

Influence of Tracheal Obstruction on the Efficacy of Superimposed High-frequency Jet Ventilation and Single-frequency Jet Ventilation

Robert Sütterlin, Ph.D., Antonella LoMauro, M.Sc., Stefano Gandolfi, M.Sc., Rita Priori, Ph.D., Andrea Aliverti, Ph.D., Peter Frykholm, Ph.D., Anders Larsson, Ph.D.

ABSTRACT

Background: Both superimposed high-frequency jet ventilation (SHFJV) and single-frequency (high-frequency) jet ventilation (HFJV) have been used with success for airway surgery, but SHFJV has been found to provide higher lung volumes and better gas exchange than HFJV in unobstructed airways. The authors systematically compared the ventilation efficacy of SHFJV and HFJV at different ventilation frequencies in a model of tracheal obstruction and describe the frequency and obstruction dependence of SHFJV efficacy.

Methods: Ten anesthetized animals (weight 25 to 31.5 kg) were alternately ventilated with SHFJV and HFJV at a set of different f_{HF} from 50 to 600 min^{-1} . Obstruction was created by insertion of interchangeable stents with ID 2 to 8 mm into the trachea. Chest wall volume was measured using optoelectronic plethysmography, airway pressures were recorded, and blood gases were analyzed repeatedly.

Results: SHFJV provided greater than 1.6 times higher end-expiratory chest wall volume than HFJV, and tidal volume (V_T) was always greater than 200 ml with SHFJV. Increase of f_{HF} from 50 to 600 min^{-1} during HFJV resulted in a more than 30-fold V_T decrease from 112 ml (97 to 130 ml) to negligible values and resulted in severe hypoxia and hypercapnia. During SHFJV, stent ID reduction from 8 to 2 mm increased end-expiratory chest wall volume by up to 3 times from approximately 100 to 300 ml and decreased V_T by up to 4.2 times from approximately 470 to 110 ml. Oxygenation and ventilation were acceptable for 4 mm ID or more, but hypercapnia occurred with the 2 mm stent.

Conclusion: In this *in vivo* porcine model of variable severe tracheal stenosis, SHFJV effectively increased lung volumes and maintained gas exchange and may be advantageous in severe airway obstruction. (ANESTHESIOLOGY 2015; 123:799-809)

THE new interventional bronchoscopic techniques emerging during the last 2 decades have significantly improved the outcome after treatment of tracheobronchial obstruction, particularly the patients' exercise capacity, resulting in a higher quality of life.^{1,2}

However, these interventions are high-risk procedures, especially in patients with high-grade stenosis, multiple stenoses, and/or other preexisting pulmonary conditions.³

The procedures are mainly performed using rigid tracheoscopy/bronchoscopy and jet ventilation (JV). There is a large body of clinical experience supporting the use of superimposed high-frequency JV (SHFJV) in patients undergoing airway interventions and/or laser tumor debulking procedures.⁴ Even in cases with severe airway obstruction, SHFJV has been shown to maintain adequate p_{aO_2} and carbon dioxide removal.⁵⁻⁷

Superimposed high-frequency jet ventilation is a technique that combines a high-frequency (HF) (f_{HF} ; commonly $>500 \text{ min}^{-1}$) with a normal-frequency (NF) jet (f_{NF} ;

What We Already Know about This Topic

- Clinical usefulness of high-frequency jet ventilation (HFJV) is widely accepted in unobstructed airway
- Superimposed HFJV (SHFJV) is reported to provide higher lung volume and better gas exchange than HFJV in animal unobstructed airways
- No study has systematically compared the efficacy of HFJV and SHFJV for oxygenation and ventilation in obstructed airway

What This Article Tells Us That Is New

- In a study of pigs with obstructed airway, superimposed high-frequency jet ventilation was superior over high-frequency jet ventilation in providing adequate oxygenation by increasing lung volume and carbon dioxide removal by increasing tidal volume even without increasing the risk of barotrauma

12 to 20 min^{-1}). The rationale for using a normofrequent ventilation component is to increase minute ventilation and thereby facilitate carbon dioxide removal.⁸ It may also

Corresponding article on page 747. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article has been presented as abstract/poster at the Euroanaesthesia 2014 congress in Stockholm, Sweden, June 3, 2014.

Submitted for publication July 7, 2014. Accepted for publication May 14, 2015. From the Hedenstierna Laboratory, Anaesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden (R.S., P.F., A. Larsson); and Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy (A. LoMauro, S.G., R.P., A.A.).

Copyright © 2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2015; 123:799-809

provide lung recruitment and improve oxygenation.⁹ In a recent investigation of JV at different frequencies in unobstructed airways, we found that SHFJV effectively increased end-expiratory chest wall volume (EEV_{CW}) and tidal volume (V_T) providing adequate arterial oxygen (p_{aO_2}) and carbon dioxide tension (p_{aCO_2}) levels for a wide range of frequencies.¹⁰

In this study, we hypothesized that SHFJV would also achieve better oxygenation and gas exchange than single-frequency (high-frequency) JV (HFJV) at severe airway obstruction. The aim was to systematically compare the efficacy of SHFJV with HFJV over a wide range of JV frequencies and with varying degrees of airway obstruction. Using the obtained data, we developed a descriptive model to predict the influence of variable airway obstruction and JV frequency on ventilatory parameters during SHFJV.

Materials and Methods

We studied 10 healthy pigs (Swedish mixed country breed) at 3 months of age (weight 25 to 31.5 kg) at the Hedenstierna Laboratory, Uppsala University Animal Research Ethics Committee approved the study (reference number: C 140/11), and the National Institutes of Health guidelines for animal research were followed.

Anesthesia and Animal Preparation

On arrival to the laboratory, the animal was premedicated with an intramuscular injection of xylazine 2.2 mg/kg, tiletamine 3 mg/kg, and zolazepam 3 mg/kg. When the premedication showed an effect (after approximately 10 min), the animal was placed supine on the operating table and an ear vein was cannulated with a peripheral venous catheter. A bolus of 100 to 500 μ g fentanyl was injected IV and the trachea was intubated orally (Hi-Contour Tracheal Tube, ID 8.0 mm; Mallinckrodt Medical, Ireland). Volume control ventilation was started (Servo-i[®], Sweden) with V_T of 10 ml/kg, and the respiratory rate was adjusted to achieve normocarbica (37.5 to 45 mmHg).

General anesthesia was induced and maintained intravenously using pentobarbital (7 to 9 mg $kg^{-1} h^{-1}$) and morphine (420 to 540 μ g $kg^{-1} h^{-1}$). After ascertaining adequate depth of anesthesia by painful stimulation between the front toes (absence of withdrawal reaction, awakening, or autonomous response), neuromuscular block was established and maintained by IV infusion of pancuronium (280 to 360 μ g $kg^{-1} h^{-1}$). To ensure adequate anesthesia during neuromuscular block, heart rate and blood pressure were monitored, and signs of responsiveness to manipulations were observed.

An arterial line for invasive blood pressure measurement and blood gas sampling was surgically placed in the left carotid artery. A Swan-Ganz catheter (pressure verified position in the pulmonary arterial bed) and a central venous line were inserted *via* the ipsilateral external jugular vein.

A urinary catheter was inserted *via* a minilaparotomy. Throughout the experiment, electrocardiogram was continuously monitored and oxygen saturation measured by pulse oximetry was acquired by photoplethysmography on the tail base.

