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Jet Ventilation for Airway Surgery

The Influence of Mode and Frequency on Ventilation Efficacy

ROBERT SÜTTERLIN

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Abstract

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In surgery for airway obstruction, the anesthetist and the ear-nose-throat surgeon share the approach to the airway and jet ventilation (JV) is a mutually convenient ventilation technique for both parties. As a consequence of the open system jet ventilation is applied in, bedside measurements of lung volumes are cumbersome to perform and thus, there is a lack of studies comparing different modes of JV or investigating the influence of ventilator settings on lung volumes and gas exchange. In this thesis, single frequency jet ventilation and superimposed high frequency jet ventilation (SHFJV) at different frequencies are systematically compared with respect to lung volume changes, underlying airway pressure variations and the resulting gas exchange.

We compared three single-frequency JV modalities with SHFJV in patients. Moreover, we performed a systematic investigation of single frequency JV and SHFJV in a porcine model. Single frequency JV and SHFJV were compared frequency-wise in intact airways and in a newly developed model of tracheal obstruction. This model was also used to assess the influence of variable airway diameter on ventilation effectiveness during SHFJV. We measured chest wall volume variations with opto-electronic plethysmography and obtained airway pressures as well as gas exchange parameters.

In unobstructed airways, both single-frequency JV and SHFJV provided adequate oxygenation, despite differences in lung volumes. Carbon dioxide removal was most effective using single frequency JV at a frequency of 150 min^{-1}. During SHFJV, for both intact and obstructed airways, the choice of frequency for the high frequency component had little influence on lung volumes, airway pressures and gas exchange. With decreasing airway diameter and SHFJV, we observed air trapping and lower tidal volumes and acceptable oxygenation. Carbon dioxide removal, however, was insufficient at the narrowest airway diameter. In single frequency JV, very high frequencies resulted in negligible tidal volume and inacceptable gas exchange. Airway obstruction potentiated this frequency dependence.

In conclusion, in intact airways, single frequency JV at sufficiently low frequencies provided adequate oxygenation and better CO_2 removal than SHFJV. With decreasing airway diameter, SHFJV provided better oxygenation and CO_2 removal and may therefore be the mode of choice in more complicated cases.

Keywords: jet ventilation, airway obstruction, tracheal stenosis, HFJV, SHFJV

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To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Leiter, R., Aliverti, A., Priori, R., Staun, P., LoMauro, A., Larsson, A., Frykholm, P. (2012)
Comparison of superimposed high frequency jet ventilation with conventional jet ventilation for laryngeal surgery.
British Journal of Anaesthesia, 108(4):690–7

II Sütterlin, R., Priori, R., Larsson, A., LoMauro, A., Frykholm, P., Aliverti A. (2014)
Frequency dependence of lung volume changes during superimposed high frequency jet ventilation and high frequency jet ventilation.
British Journal of Anaesthesia, 112(1):141–9

III Sütterlin, R., LoMauro, A., Gandolfi, S., Priori, R., Aliverti, A., Frykholm, P., Larsson, A. (2014)
Efficacy of Superimposed High Frequency Jet Ventilation and High Frequency Jet Ventilation in an Animal Model of Tracheal Obstruction.
Submitted manuscript

IV Sütterlin, R., Frykholm, P., LoMauro, A., Gandolfi, S., Priori, R., Larsson, A., Aliverti, A. (2014)
The Influence of the Airway Obstruction on the Efficacy of Superimposed High Frequency Jet Ventilation in an Experimental Animal Model.
Submitted manuscript

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Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body-mass-index
COPD	Chronic obstructive pulmonary disease
DP	Driving pressure (airway)
EELV	End expiratory lung volume
EEV_{CW}	End expiratory chest wall volume
ΔEEV_{CW}	Increase of EEV_{CW} above apneic FRC level
EIV_{CW}	End inspiratory chest wall volume
f_{HF}	High frequency component of superimposed high frequency jet ventilation
F_iO_2	Fraction of inspired oxygen
f_{NF}	Normal frequency component of superimposed high frequency jet ventilation
FRC	Functional residual capacity
HFJV	High frequency jet ventilation
HFV	High frequency ventilation
Index 'IG'	Infraglottic (subglottic)
Index 'SG'	Supraglottic
IM	Intramuscular
IV	Intravenous
JV	Jet ventilation
NFJV	Normal (low) frequency jet ventilation
OEP	Opto-electronic plethysmography
p_aCO_2	Arterial partial pressure of carbon dioxide
p_aO_2	Arterial partial pressure of oxygen
PIP	Peak inspiratory pressure
PEEP	Positive end expiratory pressure
PO	Per os
S_aO_2	Arterial oxygen saturation
SHFJV	Superimposed high frequency jet ventilation
S_pO_2	Peripheral oxygen saturation
V_T	Tidal volume
WP	Working pressure (jet ventilator)

Preface

Central airway obstruction, either malignant or non-malignant, is a condition that may need surgical treatment in order to avoid pulmonary complications or even death by asphyxia. Often, the anesthetist and the ear-nose-throat (ENT) surgeon share the approach to the airway. Jet ventilation (JV) is a mutually convenient and useful ventilation technique in these cases.

Since the first description of JV in 1967, several methods of JV have been developed and they are differentiated by the frequency(ies) they use and the access to the airway that is chosen. All of these modalities are considered to be more or less "experimental", as personal user experience rather than evidence-based investigations form the scientific knowledge basis of jet ventilation. Although there are data available on the influence of certain ventilator settings on gas exchange parameters, there is no certainty that the same settings will produce the same result throughout the course of the operation. It is rather more likely that the dynamics of the procedure itself make constant re-evaluation of ventilation effectiveness and adjustment of ventilator settings necessary.

As a consequence of the open system jet ventilation is applied in, and the associated difficulties in the assessment of lung volume changes during jet ventilation, little is written about how to optimally use single frequency JV. Even less is known about the optimization of superimposed high frequency jet ventilation (SHFJV), a technique that combines two ventilating jets at different frequencies.

Although JV in general is still somewhat niched, there is growing interest in jet ventilation outside the ENT departments. An increasing need for jet ventilation may challenge the prevailing concept of a handful exclusive "experts" who are experienced enough to perform jet ventilation and it should bring a broader community of anesthetists to ask questions to learn more about jet ventilation.

Introduction

Unlike other surgery, procedures performed in the central airways pose a special kind of challenge for the anesthetist and the ENT surgeon: the shared access to the airway. The surgeon's requirement for optimal access to the operation field is often in conflict with the anesthetist's task of ventilating the patient. Therefore, endotracheal intubation using conventional tubes is not a feasible option. Several ventilation techniques have been used to find a reasonable compromise between the needs of both parties. These include spontaneous breathing and topical anesthesia[1], endotracheal intubation with a narrow cuffed tube, apneic oxygenation[2,3] or intermittent apnea[4,5]. None of these approaches completely satisfied both the anesthetist and the surgeon. In spontaneously breathing patients the operating field may not remain sufficiently quiet to meet the requirements of microscopic surgery, whereas in intubated patients, even when low diameter microlaryngoscopy tubes (MLT) are used, access to the operation field may be impaired. Intermittent apnea or apneic oxygenation provide better access to the operation field, but deleterious CO_2 accumulation frequently occurs[6,7], and sets limits to the duration of the procedure.

The situation became different, when Sanders in 1967 developed the principle of jet ventilation in the airway.[8] With his technique, using ventilating attachments for bronchoscopes (*Figure 1*), oxygen could be injected intermittently at physiological frequencies in order to oxygenate the patient and remove CO_2. The attachments did not interfere with the surgeon's access to the operating field and allowed the anesthetist at the same time to ventilate the patient independently.

Later, Sanders' approach was adapted to different needs, including laryngoscopy[9,10], for emergency use by needle access to the trachea,[11,12] for routine transtracheal ventilation[13] and for translaryngeal jet ventilation[14] using small bore catheters. All of these methods shared the property of being open respiratory systems that allow air entrainment to occur. Unfortunately, comparisons of JV techniques with each other or with conventional ventilation are rare, perhaps because of the associated difficulties of measuring lung volume changes during JV, or simply because of the obvious advantages of jet ventilation in airway surgery.

At this stage, jet ventilation was delivered using only physiological frequencies, which may have disadvantages. Firstly, during the relatively long duration of inspiration, the flow of jet gas may impede surgery by unwanted

movements of the vocal cords.[15,16] Secondly, there is a theoretical risk of debris seeding towards the lung.[9]

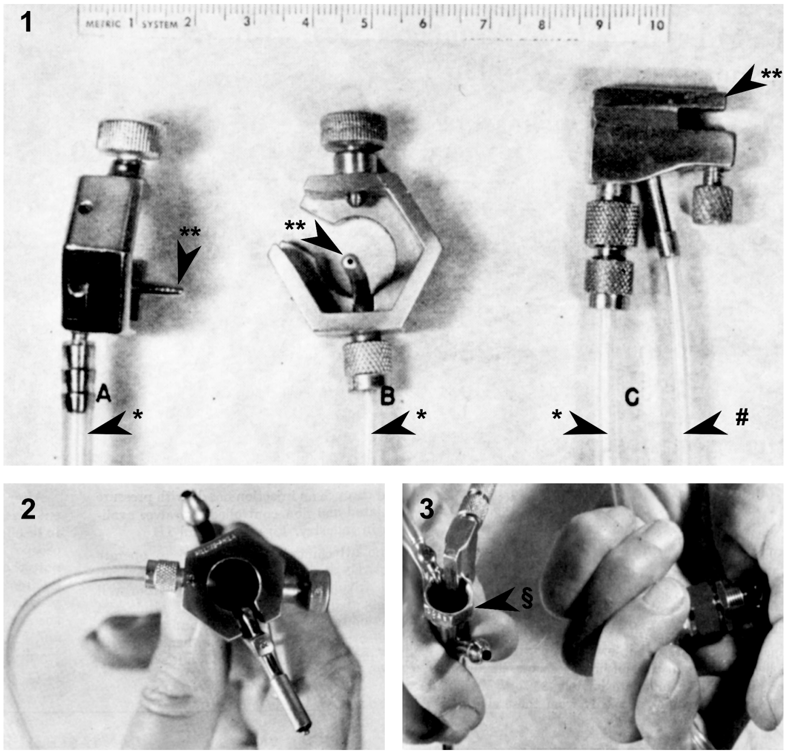

Figure 1. The “ventilating attachments for bronchoscopes” invented by Sanders. Panel 1A and 1B show versions of the jet injector for a fixed size of bronchoscope. In 1C, an ejector for the use with different sizes of bronchoscopes is shown. Panel 2 and 3: 1B and 1C attached to a bronchoscope. * Pressure supply line, ** Injector nozzle, # anesthetic vapor supply line, § bronchoscope
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In order to reduce the risk of debris seeding, aspiration of blood as well as to minimize vocal cord movements, Klain and Smith developed high frequency jet ventilation (HFJV).[17] Previously, Sjöstrand and coworkers had found that it was possible to maintain adequate gas exchange in both animals and humans with a high frequency (> 60 min^{-1}), low tidal volume ventilation.[18,19]
In their work, Klain and Smith adapted Sjöstrand’s findings to intratracheal jet ventilation for laryngoscopy[17] and showed that aspiration of fluid was fully prevented by HFJV.[20]

Although HFJV provides adequate carbon dioxide elimination in a majority of patients, severe obstructive and/or restrictive lung disease may exhaust the limits of HFJV.[21-23] In these patients, HFJV may not adequately eliminate

carbon dioxide, and merely increasing the driving pressure may not be sufficient to maintain normocapnea.[24]

Therefore, superimposed high frequency jet ventilation (SHFJV), a combination of a high (f_{HF}) and a normal frequency (f_{NF}) component for jet ventilation has been proposed to improve CO_2 elimination.[25,26]

SHFJV can be pictured as a sort of "bi-level jet ventilation", where the high frequency component creates a lower airway pressure level (PEEP) and the normal frequency component intermittently lifts airway pressure to a higher level, thereby creating a relatively large tidal volume (*Figure 2*). Common frequency ranges are 12-20 min^{-1} for f_{NF} and 400-600 min^{-1} for f_{HF}.[27,28]

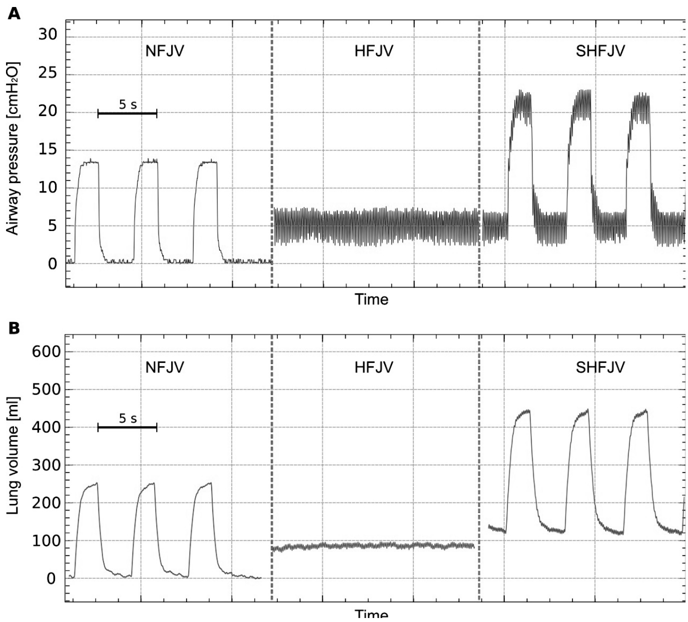


Figure 2. SHFJV and its frequency components. Panel A shows airway pressure, panel B is the resulting lung volume.

