoracale druk en zodoende een vermindering van de terugstroom van bloed naar het hart veroorzaakte.
Geconcludeerd werd, dat verschillende mechanismen bijdroegen aan de gunstige invloed van DEF op de gasuitwisseling:

- een langer verblijf van een hoeveelheid ingeademende lucht en de hogere druk in de luchtwegen dragen zorg voor een grotere hoeveelheid koolzuur dat wordt uitgeademd;
- een verbeterde equilibratie van de intra-acinaire inhomogeniteit, en
- een vollediger ledigen van de alveoli, resulterend in een gelijkmatiger distributie van de ventilatie en in een verbeterde ventilatie/perfusie verhouding.

Tijdens DEF werd een hogere koolzuur spanning in de eind-expiratoire lucht dan in het arteriele bloed gevonden. Dit kan verklaard worden, doordat de waarde van het arteriele bloed een gemiddelde waarde is, terwijl de eind-expiratoire waarde bijna de hoogste waarde van de alveolaire PCO_2 representeert.

Hoofdstuk VI

In series DEF procedures, tussen 30% en 100% van de totaal beschikbare expiratie tijd gedurende één enkele beademingscyclus, bleken koolzuuruitwas en physiologisch dode ruimte recht evenredig te zijn met de duur van de uitademing, die werd uitgedrukt in procenten van de totaal beschikbare expiratietijd. Wanneer de uitademingstijd verlengd werd, ontstond er een verbeterde koolzuuruitwas (Fig. VI-4B) en een vermindering van de physiologisch dode ruimte (Fig. VI-4C). Deze resultaten steunden de hypothese over de begunstigende invloeden van DEF, zoals die zijn beschreven in Hoofdstuk V.

APPENDIX

Type of ventilation	Equation of regressionline	Correlation-coeffficient
IPPV	y = 0.40 + 0.85x	0.93
DEF 66%	y = 0.20 + 0.89x	0.87
PEEP ∿ DEF 66%	y = -0.17 + 0.96x	0.87
DEF 100%	y = -0.35 + 1.16x	0.93
PEEP ∿ DEF 100%	y = -0.28 + 1.11x	0.89

Table A-1 Correlation between cardiac output estimated by the thermo-dilution technique and the direct Fick method for oxygen respectively during the different ventilatory modes.

	sec.	IPPV	DEF 66%	PEEP ∿ DEF 66%	DEF 100%	PEEP ∿ DEF 100%
one point average	0.0	107.2 ± 6.3	110.1 ± 6.4	106.0 ± 5.8	109.8 ± 7.8	106.8 ± 5.8
	0.5	102.0 ± 8.0	104.9 ± 5.4	101.5 ± 6.6	108.6 ± 9.5	101.0 ± 9.5
	1.0	95.6 ± 9.6	99.0 ± 7.8	96.7 ± 7.3	102.9 ± 9.2	96.2 ± 8.0
	1.5	91.1 ± 9.1	93.2 ± 7.0	89.5 ± 7.0	96.2 ± 7.2	92.0 ± 8.3
	2.0	89.3 ± 7.4	91.3 ± 8.5	91.3 ± 4.9	91.7 ± 6.0	89.4 ± 7.3
	2.5	93.3 ± 8.2	92.5 ± 5.9	94.6 ± 6.8	89.2 ± 5.6	93.2 ± 7.3
	3.0	97.1 ± 8.5	95.8 ± 8.2	95.8 ± 7.0	91.9 ± 6.4	99.5 ± 8.1
	3.5	102.6 ± 8.9	98.6 ± 5.2	103.0 ± 4.0	95.9 ± 8.3	104.5 ± 9.7
	4.0	104.8 ± 8.5	102.7 ± 7.2	102.2 ± 7.9	100.0 ± 8.3	101.0 ± 9.4
	4.5	104.9 ± 10.0	102.2 ± 10.0	106.9 ± 8.2	104.3 ± 6.1	104.3 ± 7.9
	5.0	104.8 ± 8.0	106.2 ± 7.6	106.7 ± 7.4	101.9 ± 7.6	105.3 ± 7.4
	5.5	107.1 ± 7.9	103.6 ± 7.3	106.0 ± 5.1	107.7 ± 7.9	106.8 ± 11.8
two point average	0.0-3.0	102.2 ± 5.3	103.0 ± 5.2	100.9 ± 4.5	100.8 ± 5.0	103.2 ± 5.0
	0.5-3.5	102.3 ± 6.0	101.7 ± 3.8	102.3 ± 3.8	102.3 ± 6.3	102.8 ± 6.8
	1.0-4.0	100.2 ± 6.4	100.8 ± 5.3	99.4 ± 5.4	101.5 ± 6.2	98.6 ± 6.2
	1.5-4.5	98.1 ± 6.8	97.7 ± 6.1	98.2 ± 5.4	100.2 ± 4.7	98.2 ± 5.7
	2.0-5.0	97.1 ± 5.5	98.7 ± 5.7	99.0 ± 4.4	96.8 ± 4.9	97.4 ± 5.2
	2.5-5.5	100.2 ± 5.7	98.0 ± 4.7	100.3 ± 4.3	98.4 ± 4.8	100.0 ± 6.9
three point average	0.0-2.0-4.0	100.4 ± 4.3	101.4 ± 4.3	99.8 ± 3.6	100.5 ± 4.3	99.1 ± 4.4
	0.5-2.5-4.5	100.1 ± 5.1	99.9 ± 4.3	100.9 ± 4.2	100.7 ± 4.2	99.5 ± 4.8
	1.0-3.0-5.0	99.2 ± 5.0	100.3 ± 4.5	99.7 ± 4.2	98.9 ± 4.5	100.3 ± 4.5
	1.5-3.5-5.5	100.3 ± 5.0	98.5 ± 3.8	99.5 ± 3.2	99.9 ± 4.5	101.1 ± 5.8
four point average	0.0-1.5-3.0-4.5	100.1 ± 4.3	100.3 ± 4.0	99.5 ± 3.5	100.5 ± 3.5	100.7 ± 3.8
	0.5-2.0-3.5-5.0	99.8 ± 4.1	100.2 ± 3.4	100.6 ± 2.9	99.5 ± 3.5	100.1 ± 4.3
	1.0-2.5-4.0-5.5	100.2 ± 4.3	99.4 ± 3.5	99.9 ± 3.4	99.9 ± 3.9	99.3 ± 4.6

Table A-2 Averaging stratagem for the estimation of cardiac output by the thermodilution method. Values are given as % of the mean cardiac output (=100%, mean of 12 estimations equally spread over the ventilatory cycle) for all ventilatory modes.