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

Establishing Airway Obstruction

The airway obstruction was achieved by inserting a stent (fig. 1A) into the trachea with the following method: The upper part (approximately 5 cm) of the trachea and the larynx were dissected circumferentially and a tracheostomy was performed at the proximal end of the trachea. For stent insertion/exchange, the previously inserted oral endotracheal tube was uncuffed and withdrawn as much as possible without exiting the larynx. Through the tracheostomy stoma, obstructive stents (length 2 cm, outer diameter 10.8 mm, IDs 2, 4, 6, and 8 mm) were alternately introduced into the tracheal lumen. Airflow bypassing the stent was prevented by tightening a circumferential cotton band around the trachea (fig. 1B). The stent was secured with a suture at the proximal end to restrict any caudal dislocation. After stent insertion, the oral endotracheal tube was advanced until the cuff appeared flush with the tracheostomy stoma and cuff inflation prevented air leakage through the stoma. With this setup, we were repeatedly able to manipulate the degree of tracheal obstruction by simply exchanging the stents. A schematic diagram of the experimental protocol is illustrated in figure 2.

Ventilator Interventions

A Twinstream[®] jet ventilator (Carl Reiner GmbH, Austria) was attached to the oral endotracheal tube by means of a Veres T-adaptor (Carl Reiner GmbH) and a bias flow of 55 l/min of warmed and humidified respiratory gas with $F_{IO_2} = 0.5$ (HumiCare[®] 200 breathing gas humidifier; Gröndler medical GmbH, Germany) was entrained through the proximal opening of the T-adaptor.

The Twinstream[®] jet ventilator consists of two independently adjustable modules for JV: an NF unit and an HF unit. For each module, operation (on/off), frequency (f_{NF} or f_{HF}), working pressure, and inspiratory/expiratory (I/E) ratio can be adjusted separately. Thus, the ventilator can be operated in either HFJV or NFJV mode, with only the respective module activated, or in SHFJV mode, with both modules operating simultaneously.

Throughout the experiment, the NF unit had the following settings: $f_{NF} = 16 \text{ min}^{-1}$, I/E = 1:1, and a working pressure of 1.6 bar. The HF unit was adjusted as follows: different f_{HF} were used ($f_{HF} = 50, 100, 150, 200, 300, 400$, and 600 min^{-1}), I/E = 1:1, and a constant working pressure of 0.8 bar. F_{IO_2} was globally set to 0.5, including bias flow.

Whenever a condition led to a pulmonary artery pressure greater than 60 mmHg or an occurrence of arrhythmias during a hypoxic period, the protocol was interrupted and

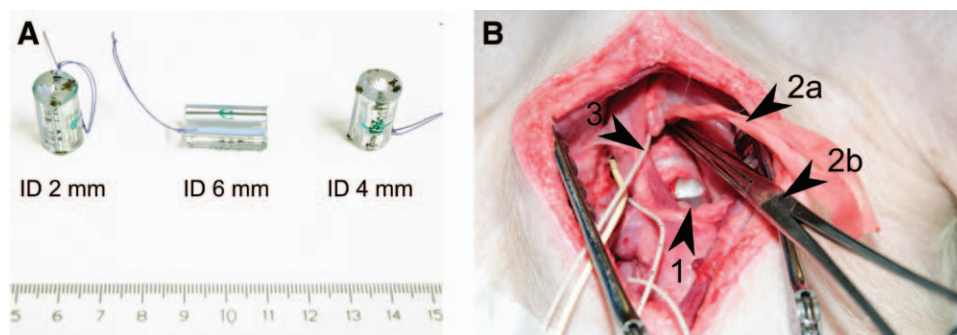


Fig. 1. (A) Dimensions of three of the obstructive stents used in the study. The stents were anchored in the trachea with sutures (A) passing through the stoma and by tying a cotton band around the trachea at the site of the stent (B). (B) Tracheostomy situs from one animal: (1) marks the stoma with the inflated endotracheal tube cuff visible, (2) indicates the cotton band (2a) around the trachea and the clamp (2b) used to tighten and secure the band around the trachea, and (3) shows the catheter for measurement of airway pressure distal of the stent.

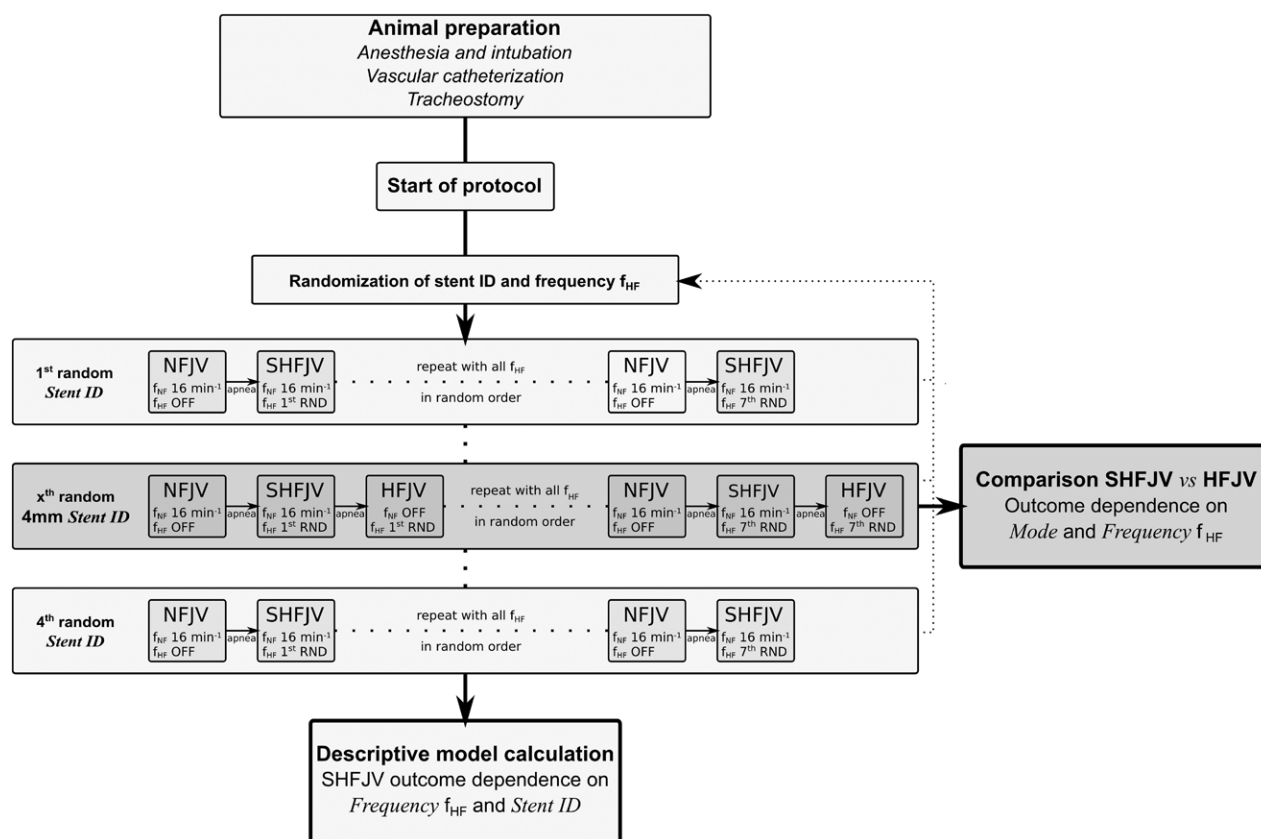


Fig. 2. Schematic overview of the experimental protocol. f_{HF} = frequency of high-frequency component; f_{NF} = frequency of normal-frequency component; HFJV = high-frequency jet ventilation; NFJV = normal-frequency jet ventilation; RND = random; SHFJV = superimposed high-frequency jet ventilation.

rescue ventilation (volume control ventilation with Servo-i® ventilator, V_T of 10 ml/kg and $FiO_2 = 1.0$) was started. After normalization of pulmonary artery pressure, acid–base status, and oxygenation, the protocol was continued.

Study Design and Outcome Variables

Primary outcome variables were ΔEEC_{CW} and chest wall V_T . Secondary outcome variables were p_{aO_2} , p_{aCO_2} , and

prestenotic (P_{UPPER}) and poststenotic airway pressure (P_{LOWER}).