SHFJV is a safe and effective mode of ventilation for laryngotracheal surgery[29,30] and may even have a potential use in the intensive care setting.[31] Despite a relatively wide range of applicable f_{HF} from 180 – 900 min^{-1},[32] little is known about the effect of different f_{HF} or when to use which of these frequencies. Further, in spite of its obvious advantages, there is a lack of studies directly comparing SHFJV with other single frequency modes of JV that are used in clinical practice. Both the latter two issues will be addressed in this thesis.

Technical Background

Jet ventilation is, unlike other ventilation, applied in a respiratory system that is completely open to the surrounding atmosphere. One of its characteristics is that upon jet injection, entrainment of the surrounding air occurs, which makes the measurement or prediction of the delivered volumes difficult.

When applied with frequencies >60 min^{-1}, additional gas-mixing effects occur that challenge our understanding of ventilation.

The following sections give an overview of physical aspects of JV, the underlying gas transport mechanisms of high frequency ventilation (HFV), routes of JV application and their features as well as techniques that can be used to measure volume changes during jet ventilation.

Important physical aspects

To understand the **working principle** of jet injection, it is convenient to draw an analogy to jet pumping. Technically, a jet pump is an arrangement of an injector (injecting a motive fluid, *i.e.* the oxygen-air jet) and a diffuser that allows for suction and transport of the fluid that is to be pumped (*Figure 3*).

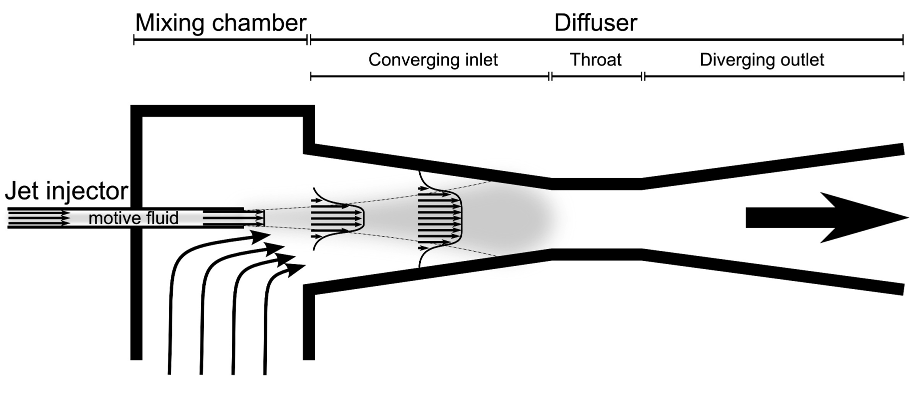


Figure 3. Schematic drawing of a technical jet pump.

In a technical jet pump, the diffuser usually is in the shape of a Venturi tube, *i.e.* has a narrow section (throat), in order to minimize the loss of kinetic energy, *i.e.* jet velocity, with increasing distance from the injector nozzle.

The suction phenomena seen in jet pumps are caused by air entrainment that occurs solely as a consequence of friction and shear forces between the fast jet stream and the stationary ambient air, not by a Venturi effect.[33]

In jet ventilation, the injector is the jet nozzle and the diffuser is either a rigid endoscope or the trachea, depending on the position of the injector. Like in a technical jet pump, friction and shear forces between the moving jet and the surrounding stationary air are the cause of entrainment.[34]

Jet **"pumping" efficiency**, *i.e.* the ability to entrain air, depends on a variety of factors. Injected gas velocity, diameter and position of the jet in relation to the diffuser,[35] as well as the cross sectional shape of the diffuser[36] and the position of the injector relative to the vocal cords[14,37,38] have been shown to influence the amount of entrainment and, successively, the airway pressure achieved by JV. Further, during **laryngoscopy** (*Figure 4*), the amount of entrainment and the airway pressure achieved by jet ventilation is dependent on a proper alignment of the endoscope in line with the trachea and tightly against the larynx.[10,14]

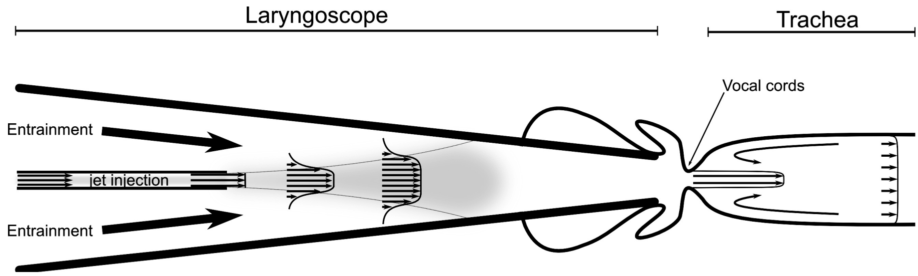


Figure 4. Entrainment situation during supraglottic JV through a laryngoscope (from Baer,[39] modified).

In the **bronchoscopic** setting, assuming a constant driving pressure, all of the above named influencing factors are held constant and thus, entrainment and the resulting airway pressure achieved by jet ventilation are predictable. For instance, the Sanders injector on a specific bronchoscope generates a peak airway pressure of around 25 cmH_2O.[40] Inflation of the lung will occur to the point that is limited by its compliance and the injected air will escape at proximal end of the endoscope.[41]

The situation is different when jet ventilation is applied **transtracheally** or when using **translaryngeal catheters** (*Figure 5*). Entrainment will occur to a lower extent and does not exert the same influence on airway pressure as in the endoscope setting.[37,42] Furthermore, with the tip of a high pressure injector at the subglottic or even substenotic level, the airway pressure becomes vitally dependent on sufficient expiration and therefore, depends on the existence of a free upper airway.[13] In case of total upper airway obstruction, the injected air cannot escape through the glottis and the risk of barotrauma increases.[43]

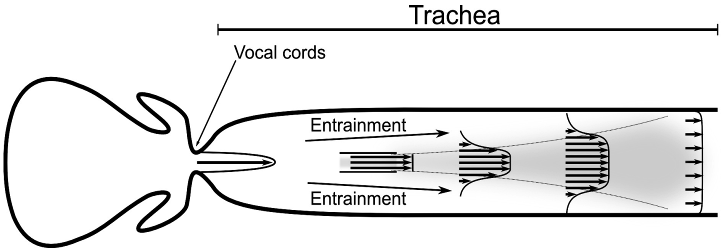


Figure 5. Entrainment situation for subglottic or transtracheal jet application (from Baer,[39] modified).

Routes of application of jet ventilation

Depending on the surgical procedure, different approaches to the airway can be chosen to apply jet ventilation.

Supraglottic jet ventilation

Supraglottic jet ventilation, *e.g.* by jet injection into a Kleinsasser laryngoscope, provides a large amount of entrainment because of the relatively proximal injection of the jet (*Figure 6*). It provides superior view of the operating field and a high level of laser safety, as there are no potentially flammable catheters in the airway.[44,45] In supraglottic jet ventilation, there is often a sufficiently long distance between the injector and a potential stenotic area and thus, the risk of barotrauma is relatively low.[38] Even though supraglottic JV "blows" into the operation field, aspiration of blood is prevented by supraglottic SHFJV.[46]

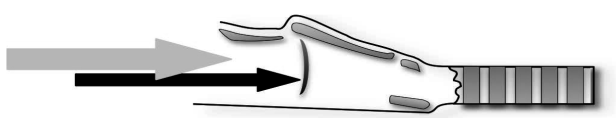


Figure 6. Schematic drawing of supraglottic JV. The black arrow shows the jet injection, the grey arrow illustrates entrainment.

Its drawbacks are that the amount of entrainment and the achieved lung ventilation depend on a proper alignment of the laryngoscope in line with the tracheal axis and tightly against the glottis.[14] Intrapulmonary air trapping may occur due to obstruction when surgical instruments are introduced.[43]

Although per definition not applied supraglottically, JV through a bronchoscope resembles ventilation through a laryngoscope. However, as a consequence of a more distal injector position and a narrower diffuser tube than in

a laryngoscope, the entrainment fraction is likely to be less than in true supraglottic JV.

Subglottic translaryngeal jet ventilation

Subglottic translaryngeal JV using a ventilation catheter is a method the anesthetist may be more familiar with (*Figure 7*). Upon induction of anesthesia, the trachea is orally or nasally intubated with a narrow, uncuffed jet ventilation catheter[47,48] and jet ventilation can immediately be instituted independently of the surgeon. Jet air is injected at the tip of the catheter that is positioned below the glottis. In this position, the air entrainment fraction is low.[49,50] With sufficiently high frequency, subglottic JV should prevent aspiration,[20] but when blood or debris enter the entrainment zone near the tip of the catheter, aspiration may still occur.[46]

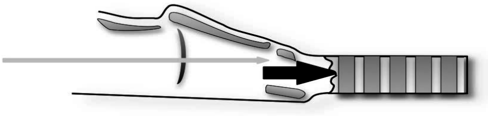


Figure 7. Subglottic translaryngeal jet ventilation. The black arrow indicates where the jet is injected, the grey arrow shows entrainment.

During translaryngeal subglottic JV, expiration is highly dependent on a free outward passage. A reduced airway diameter may be further obstructed by the catheter itself or by surgical instruments, limiting expiration and increasing the risk of barotrauma.[42,43]

Potential disadvantages of catheter-borne subglottic jet ventilation are the possible impairment of the access to the operation field and the presence of flammable[44] or, at least, meltable[48] material when laser is used during surgery.

Transtracheal jet ventilation

Like subglottic translaryngeal JV, transtracheal jet ventilation has its injection site below the vocal cords (*Figure 8*). It provides superior access to the operation field and a high degree of laser safety, as there are no catheters interfering with the surgical procedure. Unlike any other jet ventilation access to the airway, a transtracheal needle puncture can be performed to secure a difficult airway prior to induction of anesthesia. Further, it has the potential of leaving the catheter in place in case the patient needs respiratory support.[51]

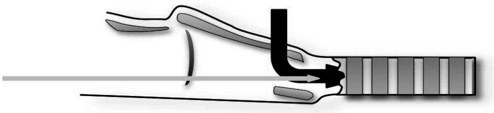


Figure 8. Transtracheal jet ventilation. Black arrow indicates the direction of the jet injection, grey arrow is entrainment.

Although there is a potential high risk of pressure-related complications when the upper airway is obstructed, safe use of transtracheal jet ventilation as been reported for both unobstructed[52,53] and obstructed upper airways.[54] In a recent audit in the UK, transtracheal JV was not associated with a higher complication risk than other routes of JV.[55]

Mechanisms of gas exchange

During jet ventilation with high frequencies, ultrafast gas transport and mixing phenomena, which are of minor importance during normofrequent ventilation, gain importance. Dead space ventilation during high frequency ventilation (HFV) decreases with increasing frequency[56]. Therefore, ventilation with tidal volumes lower than anatomical dead space is possible and direct alveolar ventilation can occur[57]. Gas exchange seems to be well correlated with minute ventilation, not however with tidal volume or ventilation frequency alone.[56,58]

There are several mechanisms that can explain gas transport and -mixing during HFV[59] and not all of them act synergistically to improve gas exchange. The following section gives a short overview of current the explanatory models for gas transport during JV.

Direct alveolar ventilation by bulk convection

Breathing gas directly passes to the alveoli as a consequence of a pressure gradient between the airway opening and the alveoli (*Figure 9*). With the low tidal volumes during HFV, this effect is most likely to occur in central regions of the lung with short distances to the conducting airways.

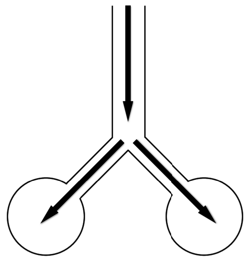


Figure 9. Direct alveolar ventilation.