	CO_{Th}								
	First series			Second series			Totals		
Protocol I	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%
$IPPV_I$	12	2.4 ± 0.3	100	6	2.8 ± 0.3	100	18	2.5 ± 0.4	100
DEF 66%		2.1 ± 0.3	90 ± 6		2.7 ± 0.4	94 ± 7		2.3 ± 0.4	91 ± 7
PEEP ∿ DEF 66%		2.2 ± 0.3	91 ± 8		2.7 ± 0.4	94 ± 7		2.3 ± 0.4	92 ± 7
$IPPV_{II}$		2.3 ± 0.3	99 ± 9		2.7 ± 0.4	96 ± 7		2.5 ± 0.4	98 ± 7
Protocol II									
$IPPV_I$	15	2.9 ± 0.4	100	6	2.4 ± 0.2	100	21	2.7 ± 0.4	100
DEF 100%		2.4 ± 0.5	84 ± 7		2.2 ± 0.2	95 ± 9		2.4 ± 0.4	87 ± 9
PEEP ∿ DEF 100%		2.4 ± 0.5	83 ± 7		2.1 ± 0.2	91 ± 8		2.3 ± 0.5	85 ± 8
$IPPV_{II}$		2.8 ± 0.5	96 ± 7		2.4 ± 0.3	104 ± 10		2.7 ± 0.5	99 ± 6

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.05$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP NS	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP NS	DEF vs PEEP $p < 0.025$	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.025$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-3 Mean absolute and relative (% of the mean during $IPPV_I$) values of cardiac output estimated by the thermodilution method (CO_{Th}) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled. Results of the statistical analysis are given comparing the absolute values during the different modes with each other. n is number of series in healthy animals.

	CO_{Fick}								
	First series			Second series			Totals		
Protocol I	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%	n	$ml \cdot kg^{-1} \cdot sec^{-1}$	%
$IPPV_I$	12	2.5 ± 0.5	100	6	2.9 ± 0.4	100	18	2.6 ± 0.5	100
DEF 66%		2.3 ± 0.4	93 ± 6		2.5 ± 0.3	89 ± 9		2.4 ± 0.4	92 ± 7
PEEP ∿ DEF 66%		2.4 ± 0.4	94 ± 8		2.5 ± 0.3	88 ± 7		2.4 ± 0.4	92 ± 7
$IPPV_{II}$		2.6 ± 0.4	103 ± 8		2.8 ± 0.4	98 ± 9		2.6 ± 0.4	101 ± 8
Protocol II									
$IPPV_I$	15	2.8 ± 0.4	100	6	2.6 ± 0.3	100	21	2.8 ± 0.4	100
DEF 100%		2.4 ± 0.4	85 ± 7		2.3 ± 0.3	87 ± 5		2.4 ± 0.3	85 ± 6
PEEP ∿ DEF 100%		2.4 ± 0.4	85 ± 6		2.2 ± 0.2	85 ± 7		2.3 ± 0.4	85 ± 6
$IPPV_{II}$		2.8 ± 0.4	98 ± 6		2.7 ± 0.3	101 ± 5		2.7 ± 0.4	99 ± 6

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP NS	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.001$
	PEEP vs $IPPV_I$ $p < 0.01$	PEEP vs $IPPV_I$ $p < 0.01$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.001$	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP NS	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-4 Mean absolute and relative (% of the mean during $IPPV_I$) values of cardiac output estimated by the direct Fick method for oxygen and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled. Results of the statistical analysis are given comparing the absolute values during the different modes with each other. n is number of series in healthy animals.

	$\bar{P}_{ao}$								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	100 ± 12	100	6	109 ± 12	100	18	103 ± 12	100
DEF 66%		96 ± 11	96 ± 6		103 ± 16	94 ± 5		98 ± 12	95 ± 5
PEEP ∿ DEF 66%		100 ± 13	100 ± 5		105 ± 16	96 ± 6		103 ± 13	99 ± 5
$IPPV_{II}$		101 ± 13	101 ± 6		107 ± 15	98 ± 5		103 ± 13	100 ± 5
Protocol II									
$IPPV_I$	15	107 ± 8	100	6	107 ± 14	100	21	107 ± 9	100
DEF 100%		99 ± 10	93 ± 6		97 ± 12	91 ± 6		99 ± 10	92 ± 6
PEEP ∿ DEF 100%		105 ± 9	97 ± 7		103 ± 14	96 ± 9		104 ± 11	97 ± 7
$IPPV_{II}$		107 ± 9	100 ± 6		105 ± 13	99 ± 6		107 ± 10	100 ± 6

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ $p < 0.005$
	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.005$
	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.005$	DEF vs PEEP NS	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.001$	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.025$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-5 Mean absolute and relative (% of the mean during $IPPV_I$) values of the mean systemic arterial pressure measured in the aortic arch ($\bar{P}_{ao}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	$\bar{P}_{pa}$								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	16 ± 4	100	6	18 ± 4	100	18	17 ± 4	100
DEF 66%		17 ± 3	104 ± 10		17 ± 3	95 ± 10		17 ± 3	101 ± 11
PEEP ∿ DEF 66%		18 ± 3	114 ± 11		19 ± 4	108 ± 13		19 ± 3	112 ± 12
$IPPV_{II}$		18 ± 4	113 ± 15		20 ± 4	111 ± 19		19 ± 4	112 ± 16
Protocol II									
$IPPV_I$	15	18 ± 3	100	6	19 ± 4	100	21	18 ± 3	100
DEF 100%		16 ± 3	93 ± 6		17 ± 3	88 ± 5		16 ± 3	91 ± 6
PEEP ∿ DEF 100%		18 ± 3	105 ± 10		20 ± 4	103 ± 11		19 ± 3	104 ± 10
$IPPV_{II}$		19 ± 3	108 ± 20		20 ± 4	103 ± 11		19 ± 3	107 ± 10

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.05$	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.01$	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.005$
Protocol II	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.01$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-6 Mean absolute and relative (% of the mean during $IPPV_I$) values of the mean pressure in the pulmonary artery ($\bar{P}_{pa}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	$P_{ra,i}$					
	First series		Second series		Totals	
Protocol I	n	mm Hg	n	mm Hg	n	mm Hg
$IPPV_I$	12	1.5 ± 0.6	6	1.2 ± 0.4	18	1.4 ± 0.5
DEF 66%		1.6 ± 0.5		1.2 ± 0.4		1.5 ± 0.5
PEEP ∿ DEF 66%		2.1 ± 0.5		1.8 ± 0.6		2.0 ± 0.6
$IPPV_{II}$		1.4 ± 0.6		1.2 ± 0.5		1.4 ± 0.5
Protocol II						
$IPPV_I$	15	1.7 ± 0.5	6	1.4 ± 0.6	21	1.6 ± 0.5
DEF 100%		1.9 ± 0.4		1.5 ± 0.6		1.8 ± 0.5
PEEP ∿ DEF 100%		2.7 ± 0.6		2.5 ± 0.7		2.6 ± 0.6
$IPPV_{II}$		1.6 ± 0.6		1.4 ± 0.7		1.5 ± 0.6

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.01$	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ $p < 0.01$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-7 Mean absolute values of the right atrial pressure measured at the end of inflation ($P_{ra,i}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	$P_{ra,e}$					
	First series		Second series		Totals	
Protocol I	n	mm Hg	n	mm Hg	n	mm Hg
$IPPV_I$	12	-1.6 ± 0.6	6	-2.0 ± 0.6	18	-1.7 ± 0.6
DEF 66%		-1.4 ± 0.6		-1.9 ± 0.6		-1.6 ± 0.7
PEEP ∿ DEF 66%		-0.8 ± 0.5		-1.3 ± 0.6		-1.0 ± 0.6
$IPPV_{II}$		-1.7 ± 0.7		-2.1 ± 0.6		-1.9 ± 0.6
Protocol II						
$IPPV_I$	15	-1.6 ± 0.5	6	-1.9 ± 0.8	21	-1.7 ± 0.6
DEF 100%		-1.2 ± 0.4		-1.6 ± 0.7		-1.3 ± 0.5
PEEP ∿ DEF 100%		-0.2 ± 0.5		-0.5 ± 0.7		-0.3 ± 0.6
$IPPV_{II}$		-1.7 ± 0.6		-1.9 ± 0.7		-1.7 ± 0.6