To preclude possible influences of preceding settings on outcome, we chose a crossover design. Using a computer-generated randomization method (Excel; Microsoft, USA), we randomized the order of application for all interventions (stent ID and HF component of JV). A diagram of the study protocol is illustrated in figure 2.

Volume Measurement

We measured chest wall volume with optoelectronic plethysmography (OEP).^{11,12} The volumes obtained by this method correspond well to lung volume changes in a variety of conditions,^{13–16} and the method has recently been used for studies of different modes of JV.^{10,17}

Optoelectronic plethysmography provides spatial (SD for repeated volume measurements 0.17%)¹⁵ and temporal resolution (60 Hz)¹⁸ adequate for the study of JV.

An OEP System® (BTS Bioengineering, Italy) with six infrared cameras acquired the position and movement of an array of 57 adhesive retro-reflective markers on the animal's trunk. The cameras were arranged on supports below the laboratory ceiling (three on each side of the animal) in a manner that each of the reflective markers was viewed by at least two cameras.

From the camera registrations, the bundled OEP Capture® motion analysis software (BTS Bioengineering) calculated the position of each marker in a three-dimensional coordinate system for each time point. The volume enclosed by the surface formed by triangulation of the markers represents the chest wall volume.

Arterial Blood Gas Analysis

Arterial blood gas samples were obtained after 5 min of each ventilation condition, and p_{aO_2} and p_{aCO_2} were immediately measured with a blood gas analyzer (ABL 500; Radiometer, Denmark).

Pressure Registration

Prestenotic airway pressure (P_{UPPER}) was measured *via* a 200-mm long 16-gauge Secalon Seldy catheter (BD Medical Surgical Systems, Sweden) at the tip of the endotracheal tube. For measurement of poststenotic airway pressure (P_{LOWER}), another Secalon Seldy catheter was introduced into the trachea below the stent by the Seldinger technique. Identical analog pressure transducers (RCM250DU; SensoMotorics GmbH, Germany) were used to acquire pressure signals that were synchronized with the OEP volume registrations and continuously recorded by the OEP Capture® software.

Definitions

Optoelectronic plethysmography measures total chest wall volume, that is, not only the lung volume. Thus, it was necessary to compensate for changes in volume that were not attributable to ventilation, for example, fluid administration or gas production in the intestines. For that purpose, each f_{HF} step (with SHFJV and HFJV) was preceded by another 5 min of ventilation with NFJV ($f_{NF} = 16 \text{ min}^{-1}$, $f_{HF} = 0$), followed by a disconnection from the ventilator. At $f_{NF} = 16 \text{ min}^{-1}$, the duration of the expiratory phase is 1.9 s resulting in a decrease of P_{LOWER} to 0 at a low degree of obstruction. With more severe stenosis, it was necessary to disconnect the ventilator for some

seconds to allow P_{LOWER} to decrease to 0. We chose chest wall volume at $P_{LOWER} = 0 \text{ cm H}_2\text{O}$ as the reference volume ($EEV_{CW_{P_{LOWER}=0}}$) as we assumed that it was approximately equal to the functional residual capacity (FRC) at apnea.

For each condition, we derived chest wall volumes and airway pressures as averages of at least five consecutive steady-state breaths.

Changes in end-expiratory chest wall volume above apneic FRC (ΔEEV_{CW}) are hence defined as follows:

$$\Delta EEV_{CW_{SHFJV}} = EEV_{CW_{SHFJV}} - EEV_{CW_{P_{LOWER}=0}}$$

and

$$\Delta EEV_{CW_{HFJV}} = EEV_{CW_{HFJV}} - EEV_{CW_{P_{LOWER}=0}}$$

Tidal volume was calculated by subtracting EEV_{CW} from end-inspiratory chest wall volume (EIV_{CW}):

$$V_T = EIV_{CW} - EEV_{CW}$$

At higher rates, there is a phase offset between the volume and the pressure signals. Hence, defining positive end-expiratory pressure (PEEP) as airway pressure at end-expiration would result in erroneous values. Therefore, we defined PEEP as the lowest observed pressure during the respiratory cycle.

Static Compliance (C_{STAT})

The length of the experiments made it necessary to investigate whether there were changes of respiratory mechanics over time that could influence the outcome. For that purpose, we assessed static compliance at the beginning and at the end of the protocol, without any degree of airway obstruction. In pressure control ventilation (Servo-i®), an incremental-decremental PEEP maneuver was performed. Starting from zero end-expiratory pressure (ZEEP), PEEP was increased by 2 cm H₂O every five breaths until a maximum of 20 cm H₂O. In the same manner, PEEP was then decreased to ZEEP.

For each animal, static compliance was computed using triplicate measurements of end-expiratory pressure and end-expiratory volume at ZEEP and at 20 cm H₂O, respectively. From all available pigs, mean and 95% CI for C_{STAT} were calculated.

Statistical Data Analysis

All statistical computations were performed with R (R Foundation for Statistical Computing, Austria). Previous experience has shown that a number of 8 to 10 animals would be adequate to detect outcome differences.

In the first part of this article, we tested the alternative hypothesis that the use of SHFJV would result in an increase of ΔEEV_{CW} and V_T compared with HFJV at the same frequency. We further hypothesized that SHFJV would maintain p_{aO_2} at higher and p_{aCO_2} at lower levels than HFJV. Statistical analyses of ΔEEV_{CW} , V_T , p_{aO_2} and p_{aCO_2} , and airway pressure were performed using linear mixed model analysis. Details on the definition of fixed and random factors can be found in table 1.

The second part of the article focuses on finding a descriptive model for the influence of variable stent ID and the HF component of ventilation on the outcomes stated in the previous paragraph. Based on our observations of lung volumes, gas exchange, and airway pressures, we used linear mixed model analysis (for details, see table 1) to predict the dependency of these outcome variables on stent ID and on the HF component of JV.

Nonlinear frequency dependency¹⁰ or obstruction dependency¹⁹ of most of our outcome variables have been reported previously. Therefore, the transformation of parameters was necessary to fit the linear mixed models to our observations (table 1).

All previously log-transformed data are presented as geometric mean (V_T , p_{aO_2} , and p_{aCO_2}) and 95% CI, and untransformed data as arithmetic mean and 95% CI. The mixed model was used to characterize the properties of our observations; therefore, significant results should be interpreted as descriptive rather than confirmatory.

Equations for the mixed models used for the analyses are provided as Supplemental Digital Content 1, <http://links.lww.com/ALN/B184>.

Testing for statistical differences in C_{STAT} between the start and the end of the protocol was performed using the paired t test.

Results

One animal was excluded from the study because of bilateral pneumothorax that occurred during a respiratory recovery phase using conventional ventilation. The results of the mixed model analyses for the comparison of SHFJV and HFJV are summarized in table 2; those for the description of frequency and stent ID dependency of SHFJV are given in table 3. In Supplemental Digital Content 2, <http://links.lww.com/ALN/>

B185, we provide observed means and 95% CI for each variable for the SHFJV–HFJV comparison (table 1) and for the description of SHFJV dependency on frequency and stent ID (table 2).

Comparison of SHFJV and HFJV

Lung Volumes. End-expiratory chest wall volume was at least 1.6 times higher with SHFJV compared with HFJV (fig. 3A) throughout the frequency range.

Tidal volumes were greater with SHFJV compared with HFJV, the difference increasing with frequency (fig. 3B). This difference relied solely on the V_T changes during HFJV, resulting in a more than 30-fold decrease of V_T when f_{HF} was increased from 50 to 600 min^{-1} , reaching negligible V_T s at f_{HF} greater than 150 min^{-1} .

Gas Exchange. Superimposed HFJV provided higher levels of p_{aO_2} than HFJV, especially at high frequencies, again explained by changes during HFJV (fig. 3C). During SHFJV, p_{aO_2} remained practically constant at levels greater than 225 mmHg throughout the frequency range, whereas increasing f_{HF} during HFJV resulted in a 5.5 times decrease of p_{aO_2} with hypoxemic values at f_{HF} greater than 150 min^{-1} .

