

ORIGINAL ARTICLE

Neurally adjusted ventilatory assist feasibility during anaesthesia

A randomised crossover study of two anaesthetics in a large animal model

Francesca Campoccia Jalde, Fredrik Jalde, Peter V. Sackey, Peter J. Radell, Staffan Eksborg and Mats K.E.B. Wallin

BACKGROUND Spontaneous breathing during mechanical ventilation improves gas exchange by redistribution of ventilation to dependent lung regions. Neurally adjusted ventilatory assist (NAVA) supports spontaneous breathing in proportion to the electrical activity of the diaphragm (EAdi). NAVA has never been used in the operating room and no studies have systematically addressed the influence of different anaesthetic drugs on EAdi.

OBJECTIVES The aim of this study was to test the feasibility of NAVA under sedation and anaesthesia with two commonly used anaesthetics, sevoflurane and propofol, with and without remifentanyl, and to study their effects on EAdi and breathing mechanics.

DESIGN A crossover study with factorial design of NAVA during sedation and anaesthesia in pigs.

SETTING University basic science laboratory in Uppsala, Sweden, from March 2009 to February 2011.

ANIMALS Nine juvenile pigs were used for the experiment.

INTERVENTIONS The lungs were ventilated using NAVA while the animals were sedated and anaesthetised with

continuous low-dose ketamine combined with sevoflurane and propofol, with and without remifentanyl.

MAIN OUTCOME MEASURES During the last 5 min of each study period (total eight steps) EAdi, breathing pattern, blood gas analysis, neuromechanical efficiency (NME) and neuroventilatory efficiency (NVE) during NAVA were determined.

RESULTS EAdi was preserved and normoventilation was reached with both sevoflurane and propofol during sedation as well as anaesthesia. Tidal volume (Vt) was significantly lower with sevoflurane anaesthesia than with propofol. NME was significantly higher with sevoflurane than with propofol during anaesthesia with and without remifentanyl. NVE was significantly higher with sevoflurane than with propofol during sedation and anaesthesia.

CONCLUSION NAVA is feasible during ketamine-propofol and ketamine-sevoflurane anaesthesia in pigs. Sevoflurane promotes lower Vt, and affects NME and NVE less than propofol. Our data warrant studies of NAVA in humans undergoing anaesthesia.

Published online 7 January 2016

Introduction

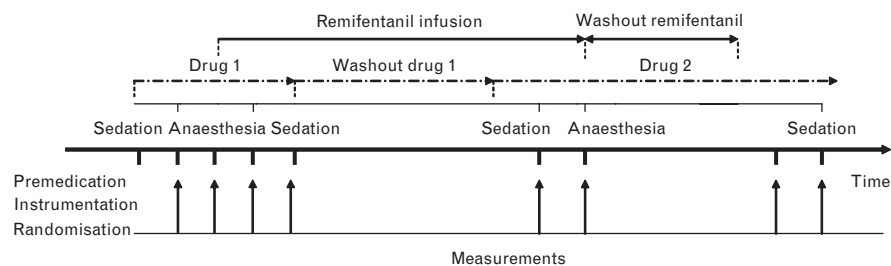
Spontaneous breathing during mechanical ventilation is known to improve gas exchange by redistribution of ventilation to dependent lung regions.¹ During general

anaesthesia, ventilation tends to be more ventrally distributed in the supine position with controlled ventilation and with pressure support (PS) ventilation.²

From the Department of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska University Hospital, Solna; Department of Physiology and Pharmacology, Karolinska Institute, Stockholm (FCJ); Maquet Critical Care (FJ); Department of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska University Hospital, Solna; Department of Physiology and Pharmacology, Karolinska Institute (PVS); Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine (PJR); Department of Women's and Children's Health (SE); Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institute, Stockholm; Maquet Critical Care, Solna, Sweden (MKEBW)

Correspondence to Francesca Campoccia Jalde, MD, Department of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska Universitetssjukhuset, Karolinska vägen, Solna, 171 76 Stockholm, Sweden
Tel: +0046 703947741; fax: +46 8 307795; e mail: francesca.campoccia-jalde@karolinska.se

Fig. 1



Study timeline.

Compared with pressure support, neurally adjusted ventilatory assist (NAVA) appears to improve the ventilation of dependent lung regions, promoting more homogeneous lung aeration.⁹ Potentially, the use of NAVA during surgery might reduce the risk of lung collapse and postoperative lung complications. NAVA in anaesthetised patients in the operating room has not yet been described. A prerequisite for NAVA function is that the electrical activity of the diaphragm (EAdi) is preserved. Potentially, EAdi, regulated by central respiratory drive, could be suppressed by anaesthetic drugs. To our knowledge, there are no studies systematically evaluating how EAdi is affected by commonly used sedatives and anaesthetics.

The primary aim of our study was to test the feasibility of NAVA during anaesthesia with two commonly used anaesthetics, sevoflurane and propofol, and to study the effects of these drugs, in sedative and anaesthetic doses, on the EAdi signal and on breathing mechanics in pigs. Volatile anaesthetics in clinically relevant doses are considered to selectively suppress consciousness and preserve respiratory drive^{4,5} and propofol partially inhibits neuromuscular transmission and contraction at the muscle membrane level.^{6–8} Consequently, a secondary aim was to compare propofol and sevoflurane with regard to breathing pattern and neuromechanical coupling.