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.005$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.025$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.001$
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.01$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-8 Mean absolute values of the right atrial pressure measured at the end of expiration ($P_{ra,e}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	Heartrate								
	First series			Second series			Totals		
Protocol I	n	$\cdot min^{-1}$	%	n	$\cdot min^{-1}$	%	n	$\cdot min^{-1}$	%
$IPPV_I$	12	156 ± 29	100	6	148 ± 20	100	18	154 ± 26	100
DEF 66%		155 ± 32	99 ± 5		150 ± 21	102 ± 15		153 ± 28	100 ± 10
PEEP ∿ DEF 66%		162 ± 29	104 ± 8		154 ± 25	105 ± 20		159 ± 27	104 ± 13
$IPPV_{II}$		166 ± 29	109 ± 13		156 ± 28	106 ± 21		162 ± 28	107 ± 15
Protocol II									
$IPPV_I$	15	156 ± 21	100	6	168 ± 36	100	21	160 ± 25	100
DEF 100%		148 ± 25	95 ± 9		167 ± 37	99 ± 4		154 ± 29	96 ± 8
PEEP ∿ DEF 100%		151 ± 23	96 ± 8		165 ± 35	96 ± 8		155 ± 27	96 ± 7
$IPPV_{II}$		157 ± 19	101 ± 8		174 ± 35	104 ± 6		162 ± 25	102 ± 8

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.01$	DEF vs PEEP NS	DEF vs PEEP $p < 0.01$
	DEF vs $IPPV_{II}$ $p < 0.01$	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP NS	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.01$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.05$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ $p < 0.005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-9 Mean absolute and relative (% of the mean during $IPPV_I$) values of heart rate and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	$P_{T,p}$								
	First series			Second series			Totals		
Protocol I	n	cmH_2O	%	n	cmH_2O	%	n	cmH_2O	%
$IPPV_I$	12	19.2 ± 2.1	100	6	17.2 ± 2.2	100	18	18.5 ± 2.2	100
DEF 66%		20.2 ± 1.9	106 ± 3		18.8 ± 2.3	110 ± 4		19.8 ± 2.0	107 ± 4
PEEP ∿ DEF 66%		22.5 ± 1.7	118 ± 6		22.0 ± 2.4	128 ± 5		22.3 ± 1.9	121 ± 7
$IPPV_{II}$		18.6 ± 1.7	97 ± 6		19.0 ± 2.9	110 ± 6		18.6 ± 2.1	102 ± 8
Protocol II									
$IPPV_I$	15	19.4 ± 2.6	100	6	18.3 ± 1.5	100	21	19.1 ± 2.3	100
DEF 100%		20.9 ± 2.5	108 ± 3		20.1 ± 1.5	110 ± 2		20.6 ± 2.2	108 ± 3
PEEP ∿ DEF 100%		23.9 ± 2.5	124 ± 6		23.6 ± 1.3	129 ± 6		23.8 ± 2.2	125 ± 6
$IPPV_{II}$		17.9 ± 2.4	93 ± 6		17.2 ± 1.4	94 ± 1		17.7 ± 2.1	93 ± 5

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.001$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.001$
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.01$	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$

Table A-10 Mean absolute and relative (% of the mean during $IPPV_I$) values of the peak tracheal pressure ($P_{T,p}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	P_aO_2								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	73.3 ± 9.2	100	6	73.9 ± 4.1	100	18	73.5 ± 7.5	100
DEF 66%		76.9 ± 8.0	105 ± 4		78.1 ± 2.3	106 ± 5		77.3 ± 6.4	106 ± 4
PEEP ∿ DEF 66%		74.8 ± 8.3	102 ± 4		74.1 ± 5.6	100 ± 6		74.5 ± 7.1	102 ± 4
$IPPV_{II}$		70.7 ± 8.5	97 ± 4		69.9 ± 5.4	95 ± 6		70.4 ± 7.2	96 ± 4
Protocol II									
$IPPV_I$	15	75.7 ± 5.3	100	6	69.4 ± 10.2	100	21	73.9 ± 7.2	100
DEF 100%		82.3 ± 4.7	109 ± 3		77.1 ± 7.2	112 ± 6		80.8 ± 5.7	110 ± 4
PEEP ∿ DEF 100%		79.0 ± 5.1	105 ± 5		72.9 ± 8.8	105 ± 4		77.3 ± 6.6	105 ± 4
$IPPV_{II}$		75.0 ± 5.1	99 ± 5		71.5 ± 10.5	103 ± 5		74.0 ± 6.8	100 ± 5

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ $p < 0.005$
	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.05$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.05$	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.005$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.01$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ $p < 0.025$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ $p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-11 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of systemic arterial oxygen (P_aO_2) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled. Results of the statistical analysis are given comparing the absolute values during the different modes with each other. n is number of series in healthy animals.

	P_aCO_2								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	42.6 ± 1.5	100	6	41.8 ± 1.4	100	18	42.3 ± 1.5	100
DEF 66%		40.3 ± 1.8	94 ± 3		39.0 ± 2.5	93 ± 4		39.9 ± 2.0	94 ± 3
PEEP ∿ DEF 66%		42.6 ± 1.8	100 ± 4		41.6 ± 2.8	100 ± 6		42.3 ± 2.1	100 ± 4
$IPPV_{II}$		42.9 ± 1.7	101 ± 2		41.9 ± 2.5	100 ± 4		42.6 ± 2.0	101 ± 3
Protocol II									
$IPPV_I$	15	43.9 ± 0.7	100	6	42.3 ± 0.8	100	21	43.4 ± 1.0	100
DEF 100%		40.6 ± 1.5	93 ± 3		37.7 ± 1.4	89 ± 3		39.8 ± 1.9	92 ± 3
PEEP ∿ DEF 100%		42.4 ± 1.5	97 ± 3		41.1 ± 0.6	97 ± 2		42.0 ± 1.4	97 ± 3
$IPPV_{II}$		42.4 ± 1.3	97 ± 3		41.5 ± 1.2	98 ± 3		42.2 ± 0.9	97 ± 3

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.001$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.01$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.005$	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$

Table A-12 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of systemic arterial carbon dioxide (P_aCO_2) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number or series in healthy animals.