Out of phase ventilation ("Pendelluft")

The lung consists of bronchoalveolar units with different time constants because of regional compliance and resistance differences. As a consequence, units with a low time constant will fill and empty faster and thus, air will be shifted between fast and slow units at the end of inspiration and at the end of expiration[57,60]. At the end of inspiration, the fast unit will equilibrate pressure with the slow unit and thereby inflate it (*Figure 10*, A). In the presence of a PEEP at end-expiration (*Figure 10*, B), the slowly emptying unit will equilibrate pressure with a faster unit and inflate it.

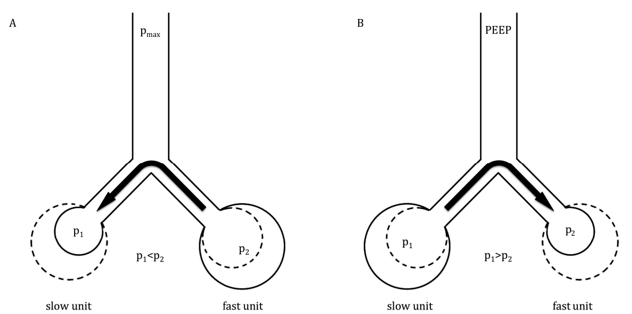


Figure 10. The "Pendelluft" principle.

Convective dispersion

Due to asymmetric velocity profiles[61-63], both at different regions within the tracheobronchial tree and also between inspiration and expiration, the breathing gas mixture disperses by convection. A simplified quantitative explanation is given in *Figure 11* (adapted from Chang *et al.*).[59] To illustrate the effect, the grey area depicts a bolus of a non-diffusible tracer gas (*Figure*

11.1). Inspiration starts with a laminar velocity profile, indicated from the left (*Figure 11*.2). As a result, the gas bolus will be deformed, with the central region travelling further than the periphery. Then, expiration starts with a more turbulent velocity profile, as depicted by the arrows from the right (*Figure 11*.3). The gas bolus will be moved outwards, but as the turbulent flow profile is almost flat, both the central and the peripheral region of the bolus will be moved to practically the same extent. At the end of a complete respiratory cycle, there is a net inward flow in the centre and a net outward flow in the periphery (*Figure 11*.4).

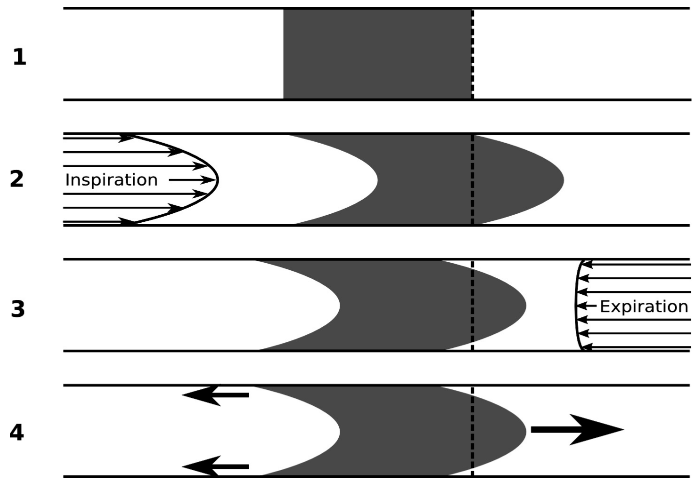


Figure 11. Convective dispersion.

Taylor type dispersion

In *Figure 11*, we assumed that the observed gas bolus was non-diffusible. This is not the case in reality as diffusion effects occur along concentration gradients. Taylor type dispersion takes radial diffusion of moving gas particles into account and describes their behavior:

In the centre of the parabolic flow profile, gas particles travel faster than in the periphery (*Figure 11*.2). With increasing travel distance, a concentration gradient between the centre and the periphery of the flow profile occurs. When a central gas molecule diffuses towards the wall, it enters a zone with lower travel speed and will subsequently be slowed down. A smaller fraction of tracer gas continues to travel along the tube and a “spike” of tracer gas is formed. Even though it may contribute to “smear out” the concentration gradient between fresh gas in the centre and exhaled gas in the periphery, Taylor type laminar dispersion seems to have little impact on gas transport in the conducting airways.[64]

Molecular diffusion

Molecular diffusion of oxygen and carbon dioxide between the alveolar gas and the blood occurs at the alveolo-capillary barrier. High frequency ventilation is thought to enhance molecular diffusion by a factor of 10^3 but this effect has not been proved scientifically so far.

Aims of the Doctoral Thesis

In this doctoral thesis, we sought

To investigate whether superimposed high frequency jet ventilation would result in better gas exchange by providing higher lung volume changes compared with single frequency jet ventilation techniques in lung-healthy individuals (*study I*).

To systematically compare superimposed high frequency jet ventilation with single frequency jet ventilation in relation to variable high frequency. We further sought to mathematically describe the frequency dependence of lung volume and gas exchange parameters during single frequency jet ventilation and superimposed high frequency jet ventilation in unobstructed airways (*study II*) as well as in the presence of severe tracheal obstruction (*study III*).

To find a mathematical model for the prediction of the behavior of lung volume, gas exchange and airway pressures during superimposed high frequency jet ventilation in relation to varying degrees of tracheal obstruction and variable high frequency (*study IV*).

Materials and Methods

Study subjects

The studies were conducted in accordance with the Helsinki declaration (*study I*) and the Helsinki convention for the use and care of animals (*study II-IV*). After thorough review, the local ethics committee approved the studies (Uppsala Human Ethical Review Board for *study I*, Uppsala Ethics Committee on Animal Experiments for *studies II-IV*).

Study I

Healthy patients scheduled to undergo surgery for minor airway obstruction meeting the following criteria were included in the study: ASA class < III, BMI < 35 kg · m^{-2}, absence of obstructive pulmonary disease (asthma, COPD) and absence of symptomatic airway stenosis.

Study II-IV

In *study II-IV*, a total of 20 healthy Swedish mixed country breed pigs of both sexes were included. The animals were around three months of age and were kept fasting but with free access to water the night before the experiment. The weight range of the animals was 23-27 kg (n=10) for *study II* and 25-32 kg (n=10) for *study III* and *IV*. For the protocols of *study III* and *IV*, the same animals were utilized.

Subject preparation

Study I

All study subjects received PO premedication with midazolam and paracetamol. Anesthesia was started and maintained IV using propofol and remifentanil. Rocuronium bromide was administered after induction and the trachea was intubated with a LaserJet® catheter (Acutronic Medical Systems AG, Hirzel, Switzerland). Repeated maintenance doses of rocuronium bromide were administered when necessary.

After induction, all subjects received an arterial line in the radial artery for the purpose of blood gas analysis. Infraglottic HFJV via the LaserJet® catheter was commenced (frequency 150 min^{-1}, I/E=0.43, driving pressure

adjusted to achieve normocarbia, delivered by an AMS1000® ventilator, Acutronic medical systems AG, Hirzel, Switzerland).

A Jet-Laryngoscope® (Carl Reiner GmbH, Vienna, Austria) was inserted and properly aligned by the ENT surgeon, and subsequently used for the application of supraglottic JV (Twinstream® ventilator, Carl Reiner GmbH, Vienna, Austria).

A catheter (Secalon Seldy™, BD Medical Surgical Systems, Stockholm, Sweden) was inserted into the trachea to about 1 cm above the carina in order to obtain airway pressure and the pressure signal was acquired using a RCEM250DU pressure transducer (Sensortechnics, Puchheim, Germany).

Study II-IV

On arrival at the laboratory, the animal was premedicated by IM injections of xylazine, tiletamine and zolazepam. After ~10 minutes, the animal was placed supine on an operating table, an ear vein was cannulated and a bolus of fentanyl was administered. Subsequently, the animal's trachea was intubated with a 8.0 mm ID endotracheal tube (HiContour™, Mallinckrodt Medical, Athlone, Ireland) and general anesthesia was started by IV infusion of a buffered glucose solution containing pentobarbital and morphine. Adequate anesthetic effect was ascertained by the absence of response (withdrawal reactions, increase in heart rate) to painful stimulation between the front toes and subsequently, neuromuscular block was established with IV pancuronium. Volume controlled ventilation with V_T of 10 ml · kg^{-1} was started (Servo-I, Maquet, Sweden) and the respiratory rate was adapted to achieve normocarbia.

The neck vessels of the animal were prepared and an arterial catheter for blood pressure monitoring and blood gas analysis was inserted into the left carotid artery.

Monitoring according to the standards of our laboratory was established and maintained throughout the experiments.

Definitive airway access was established by surgical tracheostomy and exchange of the oral endotracheal tube with another 8.0 mm ID ETT (*study II*). For *studies III-IV*, the oral ETT was kept in place and the tracheostomy served as an access to the trachea for the insertion of stents in order to create tracheal obstruction.

At completion of the experiment, the animal was euthanized by IV injection of potassium chloride under deep anesthesia.

Study design

All four studies were in crossover design: All interventions were performed in every subject. In order to preclude possible influence of preceding interventions on the outcome variables, the order of interventions was randomized using a computer-generated method (Excel, Microsoft Co., Redmond, WA, USA). *Table 1* gives an overview of the randomizations performed in each study.

Table 1. Overview of randomized interventions per study.

Study	**Randomized intervention**
Study I	Mode of JV
Study II	Frequency/f_{HF}
Study III	Frequency/f_{HF}
Study IV	Stent ID Frequency/f_{HF}

Experimental interventions

Study I

All interventions were performed before the start of surgery. Four different modalities of JV (*Table 2*) were applied in all patients in a previously determined, randomized order. At each transition, intratracheal suctioning was performed with low pressure in order to normalize lung volume history. *Figure 12* gives a schematic overview of the study protocol.

Table 2. Jet ventilation modalities and their ventilator settings used in study I. Index 'SG' indicates supraglottic ventilation that was applied through a jet laryngoscope with a Twinstream® ventilator, index 'IG' is for infraglottic (subglottic) ventilation with a LaserJet® catheter and an AMS1000® ventilator.

Mode	**f_{NF}** [min^{-1}]	**I/E**	**WP** [bar]	**f_{HF}** [min^{-1}]	**I/E**	**WP** [bar]
$SHFJV_{SG}$	12	1	0.7 - 1.7	600	1	0.6 - 1.1
$NFJV_{SG}$	12	1	0.7 - 1.7	-	-	-
$HFJV_{SG}$	-	-	-	150	1	0.6 - 1.1
$HFJV_{IG}$	-	-	-	150	0.43	1.5 - 2.5

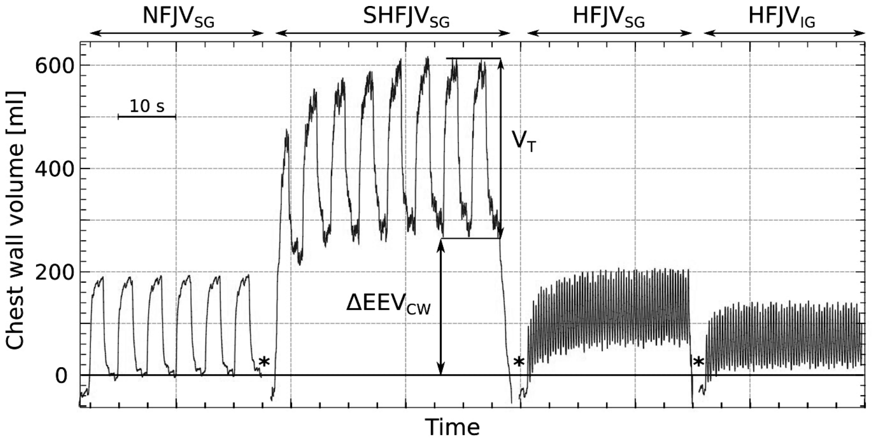


Figure 12. Schematic overview of the ventilation modes used in study I. At each mode transition, intratracheal suction was applied for ~5s (*). A zero reference volume (approximation of apneic FRC) was defined as EEV_{CW} during $NFJV_{SG}$. Changes in end expiratory chest wall volume (ΔEEV_{CW}) are volume increase above zero reference. Tidal volume was defined as the greatest cyclic change in chest wall volume.

Study II

In *study II*, the effect of different frequencies on SHFJV (f_{HF} component) and HFJV efficacy was compared using a Twinstream® jet ventilator.

All animals were alternately ventilated 5 minutes with SHFJV and HFJV with a pre-defined random order of frequencies ranging from 100 - 1000 min^{-1} (*Table 3*). For technical reasons, each pair of SHFJV-HFJV was preceded by a period of NFJV that allowed for the definition of a volume level that approximated apneic FRC. At each transition, the animal was disconnected from the ventilator for ~5 s in order to normalize lung volume history (*Figure 13*).

Table 3. Ventilation mode and ventilator settings for SHFJV and HFJV in study II.