Opioids such as remifentanil are known to produce dose-dependent respiratory depression. Although the high opioid doses typically used at induction of anaesthesia or during surgery may abolish respiratory drive, lower doses are commonly used in surgery when neuraxial blockades are employed, or towards the end of the operation. Opioids in low doses during anaesthesia could potentially allow preservation of respiratory drive. We therefore also aimed to investigate the feasibility of NAVA when propofol or sevoflurane were combined with a low dose of remifentanil.

Materials and methods

Ethical approval for this study was provided by the Animal Research Committee of Uppsala University, Uppsala, Sweden on 26 October 2007 (Dnr C230/7,

Chairperson G. Folkesson and renewal Dnr C369/9 on 29 January 2010, Chairperson E. Eriksson).

This study had a randomised crossover design. The animals received ketamine combined with sevoflurane or propofol in random order, first alone and then with remifentanil $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$. This was the highest dose of remifentanil that allowed spontaneous breathing in a previous pilot study. Each animal received both anaesthetics in sedative and anaesthetic doses (Fig. 1 and Supplemental Digital Content Table 1, <http://links.lww.com/EJA/A82>).

Nine juvenile mixed country breed male pigs with a median [interquartile range (IQR)] body weight of 27 (26 to 31) kg were studied. The animals were pre-anaesthetised with an intramuscular bolus of ketamine 10 mg kg^{-1} . An intravenous bolus dose of propofol 2 mg kg^{-1} was then injected before instrumentation. In a pilot study of five pigs, we observed that very high propofol doses were necessary to reach the anaesthetic level in pigs when propofol was used as a single agent. These high doses of propofol ultimately provoked sudden arrhythmias and refractory circulatory collapse in some animals in the pilot study. Therefore, a complementary low-dose infusion of intravenous ketamine was necessary during the experiment to reduce the total amount of propofol needed. Consequently, intravenous ketamine $5 \text{ mg kg}^{-1} \text{h}^{-1}$ and Ringer's solution $10 \text{ ml kg}^{-1} \text{min}^{-1}$ were continuously infused throughout the study, and also during sevoflurane sedation and anaesthesia.

The trachea was intubated and the lungs normoventilated with volume control during the preparation, using a SERVO-i ventilator (Maquet Critical Care, Solna, Sweden). A femoral artery was cannulated in order to monitor blood pressure and for blood gas measurements at different time points. The oxygen saturation was measured with pulse oximetry at the tail. Rectally measured body temperature was maintained between 37.5° and 39.0°C with a heated surgical table. A special 16-FG oesophageal catheter with an array of electrodes (Neurovent Research, Toronto, Canada) was inserted into the oesophagus and was used to measure EAdi.

In a pilot study using five pigs, we applied, in a stepwise manner, an increase of the anaesthetic drug after performing standardised stimuli. We defined sedation as when the animal could tolerate a needle pricked into the leg, but not a claw pinched with tongs (Digital calliper 0 to 150 mm; Mitutoyo, Upplands Väsby, Sweden). We defined anaesthesia as the level at which the animal tolerated the claw being pinched with tongs without moving the paw and without giving any sign of distress.^{9,10} The force applied by the tongs was standardised, generating a 10% reduction of the claw size for 10 s.

During instrumentation, the lungs were ventilated using volume control, a tidal volume (V_t) of 6 ml kg^{-1} , positive end-expiratory pressure (PEEP) of $3 \text{ cmH}_2\text{O}$, FiO_2 0.4 and a respiratory rate of 20 min^{-1} , until EAdi was detected. At this point, ventilation was switched to NAVA. After each level of sedation or anaesthesia was reached at a specific sedative and remifentanyl combination, the lungs were ventilated on NAVA for 15 min. Sedation and anaesthesia were set according to the standardised stimuli described above. If a $p\text{aCO}_2$ concentration below 7 kPa could not be achieved using NAVA, the ventilator was switched to volume control at normoventilation, and sedation was reduced stepwise (by 10% decrements) and titrated to fulfil the clinical criteria as well as the target $p\text{aCO}_2$ requirement in NAVA. If it was not possible to meet both criteria, the animal was excluded from the study. This happened in one out of 10 pigs. Data from the final 5 min of each period were recorded for later analysis. An arterial blood gas sample, haemodynamic data and respiratory parameters were also obtained during these 5 min.

Before changing to the next sedation or anaesthesia level, the animals were exposed to a 30-s expiratory pause to allow measurement of neuromechanical efficiency (NME; see below).

During the periods in which remifentanyl was used, the infusion was kept at $0.1 \mu\text{g kg}^{-1} \text{ min}^{-1}$, because the pilot study revealed that at higher doses, the animals became apnoeic. The infusion was followed by a 40-min washout period. The switch between sevoflurane and propofol was followed by a washout period of 1 h before any new recordings were made.

NAVA is currently available only in Maquet's ICU ventilator SERVO-i/SERVO-U, a ventilator for which there is currently no available vaporiser. Therefore, sevoflurane was delivered via additional flow through a specially designed activated carbon filter (55-ml dead space) positioned at the Y-piece. The coal filter prototype designed by Maquet Critical Care's research department was obtained by modifying a heat and moisture exchanger (Servo Filter Humidifier 172; Maquet Critical Care, Solna, Sweden) by replacing the existing filter with 1.2 g of KF-1700FL, a nonwoven activated carbon filter from Toyobo Co Ltd, Tokyo, Japan (Picture 1 in

Supplemental Digital Content, <http://links.lww.com/EJA/A82>). The sevoflurane concentration was measured continuously after the coal filter with a gas analyser (Capnomac Ultima, Datex, Finland).