	$P_{\bar{v}}CO_2$								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	48.6 ± 1.5	100	6	47.8 ± 1.8	100	18	48.3 ± 1.6	100
DEF 66%		47.3 ± 1.9	98 ± 3		45.1 ± 2.5	94 ± 3		46.6 ± 2.2	97 ± 3
PEEP ∿ DEF 66%		48.7 ± 2.0	100 ± 3		47.4 ± 2.8	99 ± 6		48.3 ± 2.3	100 ± 4
$IPPV_{II}$		49.1 ± 1.4	101 ± 2		47.4 ± 2.8	99 ± 5		48.5 ± 2.0	100 ± 4
Protocol II									
$IPPV_I$	15	50.0 ± 1.3	100	6	48.8 ± 0.4	100	21	49.7 ± 1.2	100
DEF 100%		47.1 ± 1.7	94 ± 4		45.7 ± 1.6	94 ± 3		46.7 ± 1.7	94 ± 3
PEEP ∿ DEF 100%		48.8 ± 1.4	98 ± 3		48.8 ± 0.5	100 ± 2		48.8 ± 1.2	98 ± 3
$IPPV_{II}$		48.6 ± 1.6	97 ± 3		47.9 ± 1.5	98 ± 3		48.4 ± 1.5	98 ± 4

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.025$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.01$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ $p < 0.01$	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.025$	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$

Table A-13 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled. Results of the statistical analysis are given comparing the absolute values during the different modes with each other. n is number of series in healthy animals.

	$P_ECO_{2,e}$								
	First series			Second series			Totals		
Protocol I	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	12	40.3 ± 2.4	100	6	41.6 ± 1.5	100	18	40.7 ± 2.1	100
DEF 66%		43.3 ± 2.3	107 ± 2		43.9 ± 2.1	106 ± 3		43.5 ± 2.1	107 ± 2
PEEP ∿ DEF 66%		41.0 ± 2.3	102 ± 4		41.9 ± 2.5	101 ± 5		41.3 ± 2.2	102 ± 4
$IPPV_{II}$		41.0 ± 2.1	102 ± 4		42.2 ± 2.9	101 ± 7		41.4 ± 2.3	102 ± 4
Protocol II									
$IPPV_I$	15	41.9 ± 1.7	100	6	41.2 ± 1.6	100	21	41.7 ± 1.6	100
DEF 100%		44.5 ± 1.9	106 ± 2		44.6 ± 1.2	109 ± 3		44.5 ± 1.6	107 ± 2
PEEP ∿ DEF 100%		41.6 ± 1.6	99 ± 2		42.0 ± 1.7	102 ± 3		41.7 ± 1.6	100 ± 3
$IPPV_{II}$		41.6 ± 1.5	99 ± 3		41.6 ± 1.0	101 ± 4		41.6 ± 1.3	100 ± 3

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.001$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-14 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of carbon dioxide in the end expiratory air ($P_ECO_{2,e}$) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series in healthy animals.

	V_D/V_T								
	First series			Second series			Totals		
Protocol I	n		%	n		%	n		%
$IPPV_I$	12	0.28 ± 0.04	100	6	0.23 ± 0.03	100	18	0.27 ± 0.04	100
DEF 66%		0.23 ± 0.05	82 ± 11		0.18 ± 0.04	75 ± 17		0.21 ± 0.05	80 ± 13
PEEP ∿ DEF 66%		0.27 ± 0.05	97 ± 10		0.24 ± 0.04	101 ± 16		0.26 ± 0.05	98 ± 12
$IPPV_{II}$		0.27 ± 0.05	95 ± 8		0.23 ± 0.03	98 ± 19		0.25 ± 0.04	96 ± 12
Protocol II									
$IPPV_I$	15	0.28 ± 0.04	100	6	0.24 ± 0.04	100	21	0.27 ± 0.04	100
DEF 100%		0.22 ± 0.05	78 ± 10		0.14 ± 0.05	58 ± 16		0.20 ± 0.05	72 ± 15
PEEP ∿ DEF 100%		0.27 ± 0.04	97 ± 8		0.23 ± 0.03	98 ± 6		0.26 ± 0.04	97 ± 7
$IPPV_{II}$		0.25 ± 0.04	91 ± 7		0.22 ± 0.04	93 ± 10		0.25 ± 0.04	91 ± 8

Statistical analysis

	First series	Second series	Totals
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.01$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.001$
	DEF vs $IPPV_{II}$ $p < 0.001$	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.001$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.001$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.0005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.01$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ $p < 0.005$
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.0005$

Table A-15 Mean absolute and relative (% of the mean during $IPPV_I$) values of the physiological dead space fraction (V_D/V_T) and standard deviations from the mean in protocols I and II whether performed as a first series or as a second series in the individual animal (chapter II-6) and both series totalled. Results of the statistical analysis are given comparing the absolute values during the different modes with each other. n is number of series in healthy animals.

		Histamine CO_{Th}			Acetylcholine CO_{Th}	
Protocol I	n	ml.kg.sec^{-1}	%	n	ml.kg.sec^{-1}	%
$IPPV_I$	7	3.4 ± 0.7	100	6	2.8 ± 0.6	100
DEF 66%		3.1 ± 0.8	92 ± 8		2.6 ± 0.6	94 ± 3
PEEP ∿ DEF 66%		3.2 ± 0.8	96 ± 5		2.6 ± 0.6	94 ± 3
$IPPV_{II}$		3.3 ± 0.8	97 ± 5		2.8 ± 0.6	100 ± 3
Protocol II						
$IPPV_I$	7	3.1 ± 0.7	100	7	2.8 ± 0.5	100
DEF 100%		2.8 ± 0.6	89 ± 4		2.5 ± 0.4	89 ± 5
PEEP ∿ DEF 100%		2.7 ± 0.6	88 ± 4		2.5 ± 0.4	88 ± 6
$IPPV_{II}$		3.0 ± 0.6	97 ± 4		2.7 ± 0.4	97 ± 8

Statistical analysis

	Histamine		Acetylcholine	
Protocol I	DEF vs $IPPV_I$	NS	DEF vs $IPPV_I$	$p < 0.005$
	DEF vs PEEP	NS	DEF vs PEEP	NS
	DEF vs $IPPV_{II}$	NS	DEF vs $IPPV_{II}$	$p < 0.025$
	PEEP vs $IPPV_I$	NS	PEEP vs $IPPV_I$	$p < 0.025$
	PEEP vs $IPPV_{II}$	NS	PEEP vs $IPPV_{II}$	$p < 0.025$
	$IPPV_{II}$ vs $IPPV_I$	NS	$IPPV_{II}$ vs $IPPV_I$	NS
Protocol II	DEF vs $IPPV_I$	$p < 0.001$	DEF vs $IPPV_I$	$p < 0.005$
	DEF vs PEEP	NS	DEF vs PEEP	NS
	DEF vs $IPPV_{II}$	$p < 0.01$	DEF vs $IPPV_{II}$	$p < 0.01$
	PEEP vs $IPPV_I$	$p < 0.001$	PEEP vs $IPPV_I$	$p < 0.005$
	PEEP vs $IPPV_{II}$	$p < 0.001$	PEEP vs $IPPV_{II}$	$p < 0.005$
	$IPPV_{II}$ vs $IPPV_I$	NS	$IPPV_{II}$ vs $IPPV_I$	NS