Likewise, carbon dioxide elimination was acceptable and largely unaffected by frequency when SHFJV was used (fig. 3D), whereas during HFJV, p_{aCO_2} almost doubled to a plateau at f_{HF} greater than 150 min^{-1} .

Airway Pressures. Superimposed HFJV resulted in higher PIP above and below the stenotic segment (PIP_{UPPER} and PIP_{LOWER} , respectively) (Supplemental Digital Content 3, fig. 1, <http://links.lww.com/ALN/B186>). There was a significant influence of frequency on both pressures for SHFJV and HFJV. End-expiratory pressures above the stenotic segment ($PEEP_{UPPER}$) were approximately equal for SHFJV and HFJV. Below the stenosis, this was only true for high frequencies because SHFJV increased to a maximum of 2.4 times higher end-expiratory pressure ($PEEP_{LOWER}$) at the lowest frequency.

Table 1. Mixed Model Properties and Applied Transformations for the Statistical Analyses

		Comparison of SHFJV vs. HFJV		Descriptive Model: f_{HF} and Stent ID Influence on Outcome		
Model properties	Mode: SHFJV, HFJV	Fixed factor		n.a.		
	Frequency: f_{HF} 50–600 min^{-1}	Fixed factor		Fixed factor		
	Stent ID: 2–8 mm	n.a.		Fixed factor		
	Mode \times frequency interaction	Fixed factor		n.a.		
	Stent ID \times frequency interaction	n.a.		Fixed factor		
	Animal ID: animal intrinsic properties	Random factor		Random factor		
Transformations	Outcome Variable	Variable	Frequency	Variable	Frequency f_{HF}	Stent ID
	ΔEEV_{CW}	—	—	Logarithmic	Logarithmic	Logarithmic
	V_T	Logarithmic	Logarithmic	Logarithmic	Logarithmic	Logarithmic
	p_{aO_2}	Logarithmic	Logarithmic	—	Logarithmic	Logarithmic
	p_{aCO_2}	Logarithmic	Logarithmic	Logarithmic	Logarithmic	Logarithmic
	PIP_{UPPER}	—	—	Logarithmic	Logarithmic	Logarithmic
	$PEEP_{UPPER}$	—	—	—	Logarithmic	Exponential
	PIP_{LOWER}	Logarithmic	Logarithmic	Logarithmic	Logarithmic	Logarithmic
	$PEEP_{LOWER}$	Logarithmic	Logarithmic	Logarithmic	Logarithmic	Logarithmic

Animal ID = specific intrinsic properties of each animal; ΔEEV_{CW} = end-expiratory chest wall volume change; f_{HF} = high-frequency component of jet ventilation; HFJV = single-frequency jet ventilation; index “lower” = distal of stenotic stent; index “upper” = proximal of stenotic stent; n.a. = not applicable; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; SHFJV = superimposed high-frequency jet ventilation; V_T = tidal volume.

Table 2. Mixed Model Results of the Comparison of Superimposed High-frequency Jet Ventilation vs. Single-frequency Jet Ventilation

Variables	Estimate	Unit	Coefficient	95% CI	P Value
$\Delta\text{EEV}_{\text{CW}}$	Intercept	ml	81.69	63.32 to 100.07	<0.001
	Mode	ml	97.35	77.50 to 117.20	<0.001
	Frequency	ml	2.97	-1.64 to 7.58	0.210
	Mode \times frequency	ml	-4.70	-11.12 to 1.72	0.154
V_T	Intercept	ml	53.00	46.06 to 60.99	<0.001
	Mode	Fold change	4.48	4.10 to 4.89	<0.001
	Frequency	Fold change	0.27	0.25 to 0.28	<0.001
	Mode \times frequency	Fold change	3.53	3.24 to 3.85	<0.001
$p_a\text{O}_2$	Intercept	mmHg	125.04	106.88 to 147.84	<0.001
	Mode	Fold change	1.93	1.71 to 2.17	<0.001
	Frequency	Fold change	0.46	0.42 to 0.50	<0.001
	Mode \times frequency	Fold change	2.14	1.90 to 2.41	<0.001
$p_a\text{CO}_2$	Intercept	mmHg	72.08	64.13 to 81.01	<0.001
	Mode	Fold change	0.66	0.62 to 0.70	<0.001
	Frequency	Fold change	1.27	1.22 to 1.32	<0.001
	Mode \times frequency	Fold change	0.82	0.78 to 0.87	<0.001
$\text{PIP}_{\text{UPPER}}$	Intercept	cm H ₂ O	12.98	10.92 to 15.03	<0.001
	Mode	cm H ₂ O	11.98	11.25 to 12.70	<0.001
	Frequency	cm H ₂ O	-0.87	-1.04 to -0.71	<0.001
	Mode \times frequency	cm H ₂ O	0.09	-0.14 to 0.32	0.457
$\text{PEEP}_{\text{UPPER}}$	Intercept	cm H ₂ O	0.09	-0.19 to 0.37	0.532
	Mode	cm H ₂ O	0.22	0.03 to 0.40	0.024
	Frequency	cm H ₂ O	0.24	0.19 to 0.28	<0.001
	Mode \times frequency	cm H ₂ O	-0.12	-0.18 to -0.06	<0.001
$\text{PIP}_{\text{LOWER}}$	Intercept	cm H ₂ O	7.21	6.38 to 8.14	<0.001
	Mode	Fold change	2.48	2.40 to 2.57	<0.001
	Frequency	Fold change	0.82	0.80 to 0.84	<0.001
	Mode \times frequency	Fold change	1.17	1.13 to 1.21	<0.001
$\text{PEEP}_{\text{LOWER}}$	Intercept	cm H ₂ O	2.57	2.03 to 3.24	<0.001
	Mode	Fold change	1.79	1.64 to 1.96	<0.001
	Frequency	Fold change	1.44	1.36 to 1.53	<0.001
	Mode \times frequency	Fold change	0.75	0.69 to 0.81	<0.001

The intercept corresponds to the predicted value of the outcome for high-frequency jet ventilation at zero frequency. Mode is the predicted influence of jet ventilation mode. Frequency is the predicted influence of f_{HF} on the outcome variable. 1 mmHg = 0.1333 kPa.

$\Delta\text{EEV}_{\text{CW}}$ = end-expiratory chest wall volume change; f_{HF} = frequency of the high-frequency jet ventilation component; index "lower" = distal of stenotic stent; index "upper" = proximal of stenotic stent; JV = jet ventilation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; V_T = tidal volume.

Description of SHFJV Dependency on Frequency and Stent ID

Lung Volumes. The degree of obstruction (stent ID) and frequency both affected $\Delta\text{EEV}_{\text{CW}}$ (fig. 4A) and V_T (fig. 4B). Decreasing the stent diameter from 8 to 2 mm increased $\Delta\text{EEV}_{\text{CW}}$ and V_T by a factor of three. At low stent ID, increasing frequency resulted in an increase in $\Delta\text{EEV}_{\text{CW}}$ that reached a plateau at higher frequencies, whereas V_T was independent of frequency. With minor obstruction, $\Delta\text{EEV}_{\text{CW}}$ and V_T both decreased with increasing frequency to reach a plateau.

Gas Exchange. Oxygenation during SHFJV was dependent on the stent ID, reduced by 30% at the narrowest stent, but independent of frequency (fig. 4C).

Carbon dioxide removal was strongly influenced not only by stent ID but also by frequency and the interaction of stent ID and frequency (fig. 4D). At the widest stent ID, $p_a\text{CO}_2$ was normal for all frequencies but increasing the degree of obstruction resulted in a marked increase of $p_a\text{CO}_2$ to levels greater than 75 mmHg.