NAVA supports spontaneous breathing in proportion to the electrical activity of the diaphragm (EAdi, in μV).¹¹ The multiplication factor applied for the conversion from EAdi to pressure is referred to as the NAVA level and it is the proportionality factor between the EAdi and the pressure delivered. An increase in assist leads to reduction in EAdi within the same breath due to the presence of neural feedback. We used a fixed low NAVA level of $0.5 \text{ cmH}_2\text{O } \mu\text{V}^{-1}$ in all the steps, in order to not suppress respiratory drive.

Two software programmes were used for data collection. Servo Tracker (version 3.33; Maquet Critical Care) was connected to the SERVO-i and collected signals available from the ventilator such as EAdi, airway pressure and flow. These ServoTracker signals were sent with a frequency of 100 Hz together with the analogue end-tidal sevoflurane concentration signal to the second programme Acknowledge (version 3.9.1) for simultaneous data recording. The data analysis was based on these recordings.

The analysis of EAdi and of respiratory variables was performed offline. An average of the variables was calculated for the last 5 min of each 15-min run. The variability of V_t was calculated using coefficient of variation, CV_{V_t} (SD/mean), expressed as a percentage. The incidence of sighs was calculated manually in the 5-min recording period of each study step and was expressed as sighs h^{-1} for literature comparisons. Sighs were defined as volumes more than twice the average V_t .¹² The number of apnoeic episodes longer than 5 s was also determined and expressed as apnoeas h^{-1} . In order to assess possible lung recruitment after sighs, the dynamic compliance (C_{dyn}) of five breaths before and after identified sighs was calculated and compared.

NME ($\Delta\text{Paw}/\Delta\text{EAdi}$) is an index of muscular performance measured when the individual makes an inspiratory effort with the expiratory valve closed.^{13–15} NME was obtained at the first breathing effort during administered airway occlusion. The quotient between ΔPaw and ΔEAdi was calculated all along the occluded effort (sample by sample, 100 Hz) and the NME was obtained as a median of these values. The NME values were compared between sevoflurane and propofol to detect whether the anaesthetics affected muscle performance differently. The analysis of the calculated variables was performed using an m-script developed in Matlab version R2007b (Mathworks, Natick, Massachusetts, USA).

Neuroventilatory efficiency (NVE, V_t/EAdi) is an index reflecting the capacity of the individual to translate respiratory drive (measured as diaphragmatic electrical

Table 1 Baseline respiratory parameters and blood gas analyses

	Sedation		Without remifentanyl			
	Propofol	Sevoflurane	P	Anaesthesia		P
				Propofol	Sevoflurane	
Vt (ml)	350 (217 to 392)	294 (257 to 357)	0.301	318 (238 to 408)	235 (192 to 278)	0.004
RR (min ⁻¹)	23 (19 to 25)	26 (23 to 27)	0.214	21 (15 to 23)	24 (22 to 26)	0.097
EAdi peak (μV)	8.3 (7.3 to 10.9)	6.9 (6.2 to 10.7)	0.129	8.4 (7.5 to 10.6)	4.7 (3.9 to 8.4)	0.004
Paw _{mean} (cmH ₂ O)	6.7 (6 to 7)	6.8 (5.5 to 7.2)	0.164	6.9 (6.1 to 7.4)	5.9 (5.3 to 6.4)	0.020
paO ₂ (kPa)	24 (19 to 27)	23 (22 to 24)	0.734	23 (18 to 26)	22 (18 to 22)	0.570
paCO ₂ (kPa)	5.5 (5.3 to 5.9)	5.5 (5.2 to 5.6)	0.496	6 (5.7 to 6.2)	6 (5.6 to 6.3)	0.496
	With remifentanyl					
Vt (ml)	323 (265 to 422)	316 (235 to 415)	0.359	329 (275 to 402)	270 (240 to 329)	0.008
RR (min ⁻¹)	20 (17 to 24)	26 (24 to 27)	0.012	16 (13 to 22)	22 (19 to 25)	0.021
EAdi peak (μV)	8.7 (7.1 to 12.4)	5.6 (4.7 to 10)	0.012	9.4 (7.5 to 11.8)	6.5 (4.8 to 8.5)	0.004
Paw _{mean} (cmH ₂ O)	7.2 (6.5 to 7.7)	6.5 (5.5 to 6.9)	0.004	7.1 (6.3 to 8.0)	5.9 (5.6 to 6.5)	0.004
paO ₂ (kPa)	22 (18 to 25)	22 (21 to 25)	0.203	20 (19 to 21)	22 (19 to 24)	0.734
paCO ₂ (kPa)	6 (5.5 to 6.3)	5.4 (5 to 5.6)	0.008	6.2 (6.1 to 6.8)	6.3 (6 to 6.5)	0.300

Data are median (IQR). EAdi peak, electrical activity of diaphragm inspiratory peak value; Paw, mean airway pressure; RR, respiratory rate; Vt, tidal volume.

activity) into ventilatory volume.¹⁶ This index is affected by the mechanical properties of the respiratory system (resistance and compliance) and by the NME. NVE has recently been used to study the physiological response to PEEP changes¹⁷ and as a bedside monitor during weaning.^{13,18} The NVE_{NAVA} was calculated as the quotient between Vt and the integral of the inspiratory EAdi. The NVE_{NAVA} median value over the 5-min period was obtained in our study for all the steps and compared between sevoflurane and propofol. In our study, NVE was obtained with a constant NAVA level, because the main purpose of measuring NVE was to compare values between sevoflurane and propofol.

