

Effect of flumazenil on diaphragm electrical activation during weaning from mechanical ventilation after acute respiratory distress syndrome

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Editor's key points

- The mechanism by which midazolam impairs diaphragm function is unclear.
- In this exploratory study, flumazenil increased diaphragm electrical activity in patients previously sedated with midazolam.
- Increased diaphragmatic electrical activity correlated closely with increases in tidal volume.
- This suggests that midazolam has a direct effect on the diaphragm, but more data are needed.

Background. Diaphragm electrical activation (EAdi) and the ratio of tidal volume to EAdi ($V_T/EAdi$) may provide clinical information on neuroventilatory efficiency (NVE) in patients being weaned from mechanical ventilation. We tested the hypothesis that residual sedation could interfere with respiratory recovery, by assessing the effects of flumazenil on EAdi and $V_T/EAdi$ ratio.

Methods. This observational study included 13 patients breathing with pressure-support ventilation (PSV) after a long period of controlled mechanical ventilation (i.e. >4 days) plus midazolam-based sedation for acute respiratory distress syndrome. EAdi and respiratory patterns were compared before and after a bolus of flumazenil, which was given because neurological status needed to be evaluated.

Results. Flumazenil induced a significant increase in EAdi [$+71$ (41–123)%, $P=0.0002$] and V_T [$+17$ (8–32)%, $P=0.0005$], resulting in significantly decreased NVE [-34 (15–43)%]. The increased V_T was significantly correlated with the increased EAdi ($\rho=0.70$, $P=0.009$).

Conclusions. During weaning from mechanical ventilation, the diaphragmatic contribution to the breathing process may be reduced by residual midazolam-induced ventilatory depression. The increased EAdi with reversal of residual sedation was associated with a proportional increase in V_T . These findings should be considered by the attending physician when interpreting daily EAdi and V_T changes during weaning from mechanical ventilation.

Keywords: electrical diaphragm activation; mechanical ventilation; sedation; tidal volume

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The use of neurally adjusted ventilatory assist (NAVA) has enabled measurement and monitoring of diaphragm electrical activity (EAdi) at the bedside during any mode of ventilation.¹ EAdi gives clinicians the opportunity to continuously monitor neural respiratory drive to the diaphragm.² This is presented as a waveform, in which the amplitude relates to changes in motor-unit firing rate and recruitment.³ Simultaneous recording of tidal volume (V_T) determine the V_T to EAdi ratio, which expresses the ability of the neural drive to generate inspiratory volume. Consequently, the V_T to EAdi ratio may be considered equivalent to neuroventilatory efficiency (NVE).

Assessment of NVE allows us to quantify the imbalance between increased neural drive, respiratory load, and diaphragm weakness. NVE has been investigated to set PEEP levels under NAVA, with the goal of increasing NVE by

minimizing the EAdi required for V_T generation.⁴ NVE monitoring has also been proposed to help the clinician decide the optimal time for extubation.^{5–7} Interestingly, a daily increase in EAdi^{7,8} and V_T ⁸ during the spontaneous breathing trial (SBT) has been described, but without any variation in NVE,⁷ which suggests residual sedatives have an effect.

The consequences of midazolam on diaphragmatic, intercostal, and abdominal muscle function have been previously reported through the $\Delta Pga/\Delta Ppl$ index, which is the ratio of gastric-pressure changes to the ratio of pleural-pressure changes during inspiration.⁹ The possible activation of accessory muscles renders it difficult to accurately determine the contribution of diaphragm contraction on changes to ΔPpl and V_T .¹⁰ Thus, we have conducted an observational study to test the hypothesis that residual sedation induced by

midazolam, which is still present at the beginning of the weaning process, may interfere with EAdi, and that diaphragmatic function may be recovered when the effects of sedative drugs are reversed. Therefore, the effects of flumazenil on EAdi, V_T and NVE were evaluated in patients being weaned from mechanical ventilation after prolonged sedation, ensured by midazolam, and in whom rapid assessment of neurological status was required.