Mode	f_{NF} [min^{-1}]	I/E	WP [bar]	f_{HF} [min^{-1}]	I/E	WP [bar]
SHFJV	16	1	1.6	100 - 1000	1	0.8
HFJV	-	-	-	100 - 1000	1	0.8

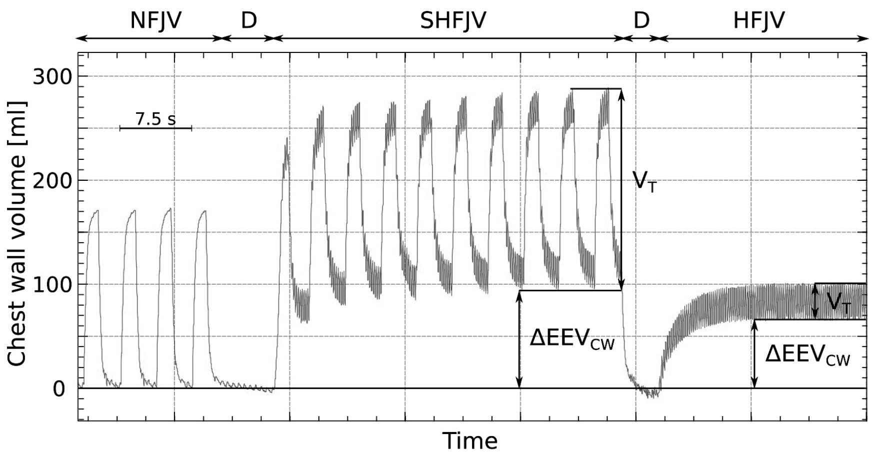


Figure 13. Schematic overview of the sequence of JV modes that were applied for each frequency: NFJV always preceded SHFJV and HFJV and was used to define the zero reference value for EEV_{CW} (approximately apneic FRC). Between each step, the animal was disconnected (marked with D) from the ventilator). Changes in end expiratory chest wall volume (ΔEEV_{CW}) for SHFJV and HFJV are related to the zero reference. Tidal volume was defined as the largest cyclic change in chest wall volume.

Study III and IV

S*tudy III* and *IV* investigate the influence of airway obstruction on the efficacy of JV.

In *study III*, a fixed degree of severe airway obstruction was used (stent with 4 mm ID) and the animals were alternately ventilated with SHFJV and HFJV. For both modes, a set of different frequencies ranging from 50 min^{-1} to 600 min^{-1} was used in a pre-defined random order.

The effect of varying cross-sectional airway diameter on the efficacy of SHFJV was investigated in *study IV*. Stents with inner diameters ranging from 2 – 8 mm were inserted into the animal's trachea in random order and the animal was ventilated with SHFJV. For each stent ID, a set of different frequencies for the f_{HF} component between 50 and 600 min^{-1} was used in a pre-defined random order, while f_{NF} was kept constant at 16 min^{-1} (*Table 4*).

Table 4. Ventilation mode and ventilator settings for SHFJV (study III and IV) and HFJV (study III only).

Mode	**f_{NF} [min^{-1}]**	**I/E**	**WP [bar]**	**f_{HF} [min^{-1}]**	**I/E**	**WP [bar]**
SHFJV	16	1	1.6	50 - 600	1	0.8
HFJV (*study III* only)	-	-	-	50 - 600	1	0.8

A new model of tracheal obstruction

For *studies III-IV*, a new experimental model for the establishment of tracheal obstruction was developed. A tracheostomy was performed that served as an access to the trachea for the insertion of stents in order to create tracheal obstruction. The oral ETT was kept in place and its cuff served as an airtight seal when inflated flush with the tracheostomy stoma. For stent exchange, the ETT was uncuffed and withdrawn to expose the tracheal access. *Figure 14* shows the tracheostomy situs and the obstructive stents used in *study III* and *IV*. *Figure 15* gives an overview of stent resistance at various flow rates.

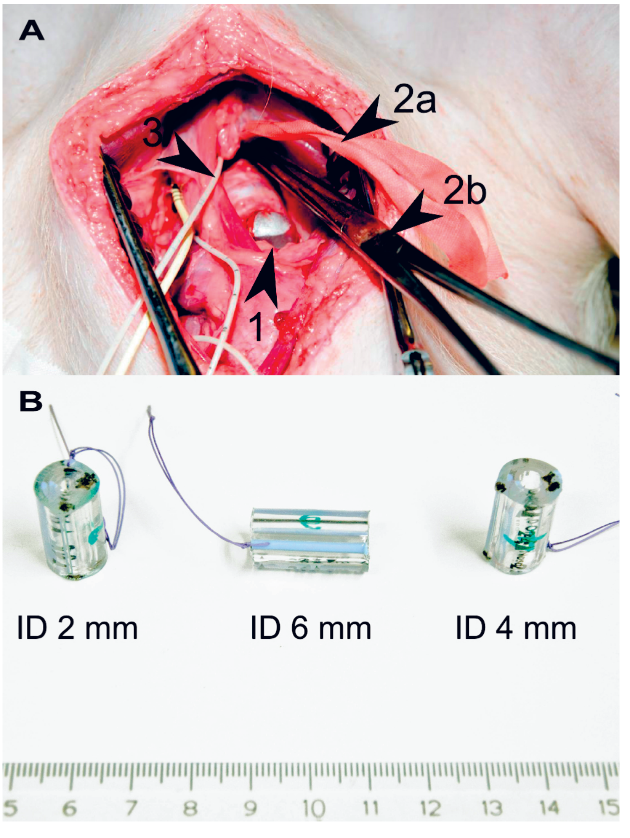


Figure 14. Tracheostomy situs (A) with the tracheostomy stoma (1), a cotton band (2a) that was tightened with a clamp (2b) in order to prevent airflow alongside the stent and the distal pressure monitoring catheter (3) are shown. Unmarked catheters are the central venous catheter, the pulmonary artery catheter and the arterial line. Panel B shows three of the obstructive stents used (2, 4 and 6 mm ID, length 2 cm, outer diameter 10.8 mm).

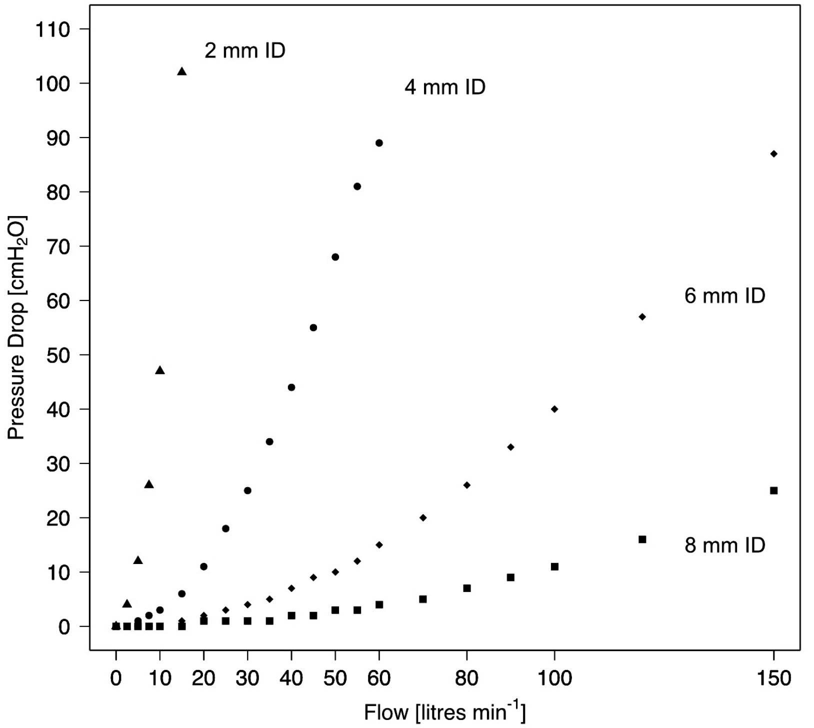


Figure 15. Resistance characteristics of the obstructive stents used in study III and IV. Flow was held constant at the respective level and the resulting pressure drop was measured against atmospheric pressure.

Measurement of outcome variables

Chest wall volume

As mentioned previously, jet ventilation is applied in an open respiratory system that makes the use of pneumotachographs or inert gas methods for the assessment of lung volume changes cumbersome. In this thesis, we used opto-electronic plethysmography (OEP) to measure lung volume changes during jet ventilation.

Opto-electronic plethysmography is a noninvasive motion analysis technique developed for the assessment of chest wall volume changes.[65,66] It has been tested in a variety of conditions – both spontaneous breathing and mechanical ventilation[67-70] – and chest wall volume measured by OEP correlates well with lung volume[68,71].

An OEP System® (BTS Bioengineering, Milan, Italy) consisting of six infrared cameras was used to acquire the position and movement of an array of reflective markers on the animal's chest wall. *Figure 16* illustrates the steps needed to derive chest wall volume from a subject with OEP (step1). In brief, OEP registers the position of each reflective marker in a three-dimensional coordinate system over time (step 2). By triangulation of the markers (using the model in step 3), a closed surface is obtained (step 4) and the divergence theorem is used to calculate the volume enclosed by it. The obtained volume represents total chest wall volume (V_{CW}, step 5).

The human supine model in *study I* consisted of 52 markers, the porcine supine model in *study II – IV* used 57 markers. Using an acquisition rate of 60 Hz, the sampling rate of the system is high enough for a lossless registration of the fast movements during high frequency ventilation.[72] Furthermore, with a percentage error of 0.17% for chest wall volume, the spatial resolution of the OEP system is high enough to accurately measure volume changes <10 ml.[71]

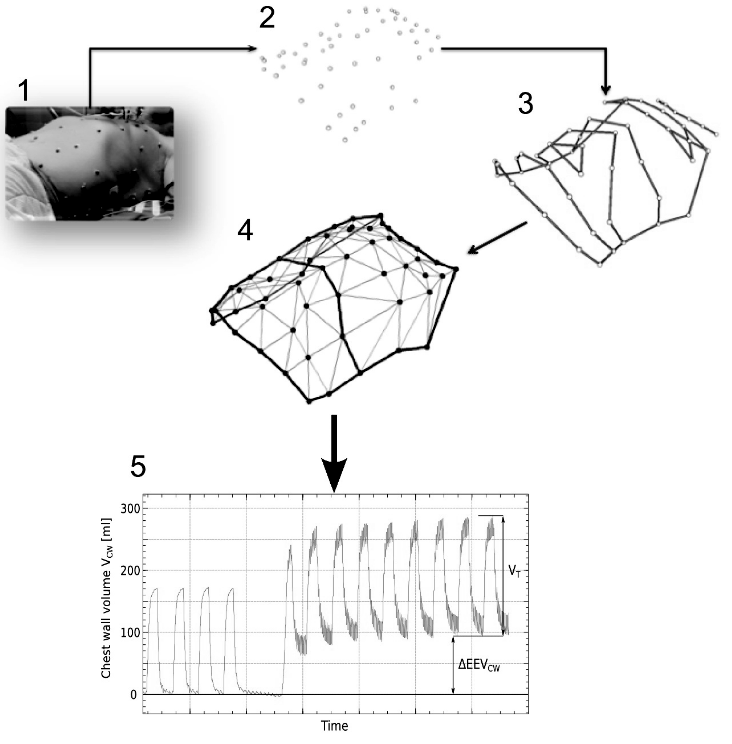


Figure 16. Steps for the measurement of volume by OEP.

Airway pressure

In all four studies, airway pressure was measured using an analogue pressure transducer (RCEM250DU, Sensortechnics GmbH, Puchheim, Germany) and an air-filled 16G Secalon™ Seldy catheter (BD Medical Surgical Systems, Stockholm, Sweden) with its tip at the target site. The pressure signal was digitalized at a sampling rate of 240 Hz and recorded continuously and was synchronized with the OEP measurements by the OEP Capture® software (BTS Bioengineering, Milan, Italy).

In *study I*, airway pressure was measured ~1 cm above the *Carina tracheae* with the pressure measurement catheter inserted transglottically. Correct catheter position was verified by flexible endoscopy.

Airway pressure in *study II* was measured at the tip of the endotracheal tube with the pressure measurement catheter inside the tube lumen.

In addition to the measurement at the tube tip as in *study II*, intrapulmonary[a] pressure downstream of the stent was registered in *study III* and *IV*. The corresponding catheter was inserted into the distal trachea with the Seldinger technique and the quality of the signal was checked with the widest stent (8 mm ID) in place. In case of difficulties with the signal acquisition, the correct position of the catheter tip distal of the stent was verified by flexible bronchoscopy.

Gas exchange

In all four studies, we obtained p_aO_2 and p_aCO_2 by intermittent arterial blood gas analysis. In *study I*, we used the i-STAT® system (Abbott Point of Care Inc., Maidenhead, UK) for sample analysis, in *study II – IV*, a stationary blood gas analyzer was used (ABL 500, Radiometer, Copenhagen, Denmark).