Statistical analysis

Statistical analysis was undertaken using IBM SPSS Statistics version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The results are expressed as median (IQR). The data were analysed using nonparametric Wilcoxon signed ranks tests for comparison of related samples. The level of significance was set to *P* values below 0.05 (two-tailed tests).

Results

In both sedation and anaesthesia, the EAdi signal, oxygenation and ventilation were preserved with both drugs, without adjustments in the NAVA level. Oxygenation and CO₂ values were similar between anaesthetics (Table 1).

During sevoflurane anaesthesia with or without remifentanyl, the EAdi amplitude, Vt and airway pressure (Paw) were lower than with propofol (Fig. 2, Table 1). Without remifentanyl, respiratory rate did not differ between anaesthetics. Respiratory rate was lower with propofol-remifentanyl than with sevoflurane-remifentanyl.

With propofol, CV_{Vt} was higher than with sevoflurane during sedation [34 (26 to 35)% vs. 13 (7 to 27)%, *P*=0.03] and during anaesthesia [27 (19 to 29)% vs. 11

(10 to 20)%, *P*=0.01] (Supplemental Digital Content Table 2, <http://links.lww.com/EJA/A82>).

Figure 3 shows the number of sighs with the different sedatives. The number of sighs observed in the 5-min recording period was higher with propofol than with sevoflurane during both anaesthesia (*P*=0.03) and sedation (*P*=0.05) without remifentanyl. The number of apnoeic episodes lasting more than 5 s followed the same pattern, being more frequent with propofol than sevoflurane during both sedation (*P*=0.04) and anaesthesia (*P*=0.03). When remifentanyl was introduced, the differences in sigh frequency between groups were no longer present (Fig. 3), but the number of apnoeic episodes lasting more than 5 s remained more frequent during sedation with propofol than with sevoflurane (*P*=0.03). During anaesthesia, this difference in sighs did not reach statistical significance (*P*=0.12) (Supplemental Digital Content Table 3, <http://links.lww.com/EJA/A82>).

Comparing the C_{dyn} of five breaths before and after the sighs did not give any indication of improvement in C_{dyn} after the sigh, with or without remifentanyl (Table 2).

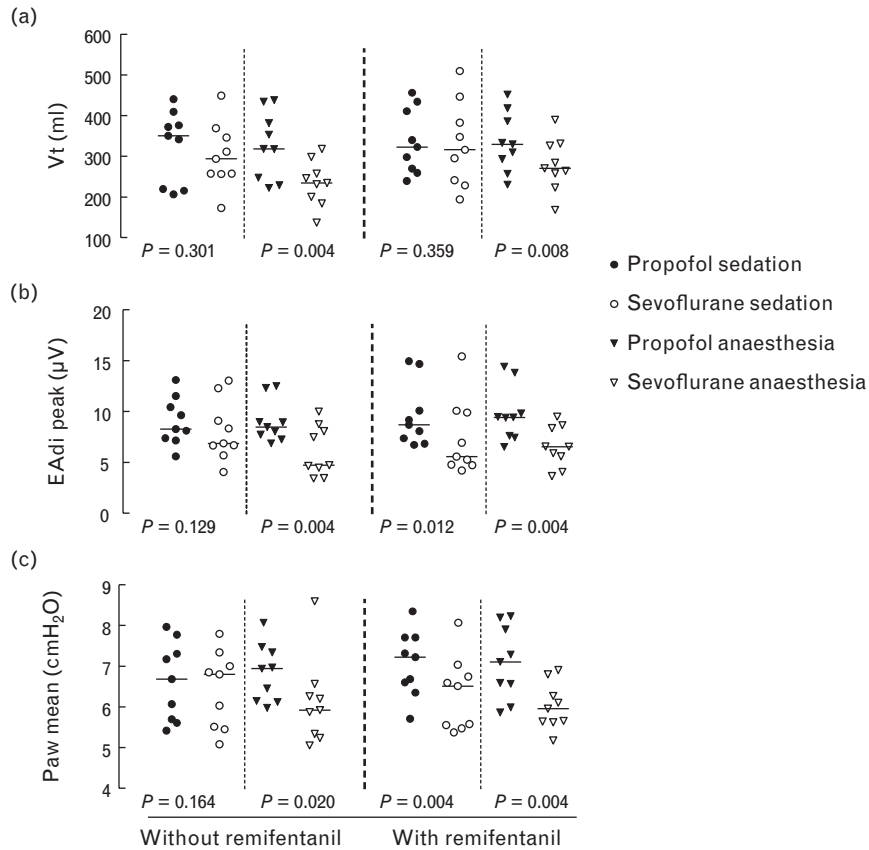
Neuromuscular and neuroventilatory efficiency

At occlusion, NME was higher with sevoflurane than with propofol during anaesthesia, both with and without remifentanyl. During sedation, NME was higher with sevoflurane-remifentanyl than with propofol-remifentanyl (Fig. 4 and Supplemental Digital Content Table 4, <http://links.lww.com/EJA/A82>). NVE_{NAVA} over the 5-min period was higher with sevoflurane than with propofol both with and without remifentanyl (Table 3).