Airway Pressures. Peak inspiratory pressure above ($\text{PIP}_{\text{UPPER}}$) and below the stenotic segment ($\text{PIP}_{\text{LOWER}}$) were dependent on stent ID, frequency, and the interaction of both parameters (Supplemental Digital Content 3, fig. 2, <http://links.lww.com/ALN/B186>).

At the widest stent ID, $\text{PIP}_{\text{UPPER}}$ was lowest, and it increased by at least 11% when the stent ID was decreased to 2 mm. With minor obstruction, $\text{PIP}_{\text{UPPER}}$ and $\text{PIP}_{\text{LOWER}}$ were inversely related.

$\text{PIP}_{\text{LOWER}}$ was approximately equal to $\text{PIP}_{\text{UPPER}}$ for the widest stent ID and expressed the same frequency dependency. With decreasing stent ID, the pressure fall over the stent increased significantly. There was no influence of the frequency f_{HF} on $\text{PIP}_{\text{LOWER}}$ in the narrowest stent ID. Importantly, $\text{PIP}_{\text{UPPER}}$ always exceeded $\text{PIP}_{\text{LOWER}}$.

Positive end-expiratory pressures above ($\text{PEEP}_{\text{UPPER}}$) and below the stenotic segment ($\text{PEEP}_{\text{LOWER}}$) were also dependent on stent ID, frequency, and the interaction of both.

Table 3. Mixed Model Results for the Obstruction and Frequency Dependence of Outcome Variables during Superimposed High-frequency Jet Ventilation

	Estimate	Unit	Coefficient	95% CI	P Value
$\Delta\text{EEV}_{\text{CW}}$	Intercept	ml	538.75	437.51 to 663.43	<0.001
	Obstruction	Fold change	0.42	0.38 to 0.46	<0.001
	Frequency	Fold change	0.76	0.66 to 0.88	<0.001
	Obstruction \times frequency	Fold change	1.30	1.18 to 1.42	<0.001
V_T	Intercept	ml	58.47	50.14 to 68.19	<0.001
	Obstruction	Fold change	2.53	2.35 to 2.73	<0.001
	Frequency	Fold change	1.12	1.01 to 1.25	0.035
	Obstruction \times frequency	Fold change	0.86	0.80 to 0.93	<0.001
$p_a\text{O}_2$	Intercept	mmHg	95.86	65.56 to 126.16	<0.001
	Obstruction	mmHg	85.58	70.66 to 100.51	<0.001
	Frequency	mmHg	-0.30	-22.20 to 21.53	0.977
	Obstruction \times frequency	mmHg	-3.68	-18.08 to 10.80	0.621
$p_a\text{CO}_2$	Intercept	mmHg	141.76	122.56 to 163.96	<0.001
	Obstruction	Fold change	0.48	0.45 to 0.50	<0.001
	Frequency	Fold change	0.92	0.85 to 1.00	0.047
	Obstruction \times frequency	Fold change	1.12	1.06 to 1.18	<0.001
$\text{PIP}_{\text{UPPER}}$	Intercept	cm H ₂ O	28.08	25.66 to 30.73	<0.001
	Obstruction	Fold change	0.90	0.88 to 0.92	<0.001
	Frequency	Fold change	0.96	0.93 to 0.98	0.001
	Obstruction \times frequency	Fold change	0.96	0.95 to 0.98	<0.001
$\text{PEEP}_{\text{UPPER}}$	Intercept	cm H ₂ O	0.41	0.21 to 0.61	<0.001
	Obstruction	cm H ₂ O	0.0009	0.0008 to 0.0010	<0.001
	Frequency	cm H ₂ O	0.18	0.08 to 0.27	<0.001
	Obstruction \times frequency	cm H ₂ O	0.0003	0.0002 to 0.0004	<0.001
$\text{PIP}_{\text{LOWER}}$	Intercept	cm H ₂ O	11.19	10.23 to 12.24	<0.001
	Obstruction	Fold change	1.39	1.35 to 1.43	<0.001
	Frequency	Fold change	1.01	0.96 to 1.05	0.782
	Obstruction \times frequency	Fold change	0.95	0.92 to 0.97	<0.001
$\text{PEEP}_{\text{LOWER}}$	Intercept	cm H ₂ O	15.19	11.55 to 19.98	<0.001
	Obstruction	Fold change	0.39	0.36 to 0.44	<0.001
	Frequency	Fold change	0.79	0.69 to 0.91	0.001
	Obstruction \times frequency	Fold change	1.32	1.20 to 1.46	<0.001

The intercept is the predicted value of the outcome variable at zero frequency and 2-mm stent ID. Obstruction is the influence of stent ID, frequency is the predicted influence of f_{HF} on the outcome variable. 1 mmHg = 0.1333 kPa.

$\Delta\text{EEV}_{\text{CW}}$ = end-expiratory chest wall volume change; f_{HF} = frequency of the high-frequency jet ventilation component; index "lower" = distal of stenotic stent; index "upper" = proximal of stenotic stent; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; V_T = tidal volume.

Positive end-expiratory pressures above ($\text{PEEP}_{\text{UPPER}}$) increased with both stent ID and frequency f_{HF} . At low degrees of stenosis, PEEP above and below the obstruction were almost equal, but with severe stenosis, we observed markedly higher values of $\text{PEEP}_{\text{LOWER}}$ compared with $\text{PEEP}_{\text{UPPER}}$.

Discussion

The current study consists of two parts: (1) a comparison between SHFJV and HFJV in a porcine model of severe airway obstruction and (2) an investigation of the interaction between the degree of tracheal obstruction and the jet frequency on ventilatory efficiency during SHFJV. It is the first *in vivo* study that systematically investigates the dependence of gas exchange on ventilation frequency for variable airway obstruction.

During HFJV, lung volumes, gas exchange, and intrapulmonary pressures were highly dependent on frequency. In

our model, the significantly obstructed airway (75% obstruction for the 4 mm stent) resulted in the deterioration of V_T and gas exchange at relatively low frequencies. Already at f_{HF} greater than 150 min^{-1} , V_T became negligible and resulted in severe hypercapnia. In intact airways, a similar dependence of V_T and $p_a\text{CO}_2$ on frequency has been described earlier,^{20–22} but in the previous studies, deterioration of tidal ventilation and carbon dioxide accumulation occurred at much higher frequencies.¹⁰

We observed an increase of intrapulmonary PEEP ($\text{PEEP}_{\text{LOWER}}$) with increasing f_{HF} but we failed to predict an accompanying increase of end-expiratory chest wall volume. In contrast, other investigators found that end-expiratory chest wall volume increased with increasing frequency.²⁰ Ihra *et al.*²³ made similar observations for intrapulmonary pressure, and theoretically, the increased end-expiratory pressure is caused by an increase of end-expiratory volume (air trapping). In our results, the deviant value of $\Delta\text{EEV}_{\text{CW}}$