Table A-16 Mean absolute and relative (% of the mean during $IPPV_I$) values of cardiac output estimated by the thermodilution technique (CO_{Th}) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine CO_{Fick}			Acetylcholine CO_{Fick}	
Protocol I	n	ml.kg.sec^{-1}	%	n	ml.kg.sec^{-1}	%
$IPPV_I$	7	3.4 ± 0.5	100	6	3.2 ± 0.8	100
DEF 66%		3.0 ± 0.5	89 ± 6		2.9 ± 0.6	89 ± 11
PEEP ∿ DEF 66%		3.0 ± 0.5	89 ± 8		2.8 ± 0.5	88 ± 8
$IPPV_{II}$		3.4 ± 0.5	100 ± 6		3.1 ± 0.7	96 ± 4
Protocol II						
$IPPV_I$	7	3.3 ± 0.5	100	7	3.2 ± 0.7	100
DEF 100%		2.7 ± 0.4	83 ± 4		2.9 ± 0.6	91 ± 10
PEEP ∿ DEF 100%		2.8 ± 0.4	86 ± 5		2.9 ± 0.7	89 ± 10
$IPPV_{II}$		3.2 ± 0.4	97 ± 6		3.2 ± 0.7	99 ± 7

Statistical analysis

	Histamine	Acetylcholine
Protocol I	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ NS
	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ $p < 0.01$	PEEP vs $IPPV_I$ $p < 0.025$
	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ $p < 0.025$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.001$	DEF vs $IPPV_I$ NS
	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.001$	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ $p < 0.001$	PEEP vs $IPPV_I$ $p < 0.05$
	PEEP vs $IPPV_{II}$ $p < 0.001$	PEEP vs $IPPV_{II}$ $p < 0.01$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-17 Mean absolute and relative (% of the mean during $IPPV_I$) values of cardiac output estimated by the direct Fick method for oxygen (CO_{Fick}) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different modes with each other.
n is number of series.

		Histamine $\bar{P}_{ao}$			Acetylcholine $\bar{P}_{ao}$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	79 ± 8	100	6	72 ± 8	100
DEF 66%		75 ± 8	95 ± 4		73 ± 10	101 ± 8
PEEP ∿ DEF 66%		77 ± 7	98 ± 5		71 ± 9	99 ± 2
$IPPV_{II}$		82 ± 7	105 ± 7		73 ± 10	101 ± 5
Protocol II						
$IPPV_I$	7	83 ± 7	100	7	73 ± 10	100
DEF 100%		78 ± 7	94 ± 3		70 ± 11	95 ± 7
PEEP ∿ DEF 100%		81 ± 7	99 ± 3		71 ± 12	97 ± 6
$IPPV_{II}$		85 ± 9	103 ± 3		75 ± 13	102 ± 8

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	$p < 0.01$	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	NS	DEF	vs PEEP	NS
	DEF	vs $IPPV_{II}$	$p < 0.01$	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	$p < 0.005$	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	$p < 0.01$	DEF	vs PEEP	NS
	DEF	vs $IPPV_{II}$	$p < 0.005$	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-18 Mean absolute and relative (% of the mean during $IPPV_I$) values of the mean systemic arterial pressure measured in the aortic arch ($\bar{P}_{ao}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine $\bar{P}_{pa}$			Acetylcholine $\bar{P}_{pa}$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	23 ± 4	100	6	24 ± 2	100
DEF 66%		21 ± 3	93 ± 6		24 ± 3	100 ± 5
PEEP ∿ DEF 66%		23 ± 4	99 ± 7		24 ± 3	100 ± 9
$IPPV_{II}$		25 ± 4	109 ± 15		25 ± 3	104 ± 12
Protocol II						
$IPPV_I$	7	25 ± 3	100	7	25 ± 3	100
DEF 100%		22 ± 2	88 ± 6		23 ± 3	92 ± 4
PEEP ∿ DEF 100%		24 ± 3	97 ± 9		25 ± 3	98 ± 5
$IPPV_{II}$		26 ± 4	104 ± 14		25 ± 4	97 ± 7

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	NS	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	NS	DEF	vs PEEP	NS
	DEF	vs $IPPV_{II}$	$p < 0.01$	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	$p < 0.001$	DEF	vs $IPPV_I$	$p < 0.005$
	DEF	vs PEEP	$p < 0.001$	DEF	vs PEEP	$p < 0.001$
	DEF	vs $IPPV_{II}$	$p < 0.001$	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-19 Mean absolute and relative (% of the mean during $IPPV_I$) values of the mean pressure in the pulmonary artery ($\bar{P}_{pa}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine $P_{ra,i}$			Acetylcholine $P_{ra,i}$	
Protocol I	n	mm Hg		n	mm Hg	
$IPPV_I$	7	1.2 ± 0.4		6	2.8 ± 0.7	
DEF 66%		1.5 ± 0.7			2.8 ± 0.6	
PEEP ∿ DEF 66%		2.0 ± 0.4			3.6 ± 0.7	
$IPPV_{II}$		1.4 ± 0.5			2.8 ± 0.7	
Protocol II						
$IPPV_I$	7	1.4 ± 0.5		7	2.8 ± 0.6	
DEF 100%		1.6 ± 0.4			2.9 ± 0.7	
PEEP ∿ DEF 100%		2.4 ± 0.4			4.2 ± 1.0	
$IPPV_{II}$		1.4 ± 0.4			2.8 ± 0.8	

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	NS	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	$p < 0.01$	DEF	vs PEEP	$p < 0.001$
	DEF	vs $IPPV_{II}$	NS	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	$p < 0.001$	PEEP	vs $IPPV_I$	$p < 0.001$
	PEEP	vs $IPPV_{II}$	$p < 0.001$	PEEP	vs $IPPV_{II}$	$p < 0.001$
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	NS	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	$p < 0.001$	DEF	vs PEEP	$p < 0.001$
	DEF	vs $IPPV_{II}$	NS	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	$p < 0.001$	PEEP	vs $IPPV_I$	$p < 0.001$
	PEEP	vs $IPPV_{II}$	$p < 0.001$	PEEP	vs $IPPV_{II}$	$p < 0.001$
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-20 Mean absolute values of the right atrial pressure measured at the end of inflation ($P_{ra,i}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively. Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine $P_{ra,e}$			Acetylcholine $P_{ra,e}$	
Protocol I	n	mm Hg		n	mm Hg	
$IPPV_I$	7	-2.2 ± 0.5		6	-0.5 ± 0.7	
DEF 66%		-1.9 ± 0.7			-0.4 ± 0.7	
PEEP ∿ DEF 66%		-1.1 ± 0.5			+0.5 ± 1.0	
$IPPV_{II}$		-2.1 ± 0.4			-0.4 ± 0.9	
Protocol II						
$IPPV_I$	7	-2.1 ± 0.5		7	-0.6 ± 0.7	
DEF 100%		-1.6 ± 0.3			-0.3 ± 0.7	
PEEP ∿ DEF 100%		-0.4 ± 0.1			+1.0 ± 0.9	
$IPPV_{II}$		-2.0 ± 0.2			-0.7 ± 0.6	