Discussion

To our knowledge, this is the first study assessing the feasibility of NAVA during sedation and anaesthesia in a large animal model. We found that with both propofol and sevoflurane as the main anaesthetic, EAdi and spontaneous breathing were well preserved (Table 1). These

Fig. 2

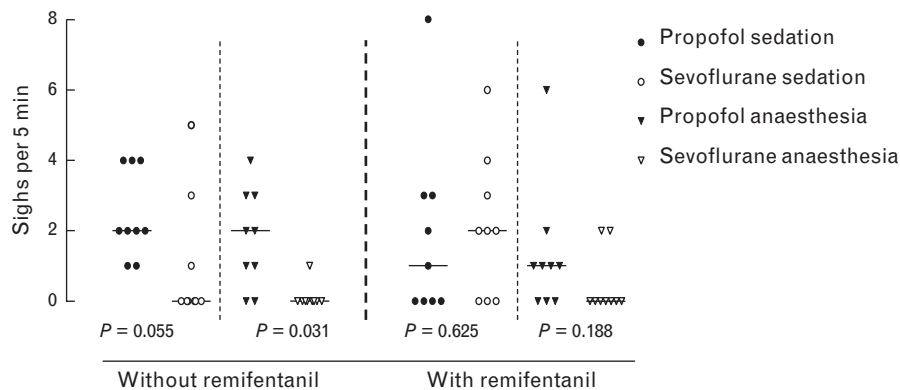


Changes in tidal volume, EAdi and airway pressure with propofol and sevoflurane. (a–c) Values of tidal volume (V_t), peak electrical activity of the diaphragm (EAdi peak), mean airway pressure (Paw mean) during sedation (dots) and anaesthesia (triangles). Left, propofol or sevoflurane alone; right, propofol or sevoflurane combined with remifentanil. P values refer to comparison between propofol and sevoflurane at each sedation level. Median value represented by horizontal line.

drugs could also be combined with remifentanil at a low dose. Our study shows that NAVA is feasible in pigs during sedation and anaesthesia with both propofol

and sevoflurane, and the findings suggest that NAVA could be used in anaesthetised patients in the operating room.

Fig. 3



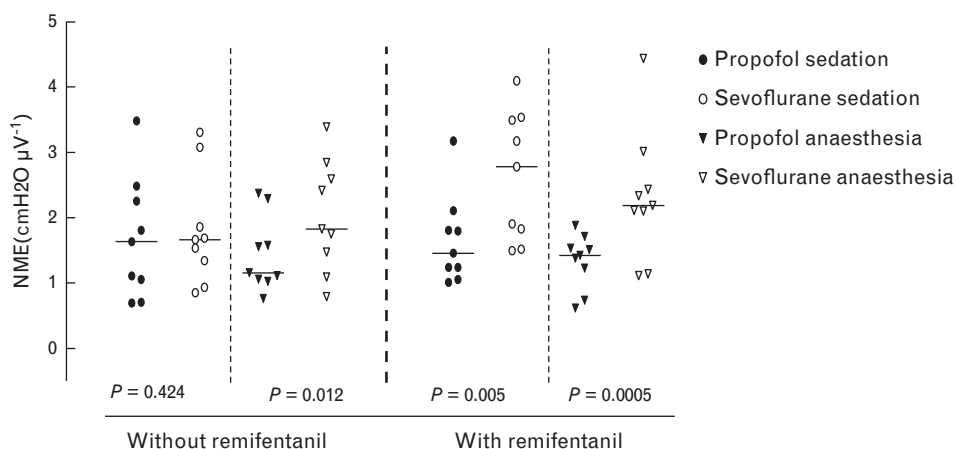
Number of sighs per 5 min during sedation (dots) and anaesthesia (triangles). Left, propofol or sevoflurane alone; right, propofol or sevoflurane combined with remifentanil. P values refer to comparison between propofol and sevoflurane at each sedation level. Median value represented by horizontal line.

Table 2 Dynamic compliance before and after a sigh

	Sedation		Without remifentanil					
	Propofol	P	Sevoflurane	P	Propofol	Anaesthesia	P	
					Propofol	P	Sevoflurane	P
Cpl _{dyn} before (ml cmH ₂ O ⁻¹)	35 (31 to 41)		53 (38 to 58)		40 (33 to 59)		43 (21 to 46)	
		0.245		0.899		0.352		0.067
Cpl _{dyn} after (ml cmH ₂ O ⁻¹)	34 (32 to 40)		51 (39 to 58)		42 (32 to 58)		39 (20 to 42)	
					With remifentanil			
Cpl _{dyn} before (ml cmH ₂ O ⁻¹)	39 (32 to 52)		47 (32 to 59)		47 (30 to 54)		39 (30 to 55)	
		0.008		0.033		0.732		0.008
Cpl _{dyn} after (ml cmH ₂ O ⁻¹)	36 (30 to 50)		44 (30 to 57)		47 (30 to 57)		34 (29 to 54)	

Dynamic compliance of 10 breaths before and after sigh within each sedation type. Data are median (IQR). Cpl_{dyn}, dynamic compliance.

Fig. 4



Neuromechanical efficiency at first occluded breath during sedation (dots) and anaesthesia (triangles). Left, propofol or sevoflurane alone; right, propofol or sevoflurane combined with remifentanil. P values refer to comparison between propofol and sevoflurane at each sedation level. Median value represented by horizontal line.

Keeping the diaphragm active during surgery may reduce intraoperative formation of lung atelectasis and thus reduce postoperative lung complications. There may be a need for higher opioid doses or neuromuscular blocking agents for induction of anaesthesia or during certain types of surgery. Furthermore, if a target *p*aco₂ cannot be reached while ventilating the lungs using NAVA, it might be more appropriate to change to a mode

of controlled mechanical ventilation. In such cases, NAVA might be considered towards the end of surgery. However, before attempts are made to use NAVA in the OR, our findings need to be confirmed in human trials.