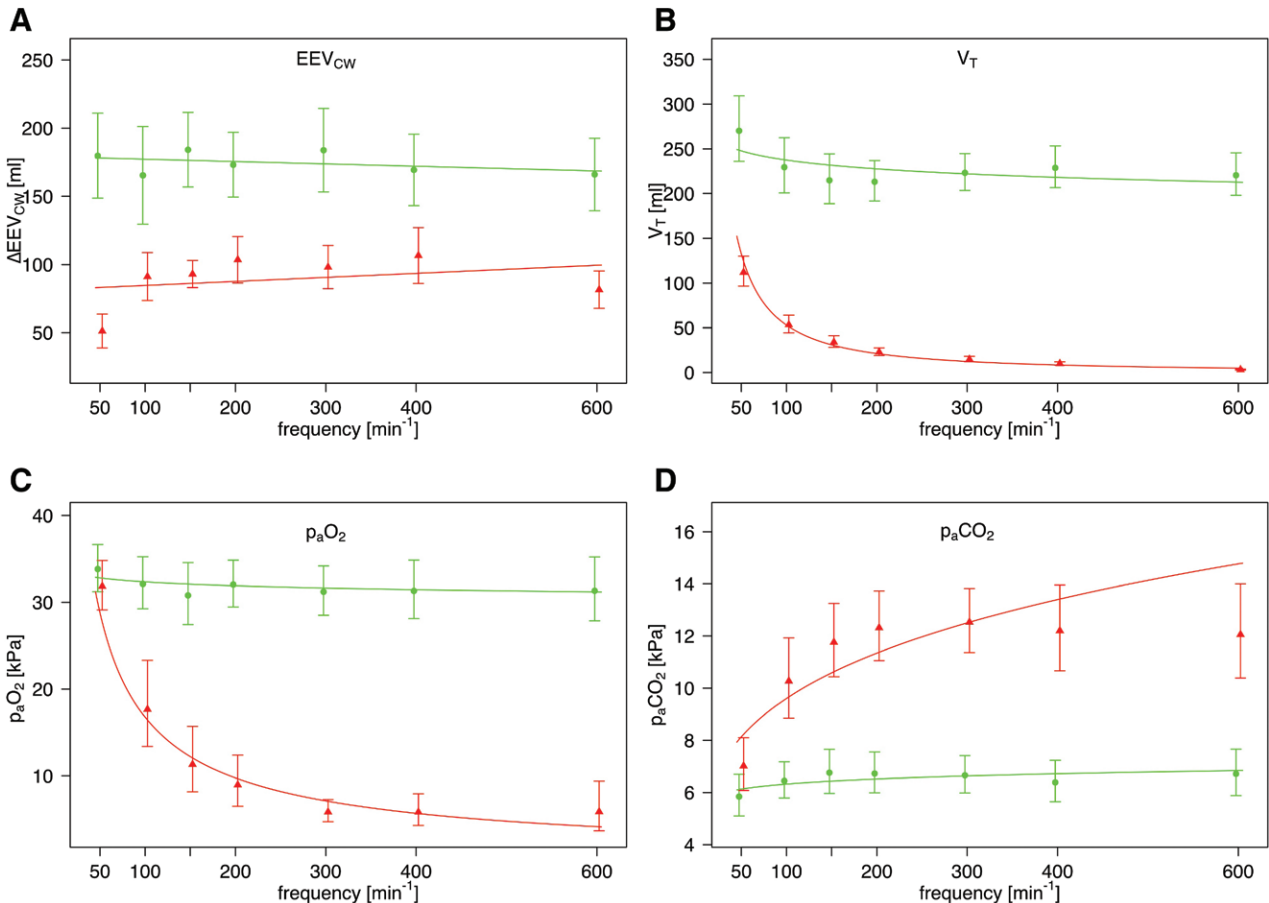


Fig. 3. Lung volumes and gas exchange plotted over frequency. (A) End-expiratory chest wall volume ($\Delta\text{EEV}_{\text{CW}}$ increase), (B) tidal volume (V_T), as well as (C) $p_a\text{O}_2$ and (D) $p_a\text{CO}_2$. Green circles represent observed values during superimposed high-frequency jet ventilation, and the mixed model prediction is shown as a green line. Red triangles are observed values from single-frequency jet ventilation, with the red line indicating mixed model prediction. All observed values are mean and 95% CI. The predictive functions were derived from the mixed models that were applied on a continuous frequency spectrum (50–600 min^{-1}). 1 kPa = 7.5 mmHg.

at a frequency of 600 min^{-1} could be responsible for why the model failed to detect the frequency dependence of $\Delta\text{EEV}_{\text{CW}}$. Another explanation is that we used rather low working pressures for HFJV, and that changes in $\Delta\text{EEV}_{\text{CW}}$ with increasing frequency would have become evident if higher driving pressures had been used.

Interestingly, we found in agreement with some previous studies that oxygenation deteriorated when a certain frequency was exceeded,^{10,24} whereas other investigators have found normoxia or hyperoxia even at very high rates.^{25,26} When using an FiO_2 of 1.0, oxygen transport at higher frequencies would be expected to mimic apneic oxygenation.²⁷ In the case of our study and that of Lin *et al.*,²⁴ FiO_2 was set at 0.5 and 0.4, respectively. A possible mechanism for the rapid decrease of $p_a\text{O}_2$ in the latter studies could be alveolar nitrogen accumulation²⁸ at very low V_T with negligible alveolar ventilation. Therefore, for HFJV, sufficiently low frequencies of less than 150 min^{-1} must be used to ensure adequate oxygenation and carbon dioxide removal in subjects with airway obstruction unless the FiO_2 is set at 1.0. Further studies could focus on or include the

influence of working pressure and FiO_2 on JV efficacy *versus* resulting airway pressure.

In contrast to the observations for HFJV, changes of the f_{HF} component of SHFJV had less distinctive effect on lung volumes, gas exchange, and airway pressures. These findings support a previous report of the successful use of SHFJV with f_{HF} ranging from 180 to 900 min^{-1} in subjects with stenotic airways.²⁹ In our investigation, the greatest effect of f_{HF} was observed with the widest airway stent in place. The largest alterations were observed for $\Delta\text{EEV}_{\text{CW}}$, V_T , airway pressures, and $p_a\text{CO}_2$ at the very low-frequency end and a more stable plateau was seen at higher frequencies.

With decreasing stent ID, the stenotic segment increasingly acted as a low-pass filter³⁰ with a lower flow rate across the stenosis.³¹ Accordingly, reduction of stent ID displaced the range of frequencies with significant ventilation alterations toward a lower f_{HF} spectrum. The passive process of expiration was most affected, as we noted an increase in intrapulmonary PEEP caused by air trapping and a reduction of tidal pressure variations with lower V_T . These findings corroborate previous results from bench studies.^{19,32}