Compliance

In *study II – IV*, the length of the experiments made it necessary to ensure that there were no changes in lung compliance over time. Therefore, we assessed static lung compliance in each animal in the beginning and at the end of the experiment. In brief, an incremental-decremental PEEP maneuver was performed. The animals were ventilated in pressure control mode with a driving pressure of 10 cmH_2O at a low respiratory rate. Starting at zero (ZEEP), PEEP was increased by 2 cmH_2O every five breaths until a maximum of 20 cmH_2O and subsequently, PEEP was decreased to zero in the same manner.

[a] Although not measured at the alveolar level, the term "intrapulmonary pressure" is henceforth used synonymously with substenotic airway pressure.

Static compliance was then calculated from end expiratory chest wall volume and the corresponding end expiratory airway pressure at ZEEP and at PEEP=20 cmH_2O.

Statistical analysis

Study I

For normally distributed variables, parametric one-way repeated measures ANOVA was used to detect statistical differences between the JV modes. When a statistically significant difference was found, multiple comparisons between the groups were performed and *p* was adjusted for using Bonferronis method.

In case of non-normal distribution, a non-parametric repeated measures ANOVA on ranks was performed and the Tukey method was used to adjust *p* for multiple comparisons.

The influence of minute ventilation on CO_2 removal was determined by linear regression analysis.

All statistical computations in *study I* were performed using commercial software (SigmaStat®, Systat Software Inc., Chicago, IL, USA). Data are presented as mean (SD). Statistical significance was assumed for all $p<0.05$

Studies II – IV in common

In order to preclude the need for multiple comparisons, statistical analysis of the outcome variables was performed using linear mixed model analysis.

All statistical analyses and data processing were performed with R using the *nlme* package (R Foundation for Statistical Computing, Vienna, Austria). Random factor for all studies was pig ID and fixed factors in *study II – III* were JV mode (*Mode*), ventilation frequency (*Frequency*) and the interaction of mode and frequency (*Mode*Frequency*). Fixed factors in *study IV* were stent ID (*Obstruction*), ventilation frequency (*Frequency*) and the interaction between stent ID and frequency (*Obstruction*Frequency*). All $p<0.05$ were considered statistically significant.

Most of the outcome variables have previously been shown to express a nonlinear frequency or obstruction dependency[73], which made transformations necessary in order to fit the linear model to our data. Detailed information on the performed transformations is given in respective section.

Observed data are presented as follows: Untransformed data are arithmetic mean (95% CI), whereas all previously log transformed outcome observations are presented as geometric mean (95% CI).

The mixed model was used to analyze the properties of our observations; therefore, significant results should be interpreted as descriptive rather than confirmatory.

Study II and III specifics

The alternative hypothesis was that SHFJV would provide higher EEV_{CW}, V_T and better gas exchange compared with single frequency jet ventilation at the same frequency as used for f_{HF} during SHFJV.

In particular, the following transformations have been performed: In *study II*, V_T, p_aO_2 and p_aCO_2 were log transformed. For *study III*, log transformations of the outcome variable as well as frequency were performed for V_T, p_aO_2, p_aCO_2, intrapulmonary driving pressure and intrapulmonary PEEP.

Study IV specifics

The alternative hypothesis was that increasing airway obstruction would result in higher EEV_{CW} and p_aCO_2 as well as lower V_T and p_aO_2 in a frequency dependent fashion. Further, the hypothesis that increasing airway obstruction would lead to an increase in substenotic PEEP and a decrease in substenotic PIP was tested.

In particular, all observed outcomes except p_aO_2 and prestenotic PEEP were log-transformed. Log-transformation of stent ID was performed for all outcome variables except prestenotic PEEP (exponential transform of stent ID) and log transform of frequency was performed for all outcome variables.

Interpretation of the mixed model results

In the results section, mathematical functions *f(m,n)* (*study II* and *III*) or *f(ID,n)* (*study IV*) are presented where applicable.

In *study II* and *III*, the function is dependent on the mode of ventilation (*m,* with *m* being o for HFJV and 1 for SHFJV) and frequency (*n*, with n being the *n*-th increase of frequency by 100 min^{-1}, *e.g.* *n*=3 for a frequency of 300 min^{-1}).

In *study IV*, the function is dependent on stent ID (*ID*) and frequency (*n*, with n being the *n*-th increase of frequency by 100 min^{-1}, *e.g.* *n*=3 for a frequency of 300 min^{-1}).

The equations can be used to calculate the predicted value of an outcome variable for a given condition according to respective study.

Results

Study I: The role of jet ventilation mode in the absence of airway obstruction

End expiratory chest wall volume and PEEP

The highest increase of EEV_{CW} above apneic FRC was observed using $SHFJV_{SG}$ with ΔEEV_{CW} of at least 1.6 times greater than during any other investigated JV mode (*Figure 17*). Ventilation with any mode involving the use of frequencies above the normal range resulted in an increase of EEV_{CW} above apneic FRC. The observed changes in ΔEEV_{CW} were accompanied by corresponding changes in PEEP. The two latter finding were confirmed by the results of *study II* and *III*.

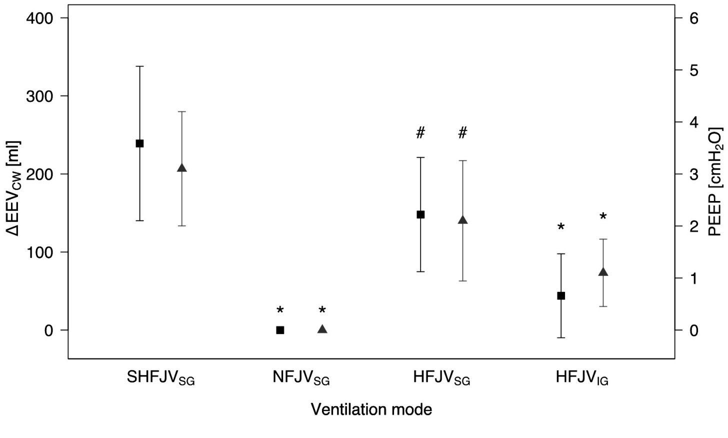


Figure 17. End expiratory chest wall volume (ΔEEV_{CW}, black squares, left y-axis) and PEEP (grey triangles, right y-axis) for the four investigated JV modes. Symbols are mean values, error bars are 95% CI.
*: significant difference compared with $SHFJV_{SG}$ ($p<0.05$)
#: significant difference compared with $NFJV_{SG}$ ($p<0.05$)

Tidal volume and driving pressure

Tidal volume was highest for the two modes involving a normal frequency, *i.e.* $SHFJV_{SG}$ and $NFJV_{SG}$ (*Figure 18*). For HFJV, tidal volume was at least 46% lower than during $SHFJV_{SG}$.

Likewise, driving pressure, *i.e.* pressure over PEEP, was highest during $SHFJV_{SG}$.

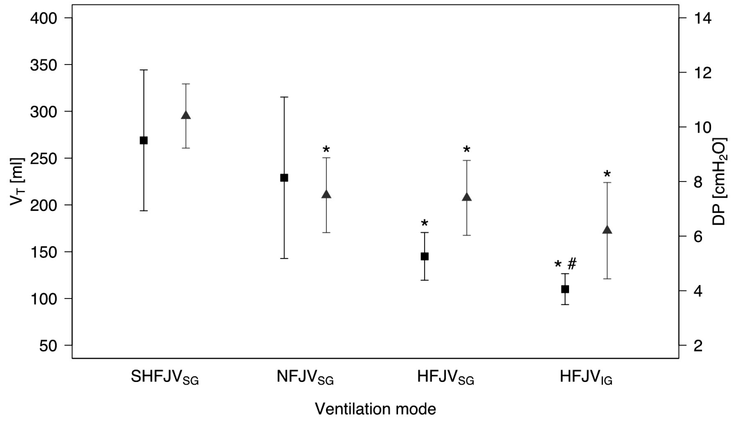


Figure 18. Mean and 95% CI for tidal volume (V_T, black squares, left y-axis) and driving pressure (DP, grey triangles, right y-axis) for the four investigated JV modes.
*: significant difference compared with $SHFJV_{SG}$ ($p<0.05$)
#: significant difference compared with $NFJV_{SG}$ ($p<0.05$)

Oxygenation and ventilation

All four modes of JV provided adequate oxygenation, however, CO_2 removal was significantly higher with the two HFJV modes. P_aCO_2 during $SHFJV_{SG}$ was ~30% higher than during $HFJV_{SG}$ (*Figure 19*).

Correspondingly, minute ventilation was lowest for the two modes involving a low frequency, *i.e.* SHFJV and NFJV, whereas it was at least 5 times higher during HFJV. There was a significant influence of minute ventilation on p_aCO_2, as detected by linear regression analysis ($p<0.01$, $r^2=0.35$).

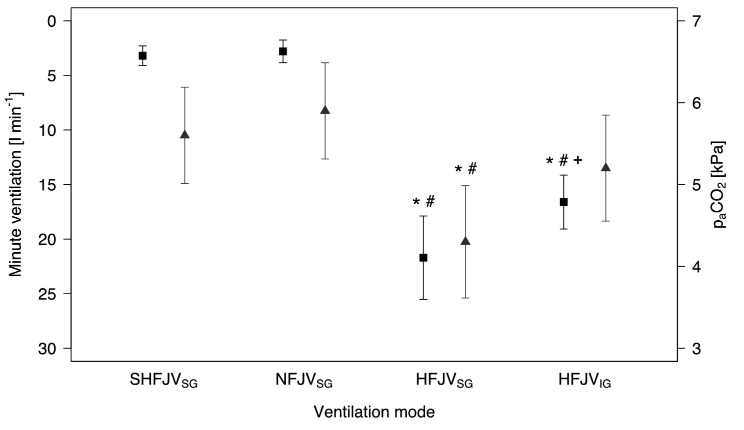


Figure 19. Mean and 95% CI for minute ventilation (black squares, left y-axis) and p_aCO_2 (grey triangles, right y-axis) for the four investigated JV modes.
*: significant difference compared with $SHFJV_{SG}$ ($p<0.05$)
#: significant difference compared with $NFJV_{SG}$ ($p<0.05$)
+: significant difference compared with $HFJV_{SG}$ ($p<0.05$)

Study II: The role of frequency during SHFJV and HFJV

No difference in compliance was observed before and after the experiments. Therefore, we assumed that the lung volumes measured during the course of the experiments were comparable for each condition.

Lung volumes

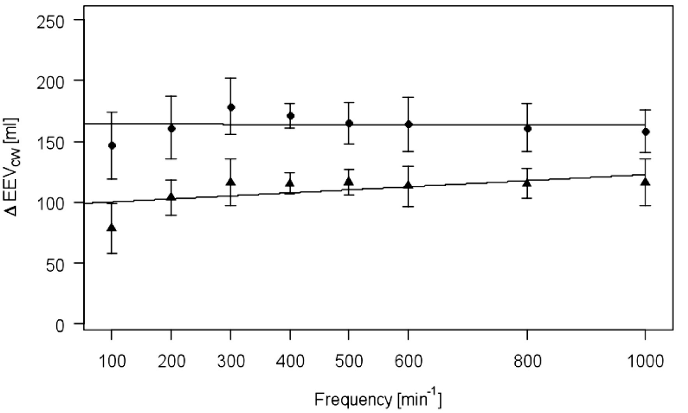
SHFJV provided the highest ΔEEV_{CW} throughout the investigated frequency range and there was no dependence of ΔEEV_{CW} on frequency.

During single frequency jet ventilation, ΔEEV_{CW} was up to 31 % lower than during SHFJV and ΔEEV_{CW} was found to increase slightly with increasing frequency.

Tidal volume during SHFJV was greatest for all investigated f_{HF}. Although a slight decrease of V_T was seen with increasing f_{HF}, V_T remained at clinically fully adequate levels even at the highest frequencies.

For single frequency JV, tidal volume was acceptable at low frequencies, but decreased markedly when frequency was increased. Negligible values of V_T were reached when frequencies >300 min^{-1} were used (*Figure 20*).

A



B

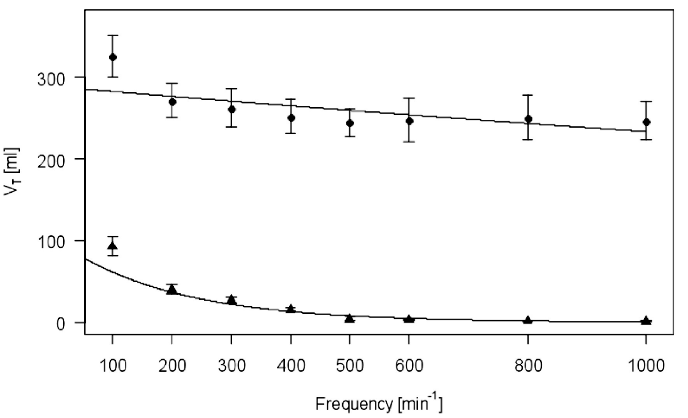


Figure 20. Mean values and 95% CI of ΔEEV_{CW} (A) and V_T (B). Observed values are illustrated as dots for SHFJV and triangles for single frequency JV. Lines are the mixed model prediction for the frequency dependence of the outcome variables.