Methods

Study population

This observational study was approved by our institutional review board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France) and was conducted in our 22-bed intensive care unit. Informed consent from all patients or next of kin was obtained. Patients under PSV, who had been under controlled ventilation and sedated with midazolam for at least 4 consecutive days (with Ramsay scores of >3) and without a contraindication to flumazenil, were included in this study. All sedative drugs had been stopped for at least 24 h and the patients had no signs of respiratory distress under PSV. The attending physician planned an injection of flumazenil, to assess neurological status, while the patients still had positive midazolam measurements in their blood. An initial 0.5 mg bolus of flumazenil was given i.v. and could be repeated once, if necessary, until the patient was awoken.

Ventilatory management

Patients were ventilated with pressure-support ventilation (PSV), using a Servo-I ventilator that integrated the NAVA module (Maquet Critical Care, Solna, Sweden). Attending physician chose the assist level under PSV.

EAdi was registered via a feeding nasogastric tube with a multiple array of electrodes placed at its distal end (EAdi catheter, Maquet Critical Care). Initial placement of the tube was done according to anatomical considerations. Then, correct positioning of the EAdi catheter was ensured using a specific function of the ventilator, entitled 'EAdi catheter positioning'.¹¹

Each EAdi peak and all corresponding respiratory parameters, such as respiratory rates (RRs), V_T , airway pressures, and flow rates, were recorded before and after flumazenil (maximal or minimal value within 5 min after the bolus was given). The NVE at EAdi peak before injecting flumazenil and at just after the injection were also calculated. Data were collected on a computer through the Servo-I using specific software: RCR (Maquet Critical Care).

Statistical analyses

Data are expressed as means (sd) for normally distributed continuous variables, and medians (inter-quartile range, IQR) for non-normally distributed continuous variables. The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. A paired Student's *t*-test and Wilcoxon's matched-pair signed-rank tests were used to compare means and medians, respectively. Correlations between parameters were tested using Pearson's correlation

test on normally distributed variables (with confidence intervals) and Spearman's correlation test for non-normally distributed variables. All *P*-values were two-tailed, and a *P*-value of <0.05 was required to reject the null hypothesis. Statistical analyses were performed with NCSS software (Statistical Solutions Ltd, Cork, Ireland).

Results

Between February 2011 and April 2013, we prospectively included 13 consecutive patients who were weaned-off mechanical ventilation using PSV and who had received flumazenil. The patients' characteristics are summarized in Table 1. Nine of these patients (69%) were men. The median duration of mechanical controlled ventilation was 7 days (5–11) and the median duration of PSV between until flumazenil was injected was 1 day (1–2). All patients had a Ramsay score of >3 and only one patient received 0.5 mg of flumazenil twice. The mean plasma levels of benzodiazepine were 659 (674) ng ml⁻¹.

Effects of flumazenil on EAdi, V_T , and NVE

Flumazenil provoked a significant increase in EAdi and V_T , and a decrease in NVE (Table 2). The median differences were +17 (8–32)% for V_T ($P=0.0005$), +71 (41–123)% for EAdi ($P=0.0002$), and –34 (15–43)% ml μV^{-1} for NVE ($P=0.0002$) (Fig. 1). These increases of EAdi and V_T with flumazenil were not correlated to the level of plasma benzodiazepine ($\rho=0.13$; $P=0.65$ and $\rho=-0.01$; $P=0.77$, respectively).

Correlations between EAdi and V_T

There was no correlation between EAdi and V_T before and after the flumazenil injection ($\rho=0.05$, $P=0.85$ and $\rho=-0.3$, $P=0.30$, respectively). However, as shown in Figure 1, changes in V_T induced by flumazenil, in each patient, were correlated to changes in EAdi ($\rho=0.70$, $P=0.009$) (Fig. 2).