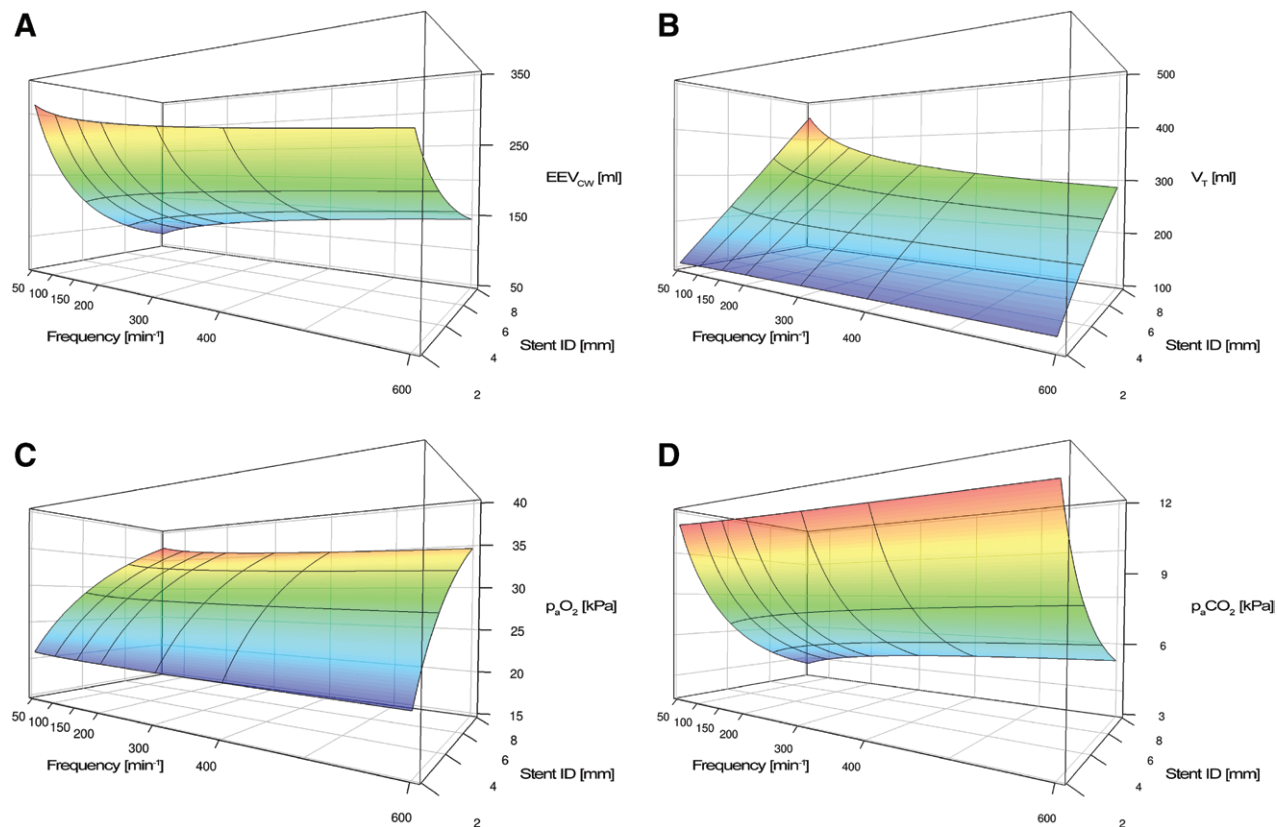


Fig. 4. Three-dimensional illustration of the mixed model prediction for superimposed high-frequency jet ventilation in relation to stent ID and frequency (f_{HF}): (A) End-expiratory chest wall volume (ΔEEV_{CW} increase), (B) tidal volume (V_T), (C) p_aO_2 , and (D) p_aCO_2 . Blue color indicates low values of the outcome variable, and red color codes for high values. The predictive functions were derived from the mixed models that were applied on a continuous frequency (50–600 min^{-1}) and obstruction spectrum (2–8 mm). 1 kPa = 7.5 mmHg.

Increasing frequency further accentuates this effect³¹ and stresses the importance of the use of sufficiently low ventilation frequencies for subjects with airway obstruction.

In analogy to the reduction of V_T , we found a gradual increase in p_aCO_2 with decreasing stent ID.³² Interestingly, p_aO_2 was only mildly reduced for the downsizing step from 8- to 4-mm stent ID (*i.e.*, 75% obstruction). Further reduction of stent ID to 2 mm (94% obstruction) decreased p_aO_2 by approximately 30 to 50%, but notably, still within the clinically acceptable range. It is obvious that the low-frequency component of SHFJV was responsible for the observed differences between HFJV and SHFJV. Apparently, the low-frequency component was low enough to allow for the passage of greater than 100 ml of V_T even at 94% airway obstruction.

There has been some controversy about the safety of prestenotic JV in obstructed airways. From their results from bench studies, some claim that detrimental intrapulmonary pressures occur during prestenotic JV,^{32,33} whereas others report intrapulmonary pressures within acceptable limits.^{34,35} In this *in vivo* investigation, intrapulmonary peak pressure never exceeded 25 cm H₂O. Airway pressure measured at the prestenotic level always overestimated true intrapulmonary

pressure, despite a stark discrepancy between the two measurements in severe obstruction. Although we noted a concomitant underestimation of intrapulmonary PEEP, we believe that prestenotic JV with (1) a jet injector position at sufficient distance from the stenotic segment³⁵ and (2) airway pressure monitoring more than 6 cm distal of the jet injector³⁶ help prevent inadvertently high intrapulmonary peak pressure and its complications in subjects with severe airway obstruction.

Limitations

The amount of PEEP produced by JV depends on the frequency used. At very low rates, there is practically no PEEP, whereas increasing f_{HF} is known to lead to the development of an “auto-PEEP”^{10,17} In our protocol, we chose to define PEEP not as the pressure at end-expiration, but as the lowest observed pressure during a respiratory cycle. At lower frequencies, this probably reflects the true value of PEEP. At higher rates however, the “PEEP effect” has been suggested to be more closely related to the mean airway pressure.²⁶ Thus, at f_{HF} greater than 100 min^{-1} , our definition of PEEP may have underestimated the effective PEEP. However, our definition allows us to describe more exactly the influence of

frequency on airway pressure and permits direct comparison of the minimum airway pressure at different frequencies.

Furthermore, the interaction of JV delivery mode and various ventilator settings during HFJV is not well elucidated. We exclusively used above-stenosis JV in the current study, and therefore, our observations of pre- and poststenotic pressure and the resulting safety implications apply exclusively to above-stenosis, catheter-free JV. Further systematic research is needed to appraise to what extent our findings on above-stenosis ventilation can be extrapolated to other routes of JV application.

We used OEP to noninvasively monitor chest wall volume changes as a surrogate for lung volume changes. Blood volume shifts, gas compression, and airway distension rather than true recruitment could theoretically be sources of error. However, previous studies have shown a good correlation between chest wall and lung volumes.^{11,15}

A statistical limitation of the study is that the mixed model equation is calculated from our observed values. Therefore, the results from the model analysis apply with the stated CIs to the range of frequencies we investigated, which restricts the applicability of the model outside of these boundaries. However, we have previously shown that higher frequencies are unlikely to be useful for JV.¹⁰

Finally, we performed our investigations in a porcine model, and the results cannot be directly transferred to the behavior of humans with severe airway obstruction. For instance, the respiratory system compliance is lower in pigs, and airway closure occurs at much lower FRC than in humans. Furthermore, upon positive pressure, stenotic tissue may have a greater expansion capacity than the stents we used in our model in which each stent was fixed in diameter. In patients, especially during spontaneous ventilation, dynamic obstruction may contribute to the deterioration of ventilation. The latter phenomenon is less likely to significantly influence the ventilation efficacy during positive pressure ventilation such as (S)HFJV, but the development of intrinsic PEEP may go undetected when pressure is monitored only above the stent.²³

Conclusion

To conclude, HFJV may provide adequate oxygenation at most frequencies when the degree of stenosis is low, but the addition of a low-frequency jet results in improved gas exchange and lung volume, especially when challenged with a high-degree stenosis.

The choice of frequency for the f_{HF} component has little impact in SHFJV, whereas for HFJV, the chosen frequency has an important impact on carbon dioxide removal and oxygenation, in a reciprocal manner. Thus, the HFJV frequency should not exceed 150 min^{-1} in subjects with severe airway obstruction.

Acknowledgments

The skilled technical laboratory assistance of Agneta Roneus, M.Sc., Karin Fagerbrink, M.Sc., and Maria Swålas, M.Sc. (all from Hedenstierna Laboratory, Department of Surgical

Sciences, Uppsala University, Uppsala, Sweden), is gratefully acknowledged. The authors also thank Marcus Thureson, Ph.D., Statisticon AB, Uppsala, Sweden, for assistance with the statistical analyses.

This work was supported by grants from Uppsala University Hospital (Uppsala, Sweden), the Tore Nilsson Research Foundation (Stockholm, Sweden), the Swedish Heart Lung Foundation (Stockholm, Sweden), Swedish Medical Research Council (Stockholm, Sweden, grant no. 5315), ALF funds (Uppsala County, Sweden), and Politecnico di Milano (Milan, Italy).