Oxygenation and CO_2 Removal

Oxygenation during SHFJV was good with p_aO_2>32 kPa for all investigated f_{HF}. No alterations were observed with increasing frequency.

During single frequency JV, oxygenation was comparable to that of SHFJV at the lowest frequency of 100 min^{-1}, but increase of frequency resulted in a rapid and marked decrease in p_aO_2, reaching hypoxemic values at frequencies >300 min^{-1} (*Figure 21*).

Carbon dioxide removal was adequate with SHFJV throughout the f_{HF} range, with p_aCO_2 around 5.5 kPa. Increase of f_{HF} resulted in a marginal increase of p_aCO_2 within the normal interval.

Carbon dioxide removal during single frequency JV at the lowest frequency of 100 min^{-1} was comparable to that observed during SHFJV. Increase of frequency resulted in hypercapnea.

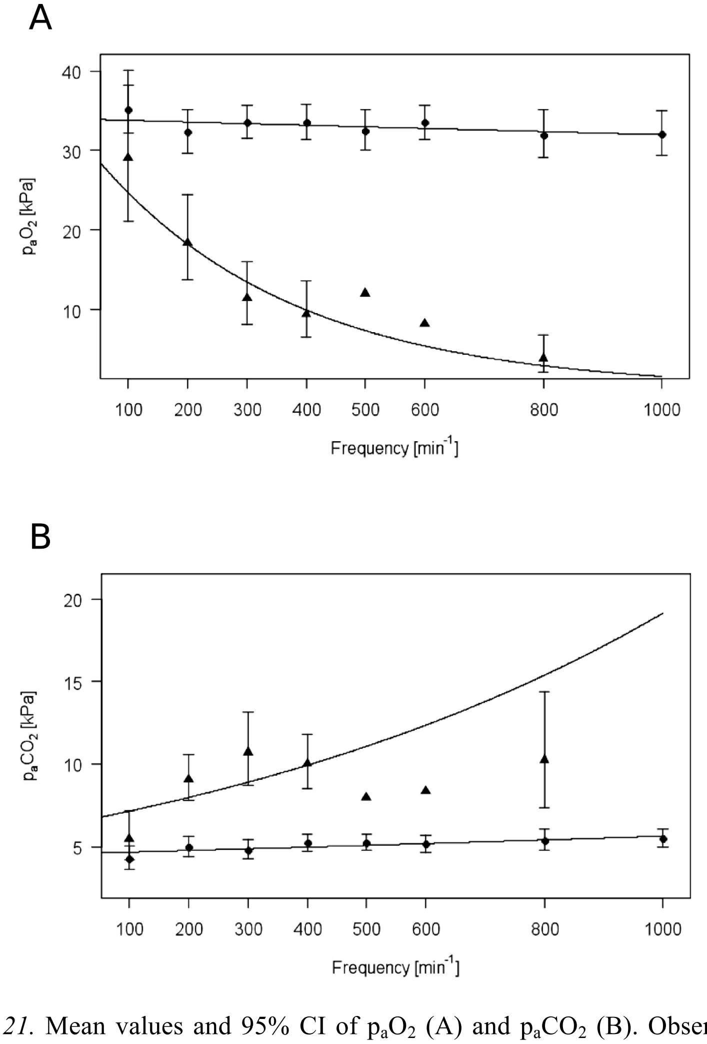


Figure 21. Mean values and 95% CI of p_aO_2 (A) and p_aCO_2 (B). Observed values are dots for SHFJV and triangles for single frequency JV. Lines are mixed model predictions.

Study III and *IV*: Jet ventilation in the stenotic airway

Study III compared SHFJV and single frequency JV at a fixed level of airway obstruction. In *study IV*, the impact of various levels of airway obstruction on ventilation parameters during SHFJV was investigated.

No difference in compliance was observed before and after the experiments. Therefore, we assumed that the lung volumes measured during the course of the experiments were comparable for each condition.

Lung volumes

Study III

During SHFJV, ΔEEV_{CW} was greatest and remained at levels of >165 ml for all frequencies. No significant influence of f_{HF} on ΔEEV_{CW} was detected (*Figure 22*A).

For single frequency JV, ΔEEV_{CW} was observed to be lowest at the lowest frequency of 50 min^{-1} and reached a plateau of around 95 ml at higher frequencies. This observation was not confirmed by the model prediction, which did not detect any influence of ventilation frequency on ΔEEV_{CW}.

Tidal volumes were highest and always greater than 213 ml with SHFJV for all investigated frequencies. However, a slight decrease of V_T with increasing f_{HF} was detected, with the greatest changes in the lower f_{HF} range (*Figure 22*B).

In analogy to *study II*, V_T during single frequency JV was at least ~70 % lower than during SHFJV. The highest V_T was observed at the lowest frequency of 50 min^{-1} and increase of frequency resulted in an even more rapid decrease of V_T to negligible values than seen in *study II*.

Study IV

A complex influence of stent ID and frequency as well as the interaction of both on ΔEEV_{CW} was found in *study IV* (*Figure 23*A).

At 6 and 8 mm stent ID, the smallest ΔEEV_{CW} were observed for all investigated f_{HF}, whereas ΔEEV_{CW} was highest with the 2 mm stent. The largest observed differences in ΔEEV_{CW} were ~220 ml.

Further, ΔEEV_{CW} was strongly influenced by frequency. For the two largest stent ID, ΔEEV_{CW} was lowest at f_{HF}=50 min^{-1} and increased with increasing f_{HF}, reaching at least ~50% higher values at f_{HF}=600 min^{-1}. At 2 mm stent ID, frequency dependence became inverted, with higher predicted ΔEEV_{CW} at low frequencies.

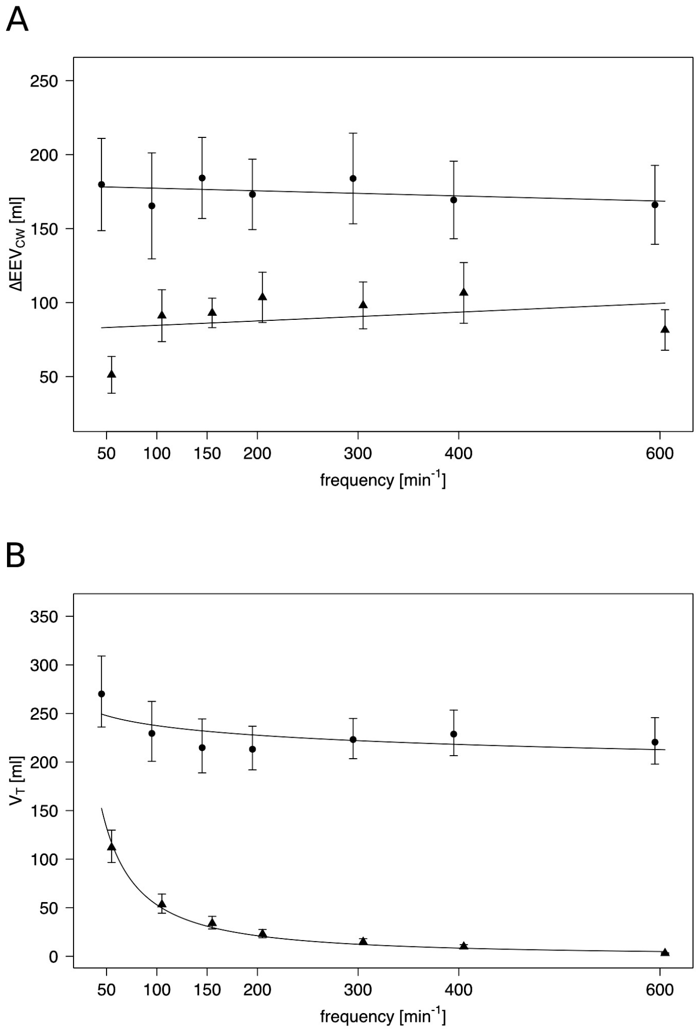


Figure 22. Mean and 95% CI for ΔEEV_{CW} (A) and V_T (B). Dots illustrate observations during SHFJV, triangles show single frequency JV. Lines are model predictions of the frequency dependence of respective outcome variable.

Tidal volume during SHFJV was influenced by stent ID and frequency as well as their interaction (*Figure 23*B).

Decrease of stent ID resulted in a marked decrease of V_T for all investigated frequencies. The observed decrease in V_T when changing stent ID from 8 mm to 2 mm was at least ~55 % and had a maximum of ~76 % at the lowest frequency.

A frequency dependence of V_T similar to that observed in *study II* was seen for the 8 mm ID stent. The highest V_T was observed at the lowest frequency and frequency alterations resulted in greater changes of V_T at the

lower frequency end than they did at high rates. With decreasing stent ID, V_T became less dependent on ventilation frequency.

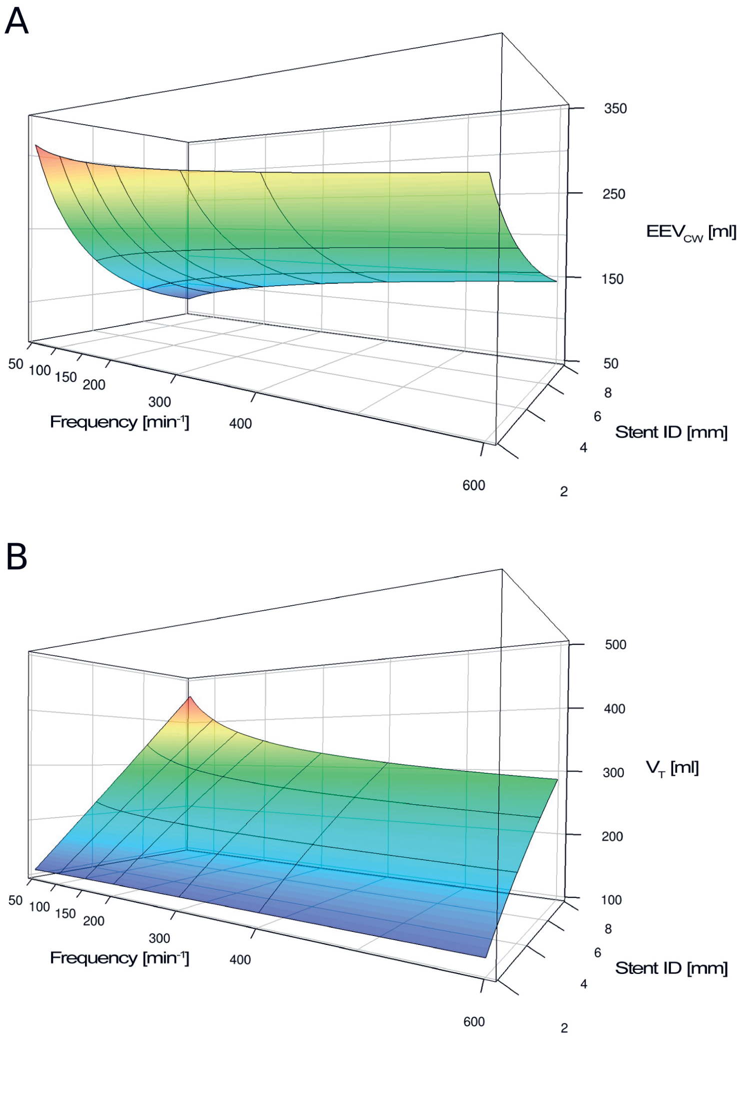


Figure 23. Mixed model predictions of the frequency and obstruction dependence of EEV_{CW} (A) and V_T (B).

Gas exchange

Study III

Good oxygenation with p_aO_2 of >30 kPa was observed for all frequencies during SHFJV. A slight decrease of p_aO_2 with increasing f_{HF} was detected, but it gained no clinical significance in the experimental setting.

During single frequency JV, a similar level of oxygenation was observed at a frequency of 50 min^{-1}, but p_aO_2 decreased rapidly when frequency was increased and resulted in hypoxemia at frequencies >150 min^{-1} (*Figure 24*A).

During SHFJV, slight hypercapnea with p_aCO_2 up to 6.8 kPa was observed for all investigated frequencies. There was a nonlinear dependence of p_aCO_2 on f_{HF}, with lower p_aCO_2 and larger frequency-induced alterations at the lower end of the f_{HF} range.

For single frequency JV, p_aCO_2 was also lowest for low frequencies, but increase of frequency resulted rapidly in severe hypercapnea with p_aCO_2>12 kPa. The influence of frequency on CO_2 removal was most pronounced in the low frequency range (*Figure 24*B).