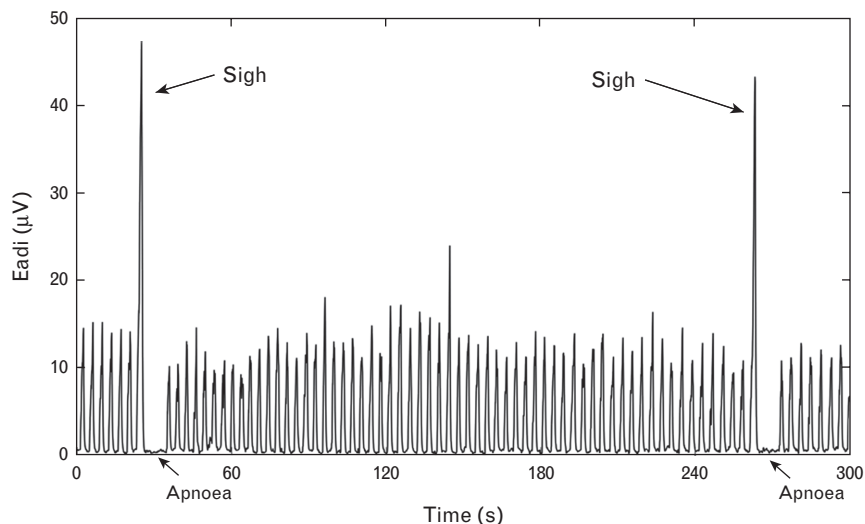
The gas exchange results show that the pigs were similarly ventilated regardless of the drug used

Table 3 Effect of propofol and sevoflurane with and without remifentanil on neuroventilatory efficiency

Sedation type	Sedation		Without remifentanil	
	NVE _{NAVA}	P	NVE _{NAVA}	Anaesthesia
Propofol	76.4 (58.9 to 105.6)	<0.001	81.5 (57.7 to 111.0)	<0.001
Sevoflurane	77.2 (61.2 to 113.6)		98.1(69.7 to 129.4)	
			With remifentanil	
Propofol	94.4 (71.0 to 129.4)	<0.001	81.4 (64.5 to 127.0)	<0.001
Sevoflurane	131.1 (96.2 to 195.0)		109.4 (84.6 to 179.0)	

Data are median (IQR). Neuroventilatory efficiency at NAVA level 0.5 for all breaths in the 5-min period. NVE_{NAVA}, neuroventilatory efficiency (ml μV⁻¹) during neurally adjusted ventilatory assist.

Fig. 5



Example of sighs in one pig during anaesthesia with propofol. The tracing shows the EAdi curve and two sighs during 5-min period. Each sigh is followed by an apnoeic period >5 s long.

(Table 1). In this short-term study, the marginally higher $p\text{aCO}_2$ with propofol-remifentanyl sedation than with sevoflurane-remifentanyl was not clinically relevant. Whether this would have clinical implications during more prolonged administration of propofol and remifentanyl is not clear.

Tidal volume variability similar to that in resting healthy individuals¹⁹ was observed in our animal model during NAVA at sedation and anaesthesia with both anaesthetic agents (Supplemental Digital Content Table 2, <http://links.lww.com/EJA/A82>). This finding is in line with recent studies in which variability in the breathing pattern was shown to be reduced in patients ventilated with PS, compared with NAVA.^{20–22} Schmidt *et al.*²¹ reported Vt variability of 20 to 30% with NAVA. Vt variability has been shown to be associated with better gas exchange²³ and gas distribution.³ The improvement in ventilation obtained with a variable breathing pattern has encouraged some groups to simulate natural variability with the so-called ‘Noisy Pressure Support’.^{24,25} With Noisy PS, a computer induces random changes in the PS level in order to produce artificial variation in the otherwise fixed Vt, which has been shown to improve gas exchange and respiratory mechanics^{25,26} and to reduce histological damage,²⁶ data indicating that this strategy is lung-protective.

Compared with randomly applied levels of PS, NAVA offers the advantage of better preservation of patient-ventilator synchrony, because each breath depends on the central inspiratory activity and is delivered in proportion to the EAdi. Although not proven to be superior to ‘noisy ventilation’, the variable tidal volumes and pressures in NAVA reflect natural variability

originating in the respiratory centre. NAVA thus contributes in a physiological process and is not a randomly set function.

Without remifentanyl, Vt variability was greater with propofol than with sevoflurane (Supplemental Digital Content Table 2, <http://links.lww.com/EJA/A82>). The larger number of sighs with propofol than with sevoflurane largely contributed to this difference in the present study. Vt variability decreased with propofol when changed from sedation to anaesthesia, in line with the findings of Vaschetto *et al.*²⁷ when studying different levels of propofol sedation.

The normal frequency of sighs in resting healthy individuals has been reported¹² to be around 10 h^{-1} . In our pig study, the sigh frequency with sevoflurane was similar to that in resting healthy individuals, whereas in the propofol group, the number of sighs was as high as 30 h^{-1} during sedation and 21 h^{-1} during anaesthesia. When remifentanyl was introduced, there were no longer differences between the two anaesthetics (Fig. 3). Most sighs during propofol administration were followed by prolonged apnoeic periods (Fig. 5 and Supplemental Digital Content Table 3, <http://links.lww.com/EJA/A82>). The observation of frequent sighs led us to further investigate the possibility of sighs being a function of lung recruitment. Further analysis of five breaths prior to and after the sighs did not reveal any differences regarding lung mechanics, as assessed by C_{dyn} (Table 2). Our interpretation is that the increased number of sighs during administration of propofol does not appear to be related to lung recruitment or changes in lung mechanics, but is more likely due to a central drug-induced mechanism. Whether this breathing pattern

has positive or negative effects over longer periods of ventilation is not clear.