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	NS	DEF	vs $IPPV_I$	NS
	DEF	vs PEEP	$p < 0.01$	DEF	vs PEEP	$p < 0.005$
	DEF	vs $IPPV_{II}$	NS	DEF	vs $IPPV_{II}$	NS
	PEEP	vs $IPPV_I$	$p < 0.001$	PEEP	vs $IPPV_I$	$p < 0.001$
	PEEP	vs $IPPV_{II}$	$p < 0.001$	PEEP	vs $IPPV_{II}$	$p < 0.001$
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	$p < 0.001$	DEF	vs $IPPV_I$	$p < 0.005$
	DEF	vs PEEP	$p < 0.001$	DEF	vs PEEP	$p < 0.001$
	DEF	vs $IPPV_{II}$	$p < 0.001$	DEF	vs $IPPV_{II}$	$p < 0.005$
	PEEP	vs $IPPV_I$	$p < 0.001$	PEEP	vs $IPPV_I$	$p < 0.001$
	PEEP	vs $IPPV_{II}$	$p < 0.001$	PEEP	vs $IPPV_{II}$	$p < 0.001$
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-21 Mean absolute values of the right atrial pressure measured at at the end of expiration ($P_{ra,e}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively. Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
Protocol I	n	$P_{T,p}$ (cmH_2O)	EEP (cmH_2O)	n	$P_{T,p}$ (cmH_2O)	EEP (cmH_2O)
$IPPV_I$	7	23.1 ± 2.2	0	6	24.7 ± 1.5	0
DEF 66%		23.7 ± 2.6	0		25.3 ± 1.6	0
PEEP ∿ DEF 66%		26.0 ± 1.8	2.9 ± 0.2		27.3 ± 1.9	3.0 ± 0.4
$IPPV_{II}$		23.1 ± 2.1	0		22.5 ± 1.4	0
Protocol II						
$IPPV_I$	7	23.1 ± 1.8	0	7	23.0 ± 1.7	0
DEF 100%		23.9 ± 1.4	0		24.4 ± 1.6	0
PEEP ∿ DEF 100%		27.5 ± 1.6	4.4 ± 0.2		27.7 ± 1.8	4.3 ± 0.6
$IPPV_{II}$		21.9 ± 1.7	0		21.6 ± 2.0	0

Statistical analysis

	Histamine		Acetylcholine	
Protocol I	DEF vs $IPPV_I$	NS	DEF vs $IPPV_I$	NS
	DEF vs PEEP	$p < 0.0005$	DEF vs PEEP	$p < 0.0005$
	DEF vs $IPPV_{II}$	NS	DEF vs $IPPV_{II}$	$p < 0.0005$
	PEEP vs $IPPV_I$	$p < 0.0005$	PEEP vs $IPPV_I$	$p < 0.0005$
	PEEP vs $IPPV_{II}$	$p < 0.0005$	PEEP vs $IPPV_{II}$	$p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$	NS	$IPPV_{II}$ vs $IPPV_I$	$p < 0.001$
Protocol II	DEF vs $IPPV_I$	NS	DEF vs $IPPV_I$	$p < 0.005$
	DEF vs PEEP	$p < 0.0005$	DEF vs PEEP	$p < 0.0005$
	DEF vs $IPPV_{II}$	$p < 0.001$	DEF vs $IPPV_{II}$	$p < 0.0005$
	PEEP vs $IPPV_I$	$p < 0.0005$	PEEP vs $IPPV_I$	$p < 0.0005$
	PEEP vs $IPPV_{II}$	$p < 0.0005$	PEEP vs $IPPV_{II}$	$p < 0.0005$
	$IPPV_{II}$ vs $IPPV_I$	$p < 0.0005$	$IPPV_{II}$ vs $IPPV_I$	$p < 0.0005$

Table A-22 Mean absolute values of the mean peak tracheal pressure ($P_{T,p}$) and end expiratory pressure (EEP) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively. Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
		$P_a O_2$			$P_a O_2$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	60.2 ± 4.8	100	6	67.3 ± 6.3	100
DEF 66%		66.3 ± 5.1	110 ± 4		72.7 ± 5.3	108 ± 4
PEEP ∿ DEF 66%		64.1 ± 3.8	107 ± 6		71.1 ± 5.5	106 ± 3
$IPPV_{II}$		58.8 ± 3.9	98 ± 5		67.3 ± 5.5	100 ± 4
Protocol II						
$IPPV_I$	7	57.1 ± 4.1	100	7	66.1 ± 5.6	100
DEF 100%		68.6 ± 4.8	120 ± 4		72.7 ± 5.8	110 ± 3
PEEP ∿ DEF 100%		66.1 ± 4.4	116 ± 4		70.2 ± 5.7	106 ± 2
$IPPV_{II}$		58.8 ± 3.5	103 ± 3		65.0 ± 7.6	98 ± 5

Statistical analysis

	Histamine	Acetylcholine
Protocol I	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.001$
	PEEP vs $IPPV_I$ $p < 0.025$	PEEP vs $IPPV_I$ $p < 0.01$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.0005$
	DEF vs PEEP $p < 0.01$	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.0005$	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ $p < 0.0005$	PEEP vs $IPPV_I$ $p < 0.0005$
	PEEP vs $IPPV_{II}$ $p < 0.0005$	PEEP vs $IPPV_{II}$ $p < 0.005$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-23 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of systemic arterial oxygen ($P_a O_2$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
		$P_a CO_2$			$P_a CO_2$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	45.6 ± 2.6	100	6	46.1 ± 1.6	100
DEF 66%		42.8 ± 3.0	94 ± 5		43.4 ± 1.8	94 ± 3
PEEP ∿ DEF 66%		45.5 ± 3.3	100 ± 4		44.9 ± 2.0	97 ± 3
$IPPV_{II}$		47.4 ± 3.5	104 ± 6		45.5 ± 1.0	99 ± 2
Protocol II						
$IPPV_I$	7	48.0 ± 3.2	100	7	45.3 ± 1.0	100
DEF 100%		41.8 ± 2.0	87 ± 4		42.3 ± 1.6	93 ± 3
PEEP ∿ DEF 100%		45.2 ± 2.7	94 ± 2		44.6 ± 1.6	98 ± 3
$IPPV_{II}$		46.2 ± 3.8	96 ± 4		45.1 ± 1.9	100 ± 3

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	$p < 0.01$	DEF	vs $IPPV_I$	$p < 0.005$
	DEF	vs PEEP	$p < 0.005$	DEF	vs PEEP	$p < 0.005$
	DEF	vs $IPPV_{II}$	$p < 0.005$	DEF	vs $IPPV_{II}$	$p < 0.01$
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	$p < 0.005$	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	$p < 0.0005$	DEF	vs $IPPV_I$	$p < 0.0005$
	DEF	vs PEEP	$p < 0.001$	DEF	vs PEEP	$p < 0.005$
	DEF	vs $IPPV_{II}$	$p < 0.0005$	DEF	vs $IPPV_{II}$	$p < 0.01$
	PEEP	vs $IPPV_I$	$p < 0.0005$	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-24 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of systemic arterial carbon dioxide (P_aCO_2) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
		$P_{\bar{v}} CO_2$			$P_{\bar{v}} CO_2$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	52.6 ± 3.2	100	6	51.3 ± 1.6	100
DEF 66%		50.7 ± 3.0	96 ± 2		49.4 ± 1.4	96 ± 2
PEEP ∿ DEF 66%		52.9 ± 4.0	101 ± 4		51.2 ± 1.2	100 ± 3
$IPPV_{II}$		54.2 ± 3.3	103 ± 5		51.7 ± 0.7	101 ± 3
Protocol II						
$IPPV_I$	7	55.2 ± 2.9	100	7	51.2 ± 1.7	100
DEF 100%		51.2 ± 2.8	93 ± 2		48.9 ± 1.7	96 ± 1
PEEP ∿ DEF 100%		53.0 ± 3.0	96 ± 1		50.2 ± 1.6	98 ± 1
$IPPV_{II}$		54.1 ± 4.0	98 ± 3		50.5 ± 1.9	99 ± 2