Study IV

Oxygenation, *i.e.* p_aO_2, remained fairly constant at around 30 kPa for the stent IDs ranging from 4 – 8 mm. The observed values of p_aO_2 did not decrease gradually with decreasing stent ID, there was rather an abrupt drop of p_aO_2 of ~10 kPa when the 2 mm ID stent was in place. Despite these observations, the mixed model predicts a significant influence of stent ID on p_aO_2, gradually reducing oxygenation at a lower stent ID (*Figure 25*A).

Carbon dioxide removal during SHFJV was highly dependent on the stent ID. At the highest stent ID, the animals were normoventilated with all frequencies used for f_{HF}. Decrease of stent ID resulted in a gradual accumulation of CO_2 and resulted in severe hypercapnea with p_aCO_2<10.5 kPa with the 2 mm ID stent. The observed obstruction dependence of p_aCO_2 was confirmed by the mixed model analysis (*Figure 25*B).

There was also an influence of frequency on p_aCO_2, which was observed predominantly at the larger stent IDs. Here, p_aCO_2 was lower at the low frequency end and increased to a more stable plateau for higher rates.

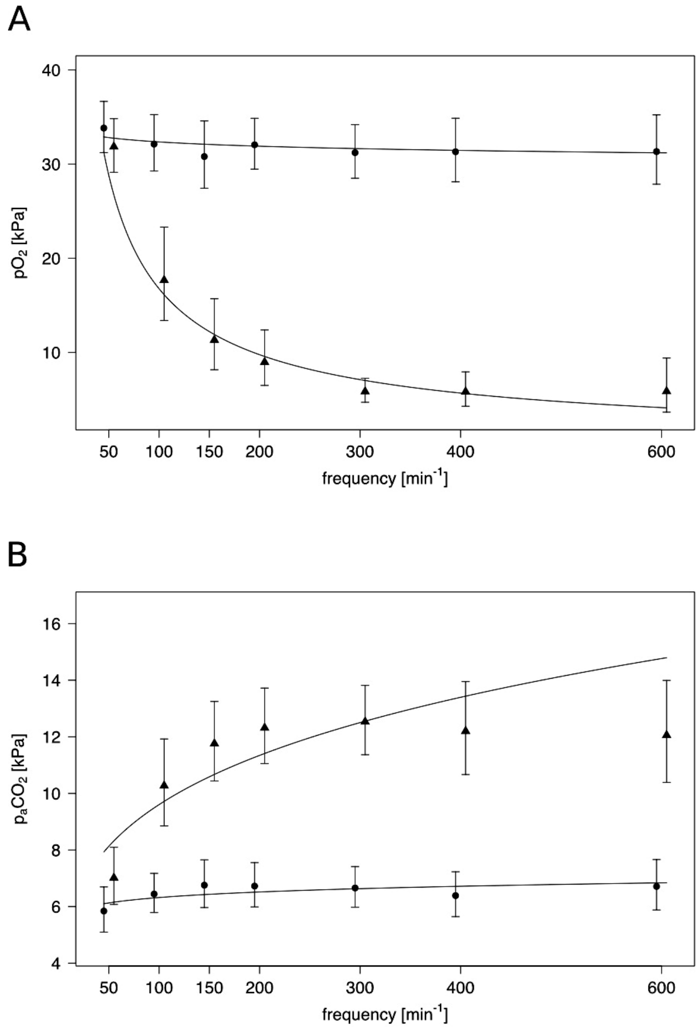


Figure 24. Mean and 95% CI for p_aO_2 (A) and p_aCO_2 (B). Dots illustrate observations with SHFJV, triangles show single frequency JV. Lines are model predictions of the frequency dependence of the outcome variable.

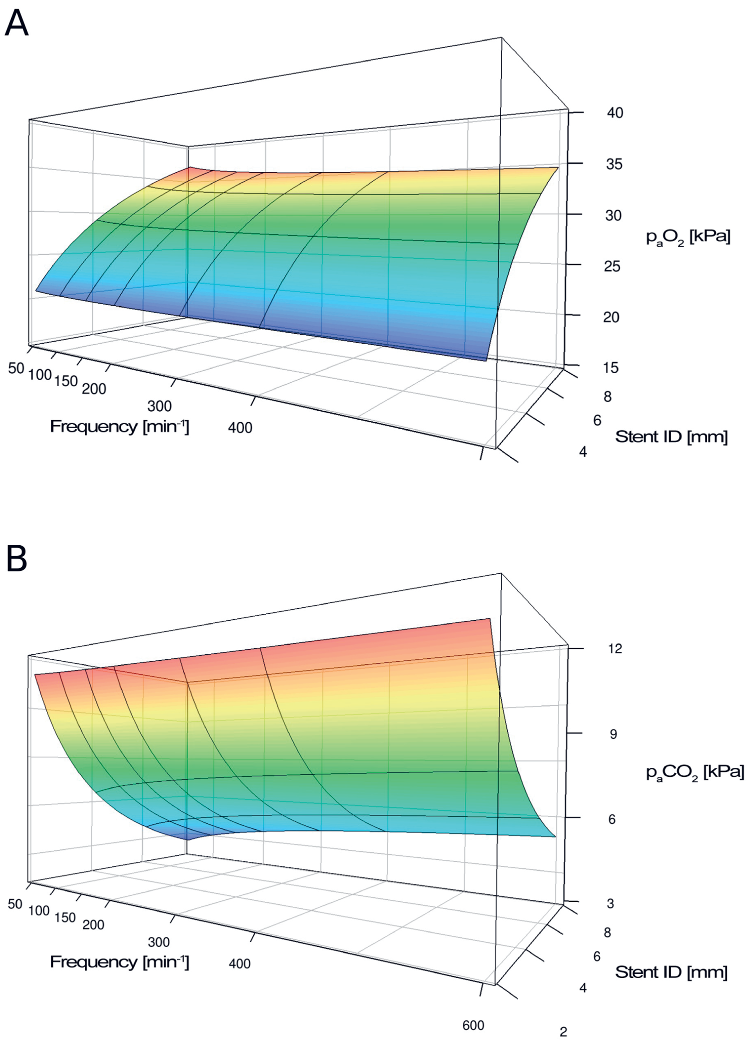


Figure 25. Mixed model prediction of the frequency and obstruction dependence of p_aO_2 (A) and p_aCO_2 (B).

Airway pressure: Intrapulmonary pressure

Study III

During SHFJV, intrapulmonary PEEP was greater than 4.1 cmH_2O for all investigated frequencies. There was a nonlinear increase of PEEP with increasing f_{HF}, with larger pressure alterations at the low f_{HF} end.

For single frequency JV, intrapulmonary PEEP at low frequencies was up to ~59% lower than during SHFJV. Intrapulmonary PEEP increased nonlinearly, reaching values comparable to those during SHFJV at the highest rates.

Intrapulmonary DP, *i.e.* pressure over PEEP, during SHFJV was at least ~twice as high as compared with HFJV and was always >11.7 cmH_2O for all frequencies. A nonlinear f_{HF} dependence of DP was detected with higher values and larger alterations of PIP in the low f_{HF} range.

With single frequency JV, intrapulmonary DP was highest with 7.0 cmH_2O at the lowest frequency. With increase of frequency, a more pronounced nonlinear decrease of DP was seen than during SHFJV, reaching values ~1 cmH_2O at the high frequency end.

Study IV

Intrapulmonary PEEP was found to depend strongly on stent ID and frequency as well as on their interaction.

At the larger stent IDs of 6 and 8 mm, PEEP was lowest and it increased nonlinearly up to ~3.2 times when the stent diameter was decreased to 2 mm.

There was also an influence of frequency on PEEP, which was most distinct for the larger stent IDs. The lowest PEEP value of 1.5 cmH_2O (stent ID 6 mm) was seen at the lowest frequency of f_{HF}, and increase of f_{HF} resulted in a logarithmic increase of PEEP.

Peak airway pressure, *i.e.* intrapulmonary PIP, depended strongly on stent ID, frequency as well as on the interaction of both.

Intrapulmonary PIP was highest for the 8 mm stent and it decreased gradually with smaller stent ID by at least ~23 % for the 2 mm stent.

The influence of f_{HF} on intrapulmonary PIP was most pronounced with larger stent IDs. At 8 mm stent ID, PIP was 23.1 cmH_2O at f_{HF}=50 min^{-1} and it decreased in a logarithmic manner by up to ~26 % for the highest f_{HF}.

At lower stent ID, intrapulmonary PIP was less dependent on frequency.

Airway pressure: Prestenotic pressure monitoring

Study III

Prestenotic PEEP above the obstructive stent was identical and practically negligible for both SHFJV and single frequency JV. There were no clinically significant alterations of PEEP within the range of applicable frequencies.

Prestenotic DP during SHFJV was at >19.3 cmH_2O for all investigated f_{HF}. There was a linear reduction of DP with increasing frequency, resulting in a 6 cmH_2O reduction of DP from the lowest to the highest investigated f_{HF}.

During single frequency JV, DP was ~12 cmH_2O lower than compared with SHFJV. A frequency dependence of DP with a similar slope as during SHFJV was observed during HFJV.

Study IV

There was a very strong influence of stent ID and f_{HF} on prestenotic PEEP. At the three lowest stent IDs, prestenotic PEEP was practically negligible. Increasing the diameter of the obstructive stent resulted in a distinct increase in PEEP up to ~9 times.

A logarithmic f_{HF} dependence was found for PEEP with lower values at the low f_{HF} end and a successive increase up to ~2.2 times to a more stable plateau at higher rates.

A strong dependence of prestenotic PIP on stent ID and frequency as well as on their interaction was found.
PIP was always higher than 22.1 cmH_2O with 2 mm stent ID and it was up to ~6.4 cmH_2O lower at 8 mm stent ID.

A logarithmic decrease of PIP was found when frequency was increased and it was most distinct for the larger stent IDs, resulting in a 6.7 cmH_2O reduction of PIP when f_{HF} was increased from 50 to 600 min^{-1}.

Discussion

Main findings

The most important findings from the studies included in this doctoral thesis are:

> Despite differences in lung volumes and airway pressures, all of the four most common jet ventilation modalities provided safe and effective ventilation of otherwise healthy patients undergoing minor airway surgery.
>
> In the absence of airway obstruction, variation of the high frequency of ventilation marginally affected lung volumes and gas exchange during SHFJV, whereas adequate lung volume changes and gas exchange during HJFV were greatly dependent on sufficiently low frequencies. Tracheal obstruction aggravated the findings for single frequency JV, whereas during SHFJV, frequency had little clinical impact on lung volumes and gas exchange. Additionally, we were able to provide a mathematical model for the description of the outcome variables during SHFJV and HFJV in both obstructed and unobstructed airways.
>
> Superimposed high frequency jet ventilation was able to maintain adequate gas exchange for a wide range of tracheal obstruction and for practically all investigated frequencies. Only at the narrowest airway diameter, severe hypercapnea occurred while adequate oxygenation was maintained. We were able to provide a mathematical description for the prediction of lung volume, gas exchange and airway pressure parameters in our model.

Is it all a matter of frequency?

In the present thesis, superimposed high frequency jet ventilation and single frequency JV were systematically compared in relation to frequency. Our findings indicate that, depending on the JV mode, variations of frequency had great impact on lung volumes, airway pressures and gas exchange. In the following section, the role of frequency and the resulting changes in ventilatory parameters during superimposed high frequency and single frequency JV are discussed.

During superimposed high frequency JV, we found a slight frequency dependence of lung volumes and the corresponding airway pressures. The largest alterations were observed at the lower end of the frequency range, both in the presence and in the absence of tracheal obstruction.

In the unobstructed airway, lower frequencies for f_{HF} resulted in smaller ΔEEV_{CW} and lower PEEP, as well as higher tidal volume and peak intrapulmonary pressure. Both findings are in line with a previous description of frequency dependence of lung volumes during jet ventilation.[74] Despite these findings for lung volumes however, the resulting alterations in gas exchange were minimal and of little clinical significance. This is in line with previous reports of superimposed high frequency JV that report good gas exchange for a wide range of frequencies used as f_{HF}.[32]

In the presence of tracheal obstruction, lower frequencies used for f_{HF} led instead to larger ΔEEV_{CW} and PEEP. With decreasing airway diameter, both tidal volume and peak intrapulmonary pressure became successively independent of the frequency used for f_{HF}. These observations were most likely caused by the low exhalation time (high time constant) observed when the effective tracheal diameter was decreased.[75] This would explain the observed successive air trapping with increasing intrapulmonary PEEP and larger end expiratory volumes. For tidal volume and intrapulmonary peak pressure, the tracheal stent seemed to act as a low pass filter. Ihra *et al.* found that decrease of airway diameter dampens the intrapulmonary pressure swing,[76] which could explain the resulting smaller tidal volumes at a given frequency[73]. Ihra and coworkers also found that this phenomenon occurs at lower frequencies with increasing airway resistance. In spite of the observed changes in lung volumes and intrapulmonary pressure, gas exchange at a high degree of tracheal obstruction was largely independent of frequency.