Propofol alone and combined with remifentanyl produced a pattern of breathing characterised by higher EAdi, higher Paw and higher Vt (during anaesthesia) and lower respiratory rate than sevoflurane (Table 1, Fig. 2). Remifentanyl increased the number of sighs during sevoflurane administration and decreased the number of sighs during propofol sedation and anaesthesia (Fig. 3), so that the difference noted between the two drugs without remifentanyl was no longer present. This latter finding is in concordance with a study from Egbert and Bendixen,²⁸ who found that morphine reduced the frequency of sighing.

In our study, NME and NVE were lower with propofol than with sevoflurane in all steps, except during sedation without remifentanyl (Fig. 4 and Supplemental Digital Content Table 4, <http://links.lww.com/EJA/A82>). These findings could suggest that sevoflurane alone and combined with remifentanyl may preserve muscle contractility more than propofol. Propofol partially inhibits neuromuscular transmission and contraction, as demonstrated in animal and human studies in clinical propofol concentrations.^{6–8} A few studies have shown that sevoflurane could have a negative inotropic effect on the diaphragm at minimum alveolar concentration (MAC) above 2 or at 3 MAC, but these doses are above those used in clinical practice.^{29,30} Despite these differences, we did not observe fatigue or respiratory insufficiency during propofol sedation or anaesthesia during the study.

Limitations of the study

To avoid confounding effects, the same ketamine infusion that was needed for propofol was used also during sevoflurane administration. Although ketamine is considered to affect respiratory function marginally, we cannot exclude some interaction effects from its use. Our comparison of sevoflurane and propofol thus needs to be interpreted with this in mind. We assessed sedation and anaesthesia levels clinically, according to previously described clinical sedation and anaesthesia levels.^{9,10} Pinching the claw with tongs has been demonstrated to be a supramaximal stimulus in pigs,⁹ translating to surgical stimulation in patients in the operating room. One might advocate the use of an Electroencephalography-based method of monitoring sedation and anaesthesia, such as bispectral index (BIS). However, some studies show inconsistent reproducibility of BIS readings^{31,32} and ketamine use might make BIS levels even more unreliable.³³

In the present study, changes in EAdi, breathing pattern and gas exchange related to propofol and sevoflurane anaesthesia were observed over a short time period. Long-term effects cannot be inferred with certainty from

our model and protocol, and our findings need to be considered in light of this limitation.

Conclusion

NAVA can be used in pigs during propofol or sevoflurane sedation and anaesthesia, in combination with low-dose ketamine, with a well preserved EAdi signal and spontaneous breathing. Both drugs can be used in combination with a low dose of remifentanyl.

The natural variability of breathing is preserved with both drugs, although propofol creates a breathing pattern with higher Vt variability than sevoflurane, mainly due to more sighs and postsigh apnoea. The neuromechanical and neuroventilatory efficiencies during sedation and anaesthesia are better preserved with sevoflurane than with propofol.

Human trials are warranted to verify the feasibility of NAVA during anaesthesia and investigate the clinical relevance of drug-related differences on EAdi and breathing mechanics during NAVA. Further studies comparing NAVA with other modes of ventilation in the operating room are warranted in order to investigate whether NAVA provides advantages extending to the postoperative period.

Acknowledgements relating to this article

Assistance with the study: we would like to thank Mario Loncar M. Sc., Maquet Critical Care, Solna, Sweden and Arne Lindy, Maquet Critical Care, Solna, Sweden for their assistance.

Financial support and sponsorship: this work was supported by the regional agreement on medical and clinical research (ALF) between Stockholm County Council and Karolinska Institute, and by a grant from Maquet Critical Care. Maquet Critical Care provided the costs related to the experiments (animal costs, EAdi catheters and animal laboratory equipment).

Conflicts of interest: Francesca Campoccia Jalde currently receives a grant from Maquet Critical Care Company, Solna, Sweden. Mats Wallin and Fredrik Jalde are currently working at Maquet Critical Care Company, Solna, Sweden.

Presentation: preliminary data for this study were presented as a poster at the International Symposium on Intensive Care and Emergency Medicine (ISICEM) Congress on 18 March 2014, Brussels, Belgium.

References

- Putensen C, Muders T, Varelmann D, Wrigge H. The impact of spontaneous breathing during mechanical ventilation. *Curr Opin Crit Care* 2006; **12**:13–18.
- Radke OC, Schneider T, Heller AR, Koch T. Spontaneous breathing during general anesthesia prevents the ventral redistribution of ventilation as detected by electrical impedance tomography: a randomized trial. *Anesthesiology* 2012; **116**:1227–1234.
- Blankman P, Hasan D, van Mourik MS, Gommers D. Ventilation distribution measured with EIT at varying levels of pressure support and neurally adjusted ventilatory assist in patients with ALI. *Intensive Care Med* 2013; **39**:1057–1062.
- Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Crit Care Med* 2004; **32**:2241–2246.