Statistical analysis

	Histamine			Acetylcholine		
Protocol I	DEF	vs $IPPV_I$	$p < 0.005$	DEF	vs $IPPV_I$	$p < 0.005$
	DEF	vs PEEP	$p < 0.01$	DEF	vs PEEP	$p < 0.001$
	DEF	vs $IPPV_{II}$	$p < 0.005$	DEF	vs $IPPV_{II}$	$p < 0.005$
	PEEP	vs $IPPV_I$	NS	PEEP	vs $IPPV_I$	NS
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS
Protocol II	DEF	vs $IPPV_I$	$p < 0.0005$	DEF	vs $IPPV_I$	$p < 0.0005$
	DEF	vs PEEP	$p < 0.0005$	DEF	vs PEEP	$p < 0.005$
	DEF	vs $IPPV_{II}$	$p < 0.01$	DEF	vs $IPPV_{II}$	$p < 0.005$
	PEEP	vs $IPPV_I$	$p < 0.0005$	PEEP	vs $IPPV_I$	$p < 0.005$
	PEEP	vs $IPPV_{II}$	NS	PEEP	vs $IPPV_{II}$	NS
	$IPPV_{II}$	vs $IPPV_I$	NS	$IPPV_{II}$	vs $IPPV_I$	NS

Table A-25 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
		$P_E CO_{2,e}$			$P_E CO_{2,e}$	
Protocol I	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	7	47.2 ± 2.7	100	6	44.1 ± 1.5	100
DEF 66%		49.1 ± 3.1	104 ± 3		46.9 ± 1.3	106 ± 2
PEEP ∿ DEF 66%		47.3 ± 2.8	100 ± 3		44.1 ± 1.1	100 ± 3
$IPPV_{II}$		47.9 ± 2.1	102 ± 4		44.2 ± 1.4	100 ± 3
Protocol II						
$IPPV_I$	7	48.6 ± 2.3	100	7	44.3 ± 1.3	100
DEF 100%		50.8 ± 2.3	105 ± 1		47.5 ± 1.8	107 ± 2
PEEP ∿ DEF 100%		47.5 ± 2.3	97 ± 2		43.7 ± 1.8	99 ± 2
$IPPV_{II}$		47.3 ± 2.6	97 ± 2		43.7 ± 2.2	99 ± 3

Statistical analysis

	Histamine		Acetylcholine	
Protocol I	DEF vs $IPPV_I$	$p < 0.025$	DEF vs $IPPV_I$	$p < 0.0005$
	DEF vs PEEP	$p < 0.001$	DEF vs PEEP	$p < 0.001$
	DEF vs $IPPV_{II}$	NS	DEF vs $IPPV_{II}$	$p < 0.005$
	PEEP vs $IPPV_I$	NS	PEEP vs $IPPV_I$	NS
	PEEP vs $IPPV_{II}$	NS	PEEP vs $IPPV_{II}$	NS
	$IPPV_{II}$ vs $IPPV_I$	NS	$IPPV_{II}$ vs $IPPV_I$	NS
Protocol II	DEF vs $IPPV_I$	$p < 0.0005$	DEF vs $IPPV_I$	$p < 0.0005$
	DEF vs PEEP	$p < 0.0005$	DEF vs PEEP	$p < 0.0005$
	DEF vs $IPPV_{II}$	$p < 0.0005$	DEF vs $IPPV_{II}$	$p < 0.0005$
	PEEP vs $IPPV_I$	NS	PEEP vs $IPPV_I$	NS
	PEEP vs $IPPV_{II}$	NS	PEEP vs $IPPV_{II}$	NS
	$IPPV_{II}$ vs $IPPV_I$	$p < 0.005$	$IPPV_{II}$ vs $IPPV_I$	NS

Table A-26 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of carbon dioxide in the end-expiratory air ($P_E CO_{2,e}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

		Histamine			Acetylcholine	
		V_D/V_T			V_D/V_T	
Protocol I	n	absolute	relative (%)	n	absolute	relative (%)
$IPPV_I$	7	0.24 ± 0.03	100	6	0.30 ± 0.03	100
DEF 66%		0.17 ± 0.06	71 ± 20		0.25 ± 0.04	83 ± 7
PEEP ∿ DEF 66%		0.23 ± 0.04	95 ± 12		0.30 ± 0.04	99 ± 10
$IPPV_{II}$		0.25 ± 0.04	102 ± 12		0.29 ± 0.03	97 ± 9
Protocol II						
$IPPV_I$	7	0.25 ± 0.04	100	7	0.29 ± 0.02	100
DEF 100%		0.15 ± 0.04	58 ± 10		0.24 ± 0.04	83 ± 9
PEEP ∿ DEF 100%		0.24 ± 0.04	94 ± 9		0.30 ± 0.03	106 ± 8
$IPPV_{II}$		0.24 ± 0.04	97 ± 9		0.29 ± 0.01	101 ± 10

Statistical analysis

	Histamine	Acetylcholine
Protocol I	DEF vs $IPPV_I$ $p < 0.005$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP $p < 0.01$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.01$	DEF vs $IPPV_{II}$ $p < 0.005$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS
Protocol II	DEF vs $IPPV_I$ $p < 0.0005$	DEF vs $IPPV_I$ $p < 0.001$
	DEF vs PEEP $p < 0.0005$	DEF vs PEEP $p < 0.0005$
	DEF vs $IPPV_{II}$ $p < 0.001$	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-27 Mean absolute and relative (% of the mean during $IPPV_I$) values of the physiological dead space fraction (V_D/V_T) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by histamine and acetylcholine respectively.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

	Oleic acid								
		CO_{Th}			CO_{Fick}			$\bar{P}_{ao}$	
Protocol II	n	ml.kg.sec^{-1}	%	n	ml.kg.sec^{-1}	%	n	mm Hg	%
$IPPV_I$	4	2.2 ± 0.1	100	4	2.2 ± 0.2	100	4	99 ± 10	100
DEF 100%		2.2 ± 0.4	98 ± 11		2.2 ± 0.1	101 ± 14		94 ± 16	96 ± 11
PEEP ∿ DEF 100%		2.1 ± 0.3	93 ± 9		2.1 ± 0.2	96 ± 14		103 ± 13	102 ± 17
$IPPV_{II}$		2.6 ± 0.3	115 ± 9		2.6 ± 0.3	117 ± 16		110 ± 9	112 ± 7

Statistical analysis / oleic acid

	CO_{Th}	CO_{Fick}	P_{ao}
Protocol II	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP NS	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.005$	DEF vs $IPPV_{II}$ $p < 0.05$	DEF vs $IPPV_{II}$ $p < 0.025$
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.001$	PEEP vs $IPPV_{II}$ $p < 0.025$	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ $p < 0.025$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.025$

Table A-28 Mean absolute and relative (% of the mean during $IPPV_I$) values of cardiac output estimated by the thermodilution technique (CO_{Th}) and the direct Fick method for oxygen (CO_{Fick}) and of the mean systemic arterial pressure measured in the aortic arch ($\bar{P}_{ao}$) and standard deviations from the mean in protocol II (chapter II-6) during pulmonary disease induced by alloxan and oleic acid.
Results of the statistical analysis are given comparing the different ventilatory modes with each other.
n is number of series.