To summarize, despite changes in lung volume and airway pressures at different frequencies used for f_{HF}, gas exchange during superimposed high frequency jet ventilation at various airway diameters was practically independent of the choice of frequency for the f_{HF} component.

During single frequency JV, the situation was different. Lung volumes, intrapulmonary pressures and gas exchange were highly dependent on frequency.

In the absence of airway obstruction (*study II*), end expiratory chest wall volume was practically constant for the investigated frequency range. This finding is somewhat contradictory, because others found end expiratory chest wall volume to increase with increasing frequency.[21] A possible reason for this discrepancy is that in our studies, rather low working pressures were used for single frequency JV and that changes in ΔEEV_{CW} with increasing frequency could have become evident with higher driving pressures. In contrast, we found that tidal volume and intrapulmonary driving pressure were both greatly dependent on frequency. When frequency was increased, tidal volumes decreased markedly, corroborating previous findings.[21] Consequently, gas exchange during single frequency JV was best at low frequencies and deteriorated with increasing frequency to inacceptable values at rates >300 min^{-1}. This is supported by previous studies showing that oxygenation decreases[77] and p_aCO_2 increases[21,77,78] with increasing frequency.

When tracheal obstruction was established, the above stated observations became even more dependent on frequency (*study III*). End expiratory chest wall volume was unchanged when frequency was altered, but intrapulmonary PEEP increased with increasing frequency. Ihra *et al.* made the same observations for intrapulmonary pressure[76] and theoretically, they should be caused by air trapping and an increase of end expiratory volume. In our results, the deviant value of ΔEEV_{CW} at a frequency of 600 min^{-1} could be responsible for why the model failed to detect the frequency dependence of ΔEEV_{CW}. Tidal volume was vitally dependent on sufficiently low frequencies. Already at rates >150 min^{-1}, V_T became negligible caused by a similar behavior of intrapulmonary driving pressure. The findings of Ihra and coworkers for intrapulmonary pressure support our observations.[76] Oxygenation and carbon dioxide removal reached inacceptable values earlier than in the unobstructed airway. The CO_2 accumulation observed at higher frequencies was caused by the reduction in tidal volume.[21,78,79]

Interestingly, in our observations and in those of Lin *et al.*,[77] oxygenation deteriorated at f_{HF} as low as ~300 min^{-1}, whereas in other investigations, normoxia or hyperoxia was present at higher rates.[74,80] When using a F_iO_2 of 1.0 like in Rouby's study, oxygen transport at higher frequencies would be expected to mimic apneic oxygenation.[81] In the case of our study and that of Lin *et al.*, F_iO_2 was 0.5 and 0.4, respectively. A possible mechanism for the rapid decrease of p_aO_2 in these cases could be alveolar nitrogen accumulation[82] when V_T became so low that practically no alveolar ventilation occurred. Sufficiently low frequencies of <150 min^{-1} must be used in order to ensure adequate oxygenation and CO_2 removal in subjects with airway obstruction.

To conclude, when the frequency of the f_{HF} component is altered, it seems that the low frequency component of SHFJV contributes to a large extent to its superiority in terms of gas exchange and lung volume. During SHFJV, the values of PEEP and peak airway pressure were always higher than those observed during single frequency JV at the same frequency and consequently, the resulting lung volume changes were greater and gas exchange was better.

Bearing that in mind, SHFJV and single frequency JV seem to be a mismatched pair and direct comparisons with regard to the frequency/f_{HF} component used seem to be problematic. With superimposed high frequency JV, the choice of frequency for the f_{HF} component has little impact. For single frequency JV, it is indeed "all a matter of frequency", and thus, frequency should not exceed 150 min^{-1} in subjects with airway obstruction.

When to use superimposed high frequency jet ventilation?

In the present thesis, we measured lung volume changes during jet ventilation and used our findings to explain differences in gas exchange with superimposed and single frequency jet ventilation at different ventilation frequencies. In clinical practice, bedside measurements of lung volume changes during JV are difficult to accomplish. More useful for the clinician, and certainly more valuable for the prediction of adverse outcome, is the efficacy of gas exchange that jet ventilation can achieve. We observed great differences in oxygenation and CO_2 removal during superimposed high frequency JV and single frequency JV at different frequencies and hence, the question is: Which one is to prefer?

In unobstructed airways, comparing only JV with the same route of administration, we saw equally effective oxygenation for SHFJV and for single frequency JV in patients, despite differences in lung volumes (*study I*). When single frequency jet ventilation was used with frequencies up to 300 min^{-1}, it provided adequate p_aO_2, p_aCO_2 despite lower ΔEEV_{CW} and V_T than observed during superimposed high frequency JV (*study II*). This is in line with previous reports on single frequency JV with either physiological rates[12,14,16,83,84] or in the high frequency range.[17,74,85] However, although p_aO_2 during single-frequency jet ventilation with frequencies lower than 300 min^{-1} was adequate, higher values of p_aO_2 were observed for superimposed high frequency JV at the same frequency and F_iO_2. During laser surgery, where low F_iO_2 are obligatory, superimposed high frequency JV may therefore provide better oxygenation and hence, more time for the procedure.

Carbon dioxide removal in *study I* was most effective with supraglottic HFJV, using lower working pressures than any other investigated mode. Although tidal volume was lower with single frequency HFJV, compared

with superimposed high frequency JV, the resulting minute ventilation was around 22 l min^{-1}. Takahashi and coworkers found an inverse nonlinear relationship between minute ventilation and p_aCO_2 during single frequency JV, which provides an explanation of our observed changes in p_aCO_2.[78] Although originally, SHFJV has been developed in order to provide a greater CO_2-removing potential, supraglottic SHFJV with the frequencies used in *study I* would require tidal volumes of around 1800 ml to achieve the same amount of minute ventilation, and thus CO_2 removal, as during supraglottic HFJV. In *study II*, we found that variation of the high frequency component of superimposed high frequency JV had little impact on gas exchange, and consequently, CO_2 removal was accomplished mostly by the normal frequency component. Increasing the normal frequency component f_{NF} of superimposed high frequency JV may increase minute ventilation, but minute ventilation levels comparable to single frequency HFJV are difficult to accomplish within the described range of f_{NF} from 6 – 30 min^{-1}.[32] Single frequency HFJV may therefore more efficiently remove CO_2 used in the unobstructed airway of lung healthy individuals than superimposed high frequency JV.

In the presence of tracheal obstruction, the situation became complex and the efficacy of carbon dioxide removal during single frequency jet ventilation was greatly dependent on sufficiently low frequencies. An interesting finding was observed at a frequency of 50 min^{-1}. At that frequency, single frequency JV provided equally effective carbon dioxide removal and oxygenation, as did superimposed high frequency JV with the same frequency as high frequency component. Interestingly, superimposed high frequency JV resulted in about twice as high PEEP, driving pressure, EEV_{CW} and V_T.

These findings raise the question whether the higher intrapulmonary pressures and the consecutive lung volume changes observed during superimposed high frequency JV may increase the risk of complications. At the same time they illustrate that single frequency JV can be effective by itself as long as it is operated within its predefined frequency boundaries.

As previously stated, the largest reported range of operating frequencies for SHFJV is in the range of 6 – 30 min^{-1} for f_{NF} and 180 – 900 min^{-1} for $f_{HF,}$[32]. Unfortunately, the authors do not provide any information on the frequency distribution of p_aO_2 and p_aCO_2 in their study. Other reports on the clinical use of SHFJV, including a trial with >1500 patients, report the use of frequencies in the range of 12 – 20 min^{-1} for f_{NF} and 400 – 600 min^{-1} for f_{HF}.[27-29,86] The reported incidence of ventilation related complications with SHFJV was equal or lower than the rate of complications associated with other JV techniques,[27,28,55,86] suggesting that the higher levels of airway pressure observed during SHFJV, as compared with single frequency JV, do not put the patients at a higher risk of complications.

Furthermore, the frequency combination of 16 and 50 min^{-1} is unusual and its rationality is questionable, despite the interesting observations that

we made at that frequency. It may rather sound reasonable that a ventilation combining two frequencies, each of them operating at large "distance" from the other may contribute to different aspects of the ventilation. Using two separately adjustable ventilator units for the delivery of a very low frequency that allows for the delivery of tidal volumes together with a very high frequency that increases mean airway pressure and thereby, improves oxygenation,[74] still seems reasonable. The concept may also feel more familiar to the anesthetist that is used to adjusting PEEP and PIP separately during conventional ventilation. Adequate pressure monitoring is necessary to prevent pressure related complications and our findings indicate that pressure monitoring above the stenosis may be appropriate. Intrapulmonary peak pressure was always overestimated, despite a huge discrepancy between intrapulmonary pressure and the pressure values above the stenosis.

With our observations and the mathematical models to describe frequency dependence of SHFJV and single frequency jet ventilation, we provide tools that may help to decide whether the use of SHFJV or single frequency JV at different frequencies would fit a specific situation better. When considering the low reported rate of complications and its high oxygenation and CO_2 removal potential at frequencies >150 min^{-1} in tracheal stenosis, superimposed high frequency JV may be the safest option in such cases.

In conclusion, under uncomplicated conditions single frequency HFJV resulted in good oxygenation and may potentially remove CO_2 more efficiently than superimposed high frequency JV. With increasing degree of tracheal obstruction, superimposed high frequency JV provided better oxygenation and CO_2-removal than single frequency JV and may therefore be the mode of choice in more complicated cases.

Validity of results

In this thesis, we used OEP to measure chest wall volume changes, as a substitute for lung volume changes. Previous studies have shown a good correlation between these two volumes.[66,71] With its high temporal and spatial resolution, OEP repeatedly provided reproducible measurements of chest wall volume during jet ventilation at different frequencies.

Chest wall and lung mechanics remained unchanged from the beginning to the end of the animal experiments. Together with the crossover design and the randomized order of interventions, this precludes the risk of bias from measurements at different time points.

The mathematical models obtained from the mixed model analysis were derived from our observations. Within the boundaries of the frequency and obstruction range we investigated, the mathematical models are valid with a confidence level of 95%.

Conclusions

In healthy subjects with maintained airway patency, SHFJV provided the overall greatest increase of end expiratory chest wall volume and delivered greater tidal volumes than HFJV. All four investigated modes of jet ventilation maintained good oxygenation and ventilation.

Despite the minor changes in lung volumes seen when the high frequency component was altered, gas exchange efficacy during SHFJV seemed to be largely independent of frequency, both in the patent as well as in the obstructed airway.

In contrast to SHFJV, HFJV performed best at lower ventilation frequencies while it resulted in severe hypoxemia and hypercapnea at frequencies >300 min^{-1}. In the presence of airway obstruction, even lower frequencies of less than 150 min^{-1} were needed to deliver clinically acceptable oxygenation and ventilation.

At low F_iO_2, such as during laser surgery, the superior oxygenation potential seen during SHFJV, as compared with HFJV, may provide a greater margin of safety and consequently more time for the procedure.

In the porcine model of tracheal obstruction used in this thesis, SHFJV maintained oxygenation and carbon dioxide elimination at a clinically acceptable level over a wide range of airway diameters.

As tracheal obstruction increased, the discrepancy between intrapulmonary pressure and prestenotic pressure increased markedly. In spite of the above, as intrapulmonary peak pressure was always lower than peak pressure at the prestenotic level, airway pressure monitoring at the latter site may be useful for the prevention of barotrauma.

Limitations and Future Perspectives

In the present thesis, the behavior of lung volume and gas exchange parameters is described with mathematical models in relation to mode of ventilation, variable frequency and airway obstruction. These important findings give an indication of how these parameters may influence jet ventilation in humans. Therefore, our findings from the animal model now need to be corroborated in the patient population.

The majority of the findings in this thesis apply to supraglottic or, at least, above-stenosis ventilation. It is of utmost importance to point out that our observations of intrapulmonary pressure in the presence of stenosis and the resulting safety implications apply exclusively to above-stenosis ventilation. Further systematic research is needed to reappraise to what extent our findings on above-stenosis ventilation can be extrapolated to other routes of JV application.

The interaction of different ventilator settings during single frequency jet ventilation is complex. The combination of two jet components in SHFJV – with double the adjustment possibilities – and their impact on ventilation efficacy is even more sophisticated. Other parameters than those investigated in this thesis, such as working pressure or I/E ratio have been shown to influence ventilation and gas exchange during HFJV. However, knowledge of the influence of working pressure and/or I/E ratio of each jet component during SHFJV is very limited, which stresses the need for further studies to gain more knowledge on the complex interplay of the two jet components. That kind of knowledge would increase our level of awareness of these aspects and could contribute to the use of SHFJV at its full potential.

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