Competing Interests

Dr. Aliverti is one of the inventors of optoelectronic plethysmography. The patents are owned by Politecnico di Milano (Milan, Italy) and licensed to BTS Spa Company (Milan, Italy). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Sütterlin: Department of Surgical Sciences, Uppsala University, Uppsala University Hospital, entrance 70, S-75185 Uppsala, Sweden. robert.sutterlin@surgsci.uu.se. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Lemaire A, Burfeind WR, Toloza E, Balderson S, Petersen RP, Harpole DH Jr, D'Amico TA: Outcomes of tracheobronchial stents in patients with malignant airway disease. *Ann Thorac Surg* 2005; 80:434–7; discussion 437–8
2. Oviatt PL, Stather DR, Michaud G, Maceachern P, Tremblay A: Exercise capacity, lung function, and quality of life after interventional bronchoscopy. *J Thorac Oncol* 2011; 6:38–42
3. Conacher ID: Anaesthesia and tracheobronchial stenting for central airway obstruction in adults. *Br J Anaesth* 2003; 90:367–74
4. Rezaie-Majd A, Bigenzahn W, Denk DM, Burian M, Kornfehl J, Grasl MCh, Ihra G, Aloy A: Superimposed high-frequency jet ventilation (SHFJV) for endoscopic laryngotracheal surgery in more than 1500 patients. *Br J Anaesth* 2006; 96:650–9
5. Schragl E, Donner A, Kashanipour A, Gradwohl I, Ullrich R, Aloy A: [Anesthesia in acute respiratory tract obstructions caused by high degree laryngeal and tracheobronchial stenoses]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 1994; 29:269–77
6. Ihra G, Hieber C, Kraincuk P, Marker E, Kashanipour A, Aloy A: [Clinical experiences with the double jet technique superimposed HFJV (high frequency jet ventilation) during laryngotracheal surgery]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2000; 35:509–14
7. Schragl E, Donner A, Grasl MC, Kashanipour A, Aloy A: [Ventilation during tracheotomy in extensive, 90% laryngeal stenosis using superimposed high frequency jet ventilation *via* the jet laryngoscope]. *Laryngorhinootologie* 1995; 74:223–6
8. Bacher A, Pichler K, Aloy A: Supraglottic combined frequency jet ventilation *versus* subglottic monofrequent jet ventilation in patients undergoing microlaryngeal surgery. *Anesth Analg* 2000; 90:460–5
9. Kraincuk P, Körmöcz G, Prokop M, Ihra G, Aloy A: Alveolar recruitment of atelectasis under combined high-frequency jet ventilation: A computed tomography study. *Intensive Care Med* 2003; 29:1265–72

10. Sütterlin R, Priori R, Larsson A, LoMauro A, Frykholm P, Aliverti A: Frequency dependence of lung volume changes during superimposed high-frequency jet ventilation and high-frequency jet ventilation. *Br J Anaesth* 2014; 112:141–9
11. Cala SJ, Kenyon CM, Ferrigno G, Carnevali P, Aliverti A, Pedotti A, Macklem PT, Rochester DF: Chest wall and lung volume estimation by optical reflectance motion analysis. *J Appl Physiol* (1985) 1996; 81:2680–9
12. Ferrigno G, Carnevali P, Aliverti A, Molteni F, Beulcke G, Pedotti A: Three-dimensional optical analysis of chest wall motion. *J Appl Physiol* (1985) 1994; 77:1224–31
13. Aliverti A, Dellacà R, Pelosi P, Chiumello D, Pedotti A, Gattinoni L: Optoelectronic plethysmography in intensive care patients. *Am J Respir Crit Care Med* 2000; 161:1546–52
14. Aliverti A, Carlesso E, Dellacà R, Pelosi P, Chiumello D, Pedotti A, Gattinoni L: Chest wall mechanics during pressure support ventilation. *Crit Care* 2006; 10:R54
15. Dellacà RL, Aliverti A, Pelosi P, Carlesso E, Chiumello D, Pedotti A, Gattinoni L: Estimation of end-expiratory lung volume variations by optoelectronic plethysmography. *Crit Care Med* 2001; 29:1807–11
16. Aliverti A, Kostic P, Lo Mauro A, Andersson-Olerud M, Quaranta M, Pedotti A, Hedenstierna G, Frykholm P: Effects of propofol anaesthesia on thoraco-abdominal volume variations during spontaneous breathing and mechanical ventilation. *Acta Anaesthesiol Scand* 2011; 55:588–96
17. Leiter A, Aliverti A, Priori R, Staun P, Lo Mauro A, Larsson A, Frykholm P: Comparison of superimposed high-frequency jet ventilation with conventional jet ventilation for laryngeal surgery. *Br J Anaesth* 2012; 108:690–7
18. Shannon CE: Communication in the presence of noise. *Proceedings of the Institute of Radio Engineers* 1949; 37:10–21
19. Mausser G, Schellauf A, Scherübl M, Arrer A, Schwarz G: Experimental model of laryngotracheal stenosis in infants: Effects of different high-frequency jet ventilation patterns on pulmonary parameters. *Paediatr Anaesth* 2011; 21:894–9
20. Rouby JJ, Simonneau G, Benhamou D, Sartene R, Sardnal F, Deriaz H, Duroux P, Viars P: Factors influencing pulmonary volumes and CO₂ elimination during high-frequency jet ventilation. *ANESTHESIOLOGY* 1985; 63:473–82
21. Rossing TH, Slutsky AS, Lehr JL, Drinker PA, Kamm R, Drazen JM: Tidal volume and frequency dependence of carbon dioxide elimination by high-frequency ventilation. *N Engl J Med* 1981; 305:1375–9
22. Takahashi H, Takezawa J, Nishijima MK, Shindoh Y, Kim SY, Taenaka N, Shimada Y, Yoshiya I: Effects of driving pressure and respiratory rate on airway pressure and PaCO₂ in rabbits during high-frequency jet ventilation. *Crit Care Med* 1985; 13:728–32
23. Ihra GC, Tsai CJ, Kimberger O: Intrinsic positive end-expiratory pressure at various frequencies of supraglottic jet ventilation in a model of dynamic upper airway obstruction. *Anesth Analg* 2010; 111:703–6
24. Lin ES, Jones MJ, Mottram SD, Smith BE, Smith G: Relationship between resonance and gas exchange during high frequency jet ventilation. *Br J Anaesth* 1990; 64:453–9
25. Smith RB, Klain M, Babinski M: Limits of high frequency percutaneous transtracheal jet ventilation using a fluidic logic controlled ventilator. *Can Anaesth Soc J* 1980; 27:351–6
26. Rouby JJ, Fuscuardi J, Bourgain JL, Viars P: High-frequency jet ventilation in postoperative respiratory failure: Determinants of oxygenation. *ANESTHESIOLOGY* 1983; 59:281–7
27. Holmdahl MH: Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chir Scand Suppl* 1956; 212:1–128
28. Nielsen ND, Andersen G, Kjaergaard B, Staerkind ME, Larsson A: Alveolar accumulation/concentration of nitrogen during apneic oxygenation with arteriovenous carbon dioxide removal. *ASAIO J* 2010; 56:30–4
29. Ihra G, Hieber C, Schabernig C, Kraincuk P, Adel S, Plöchl W, Aloy A: Supralaryngeal tubeless combined high-frequency jet ventilation for laser surgery of the larynx and trachea. *Br J Anaesth* 1999; 83:940–2
30. Dworkin R, Benumof JL, Benumof R, Karagianes TG: The effective tracheal diameter that causes air trapping during jet ventilation. *J Cardiothorac Anesth* 1990; 4:731–6
31. Spackman DR, Kellow N, White SA, Seed PT, Feneck RO: High frequency jet ventilation and gas trapping. *Br J Anaesth* 1999; 83:708–14
32. Buczkowski PW, Fombon FN, Lin ES, Russell WC, Thompson JP: Air entrainment during high-frequency jet ventilation in a model of upper tracheal stenosis. *Br J Anaesth* 2007; 99:891–7
33. Ng A, Russell WC, Harvey N, Thompson JP: Comparing methods of administering high-frequency jet ventilation in a model of laryngotracheal stenosis. *Anesth Analg* 2002; 95:764–9
34. Mausser G, Schwarz G: Air entrainment during high-frequency jet ventilation. *Br J Anaesth* 2008; 100:418; author reply 418–9
35. Ihra GC, Heid A, Pernerstorfer T: Airway stenosis-related increase of pulmonary pressure during high-frequency jet ventilation depends on injector's position. *Anesth Analg* 2009; 109:461–5
36. Aloy A, Schachner M, Cancura W: Tubeless translaryngeal superimposed jet ventilation. *Eur Arch Otorhinolaryngol* 1991; 248:475–8