	Oleic acid								
		$\bar{P}_{pa}$			$P_{ra,e}$			$P_{ra,i}$	
Protocol II	n	mm Hg	%	n	mm Hg		n	mm Hg	
$IPPV_I$	4	26 ± 3	100	4	0.8 ± 0.9		4	3.7 ± 0.7	
DEF 100%		24 ± 2	94 ± 3		0.3 ± 1.1			3.2 ± 1.0	
PEEP ∿ DEF 100%		27 ± 4	83 ± 7		1.3 ± 0.9			3.9 ± 1.0	
$IPPV_{II}$		25 ± 5	97 ± 12		-0.1 ± 0.6			2.8 ± 0.4	

Statistical analysis / oleic acid

	$\bar{P}_{pa}$	$P_{ra,e}$	$P_{ra,i}$
Protocol II	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ NS	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.05$	DEF vs PEEP $p < 0.005$	DEF vs PEEP $p < 0.005$
	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ NS	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ NS
	PEEP vs $IPPV_{II}$ $p < 0.025$	PEEP vs $IPPV_{II}$ $p < 0.025$	PEEP vs $IPPV_{II}$ $p < 0.05$
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ $p < 0.025$

Table A-29 Mean absolute and relative (% of the mean during $IPPV_I$) values of the mean pressure in the pulmonary artery ($\bar{P}_{pa}$) and mean absolute values of the right atrial pressure measured at the end of inflation ($P_{ra,i}$) and at the end of expiration ($P_{ra,e}$) and standard deviations from the mean in protocols I and II (chapter II-6) during pulmonary disease induced by alloxan and oleic acid.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

	oleic acid								
	P_aO_2			P_aCO_2			$P_{\bar{v}}CO_2$		
Protocol II	n	mm Hg	%	n	mm Hg	%	n	mm Hg	%
$IPPV_I$	4	95.1 ± 13.9	100	4	49.0 ± 4.4	100	4	58.6 ± 5.0	100
DEF 100%		118.5 ± 11.2	126 ± 19		43.2 ± 4.2	88 ± 5		52.1 ± 4.1	89 ± 8
PEEP ∿ DEF 100%		159.6 ± 9.0	171 ± 30		44.3 ± 4.3	91 ± 6		53.0 ± 5.2	91 ± 8
$IPPV_{II}$		92.1 ± 7.2	98 ± 10		47.2 ± 2.8	97 ± 6		55.2 ± 3.3	95 ± 6

Statistical analysis / oleic acid

	P_aO_2	P_aCO_2	$P_{\bar{v}}CO_2$
Protocol II	DEF vs $IPPV_I$ $p < 0.025$	DEF vs $IPPV_I$ $p < 0.01$	DEF vs $IPPV_I$ $p < 0.05$
	DEF vs PEEP $p < 0.005$	DEF vs PEEP NS	DEF vs PEEP NS
	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.025$
	PEEP vs $IPPV_I$ $p < 0.005$	PEEP vs $IPPV_I$ $p < 0.025$	PEEP vs $IPPV_I$ $p < 0.05$
	PEEP vs $IPPV_{II}$ $p < 0.005$	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-30 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressures of systemic arterial oxygen (P_aO_2), systemic arterial carbon dioxide (P_aCO_2) and mixed venous carbon dioxide ($P_{\bar{v}}CO_2$) and standard deviations from the mean in protocol II (chapter II-6) during pulmonary disease induced by alloxan and oleic acid.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

	oleic acid								
	$P_ECO_{2,e}$			V_D/V_T			$P_{T,p}$		
Protocol II	n	mm Hg	%	n		%	n	cmH_2O	%
$IPPV_I$	4	40.1 ± 0.9	100	4	0.38 ± 0.06	100	4	27.4 ± 2.5	100
DEF 100%		44.2 ± 1.8	110 ± 4		0.28 ± 0.08	74 ± 15		27.3 ± 2.2	100 ± 4
PEEP ∿ DEF 100%		41.1 ± 1.1	103 ± 3		0.31 ± 0.08	82 ± 16		28.9 ± 2.8	105 ± 2
$IPPV_{II}$		40.6 ± 2.3	101 ± 7		0.35 ± 0.04	94 ± 5		26.9 ± 3.3	98 ± 7

Statistical analysis / oleic acid

	$P_ECO_{2,e}$	V_D/V_T	$P_{T,p}$
Protocol II	DEF vs $IPPV_I$ $p < 0.01$	DEF vs $IPPV_I$ $p < 0.01$	DEF vs $IPPV_I$ NS
	DEF vs PEEP $p < 0.01$	DEF vs PEEP NS	DEF vs PEEP $p < 0.025$
	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ $p < 0.025$	DEF vs $IPPV_{II}$ NS
	PEEP vs $IPPV_I$ NS	PEEP vs $IPPV_I$ $p < 0.05$	PEEP vs $IPPV_I$ $p < 0.025$
	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS	PEEP vs $IPPV_{II}$ NS
	$IPPV_{II}$ vs $IPPV_I$ NS	$IPPV_{II}$ vs $IPPV_I$ $p < 0.05$	$IPPV_{II}$ vs $IPPV_I$ NS

Table A-31 Mean absolute and relative (% of the mean during $IPPV_I$) values of the partial pressure of end expiratory carbon dioxide ($P_ECO_{2,e}$), the physiological dead space fraction (V_D/V_T) and the peak tracheal pressure ($P_{T,p}$) and standard deviations from the mean in protocol II (chapter II-6) during pulmonary disease induced by alloxan and oleic acid.
Results of the statistical analysis are given comparing the absolute values during the different ventilatory modes with each other.
n is number of series.

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The author of this thesis was born in August 1948 in Bandung (Indonesia). He passed his final school exams, beta-section, at the "'s-Gravenhaags Christelijk Gymnasium Sorghvliet" in 1966 and started medical studies the same year at the State University of Leiden. From December 1970 - January 1972 he was a student-assistant at the postoperative recovery of the department of thoracic surgery (head then: Prof.Dr. A.G. Brom) of the Academical Hospital Leiden. In 1973 he was assistant at the department of pulmonary diseases (head then: the late Prof.Dr. J. Swierenga) of the Academical Hospital Leiden during four months.
In October 1974 he graduated from medical school and became assistant at the department of Internal Medicine II (head then: Prof.Dr. M. Frenkel) of the Academical Hospital Rotterdam-Dijkzigt. His surgical training started in July 1975 in the same hospital under the guidance of the late Prof.Dr. H. Muller and Prof.Dr. H. van Houten. The author was registered as a specialist in surgery in July 1981 and stayed at the department as a "chef de clinique" for nearly three years. At present, since April 1984, he is a surgeon in the Sophia Hospital in Zwolle.