- 5 Hooper MH, Girard TD. Sedation and weaning from mechanical ventilation: linking spontaneous awakening trials and spontaneous breathing trials to improve patient outcomes. *Crit Care Clin* 2009; **25**:515–525.
- 6 Zhang XJ, Yu G, Wen XH, *et al.* Effect of propofol on twitch diaphragmatic pressure evoked by cervical magnetic stimulation in patients. *Br J Anaesth* 2009; **102**:61–64.
- 7 Abdel-Zaher AO, Askar FG. The myoneural effects of propofol emulsion (Diprivan) on the nerve-muscle preparations of rats. *Pharmacol Res* 1997; **36**:323–332.
- 8 Lebeda MD, Wegrzynowicz ES, Wachtel RE. Propofol potentiates both pre and postsynaptic effects of vecuronium in the rat hemidiaphragm. *Br J Anaesth* 1992; **68**:282–285.
- 9 Eger EI 2nd, Johnson BH, Weiskopf RB, *et al.* Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesth Analg* 1988; **67**:1174–1176.
- 10 Boschert K, Flecknell PA, Fosse RT, *et al.* Ketamine and its use in the pig. Recommendations of the Consensus meeting on Ketamine Anaesthesia in Pigs, Bergen 1994. Ketamine Consensus Working Group. *Lab Anim* 1996; **30**:209–219.
- 11 Sinderby C, Navalesi P, Beck J, *et al.* Neural control of mechanical ventilation in respiratory failure. *Nat Med* 1999; **5**:1433–1436.
- 12 Bendixen HH, Smith GM, Mead J. Pattern of ventilation in young adults. *J Appl Physiol* 1964; **19**:195–198.
- 13 Liu L, Liu H, Yang Y, *et al.* Neuroventilatory efficiency and extubation readiness in critically ill patients. *Crit Care* 2012; **16**:R143.
- 14 American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; **166**:518–624.
- 15 Doorduyn J, Sinderby CA, Beck J, *et al.* The calcium sensitizer levosimendan improves human diaphragm function. *Am J Respir Crit Care Med* 2012; **185**:90–95.
- 16 Tuchscherer D, Z'Graggen WJ, Passath C, *et al.* Neurally adjusted ventilatory assist in patients with critical illness-associated polyneuromyopathy. *Intensive Care Med* 2011; **37**:1951–1961.
- 17 Passath C, Takala J, Tuchscherer D, *et al.* Physiologic response to changing positive end-expiratory pressure during neurally adjusted ventilatory assist in sedated, critically ill adults. *Chest* 2010; **138**:578–587.
- 18 Rozé H, Repusseau B, Perrier V, *et al.* Neuro-ventilatory efficiency during weaning from mechanical ventilation using neurally adjusted ventilatory assist. *Br J Anaesth* 2013; **111**:955–960.
- 19 Tobin MJ, Mador MJ, Guenther SM, *et al.* Variability of resting respiratory drive and timing in healthy subjects. *J Appl Physiol* 1988; **65**:309–317.
- 20 Moorhead KT, Piquilloud L, Lambermont B, *et al.* NAVA enhances tidal volume and diaphragmatic electro-myographic activity matching: a Range90 analysis of supply and demand. *J Clin Monit Comput* 2013; **27**:61–70.
- 21 Schmidt M, Demoule A, Cracco C, *et al.* Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. *Anesthesiology* 2010; **112**:670–681.
- 22 Patroniti N, Bellani G, Saccavino E, *et al.* Respiratory pattern during neurally adjusted ventilatory assist in acute respiratory failure patients. *Intensive Care Med* 2012; **38**:230–239.
- 23 Coisel Y, Chanques G, Jung B, *et al.* Neurally adjusted ventilatory assist in critically ill postoperative patients: a crossover randomized study. *Anesthesiology* 2010; **113**:925–935.
- 24 Spieth PM, Carvalho AR, Guldner A, *et al.* Effects of different levels of pressure support variability in experimental lung injury. *Anesthesiology* 2009; **110**:342–350.
- 25 Carvalho AR, Spieth PM, Guldner A, *et al.* Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury. *J Appl Physiol* 1985; **110**:1083–1092.
- 26 Spieth PM, Carvalho AR, Guldner A, *et al.* Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. *Crit Care Med* 2011; **39**:746–755.
- 27 Vaschetto R, Cammarota G, Colombo D, *et al.* Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med* 2014; **42**:74–82.
- 28 Egbert LD, Bendixen HH. Effect of morphine on breathing pattern. A possible factor in atelectasis. *JAMA* 1964; **188**:485–488.
- 29 Ide T, Kochi T, Isono S, Mizuguchi T. Diaphragmatic function during sevoflurane anaesthesia in dogs. *Can J Anaesth* 1991; **38**:116–120.
- 30 Uesugi T, Mikawa K, Nishina K, *et al.* Effects of phosphodiesterase-III inhibitors on sevoflurane-induced impairment of rat diaphragmatic function. *Acta Anaesthesiol Scand* 2005; **49**:819–826.
- 31 Niedhart DJ, Kaiser HA, Jacobsohn E, *et al.* Inpatient reproducibility of the BISxp monitor. *Anesthesiology* 2006; **104**:242–248.
- 32 Haenggi M, Ypparila-Wolters H, Buerki S, *et al.* Auditory event-related potentials, bispectral index, and entropy for the discrimination of different levels of sedation in intensive care unit patients. *Anesth Analg* 2009; **109**:807–816.
- 33 Johansen JW. Update on bispectral index monitoring. *Best Pract Res Clin Anaesthesiol* 2006; **20**:81–99.