Effects of flumazenil on RR and Ti

A significant increase in RR was noted after flumazenil was given [+11 (22)%, $P=0.03$]. This increased RR was associated with an almost significant decrease in Ti [–0.07 (0.12)%, $P=0.07$]. Ti was correlated with RR before and after flumazenil ($r=-0.84$, $P=0.0003$ and $r=-0.91$, $P<0.0001$, respectively), but not to V_T before and after flumazenil ($r=0.47$, $P=0.10$ and $r=0.54$, $P=0.05$, respectively). Moreover, the variation in V_T was not correlated with the variation in Ti ($r=-0.20$, $P=0.50$).

Effects of flumazenil on haemodynamics

Significant increases in heart rate and systolic arterial pressure were observed after injecting flumazenil [+7 (8)%, $P=0.007$ and +17 (10)%, $P<0.0001$, respectively].

Correlations between NVE pressure support and arterial blood gases

NVE before flumazenil was not correlated with the level of pressure support ($\rho=-0.13$, $P=0.65$), $Pa_{O_2}/F_{I_{O_2}}$ ($\rho=0.10$, $P=0.73$),

Table 1 Characteristics of the patients included in the study ($n=13$). Data are expressed as mean (SD) or median (inter-quartile range). VCV, volume-controlled ventilation; PSV, pressure-support ventilation; ARDS, acute respiratory distress syndrome; SAPS 2, Simplified Acute Physiology Score

Patients	Aetiology	Age (yr)	Height (cm)	SAPS 2	Plasma midazolam concentrations (ng ml ⁻¹)	VCV (days)	PSV (days)	Pressure support (cm H ₂ O)	PEEP (cm H ₂ O)	Pa _{O₂} /F _{I_{O₂}}	pH	Pa _{CO₂}
1	ARDS pneumoniae	78	175	47	546	5	1	8	4	151	7.38	4.3
2	ARDS pneumoniae	79	170	35	600	9	1	10	8	270	7.42	4.8
3	ARDS pancreatitis	68	163	64	980	5	1	12	5	240	7.47	3.9
4	ARDS pneumoniae	58	157	70	10	5	1	13	4	223	7.40	5.8
5	ARDS pneumoniae	25	180	42	770	15	1	16	5	150	7.46	5.4
6	ARDS pneumoniae	68	170	56	660	11	2	12	5	151	7.50	4.1
7	ARDS peritonitis	65	170	53	2238	7	1	16	8	250	7.38	5.2
8	ARDS pneumoniae	66	161	58	1775	5	1	14	8	132	7.37	4.2
9	ARDS peritonitis	80	181	52	291	6	1	15	4	174	7.41	4.2
10	ARDS peritonitis	69	158	72	360	7	2	12	5	270	7.38	4.4
11	ARDS pneumoniae	48	175	48	258	22	1	22	6	120	7.39	6.6
12	Pulmonary fibrosis	77	164	31	53	10	2	9	2	152	7.41	5.5
13	ARDS pancreatitis	61	160	47	24	6	2	10	4	255	7.37	4.7
		64 (15)	168 (8)	52 (12)	659 (674)	7 (5–10)	1 (1–2)	13 (4)	5 (2)	195 (56)	7.41 (0.04)	4.9 (0.8)

Pa_{CO₂} ($\rho=-0.17$, $P=0.55$), pH ($\rho=0.23$, $P=0.35$), and RR ($\rho=-0.51$, $P=0.07$).

After flumazenil, NVE was correlated with RR ($r=0.58$, $P=0.04$) but was still not correlated with the level of pressure support ($P=0.65$), Pa_{O₂}/F_{I_{O₂} ($P=0.73$), Pa_{CO₂} ($P=0.55$), and pH ($P=0.35$).}

Discussion

In the present study, the major finding is that, after prolonged ventilation and sedation, reversal of sedation by flumazenil significantly increases EAdi and V_T, whereas NVE decreases. Moreover, this significant increase in V_T was significantly correlated with the increased EAdi: ΔV_T (ml) = $3.937 \times \Delta EAdi$ (μV) + 27.43.

Residual sedative drugs probably do persist while weaning from mechanical ventilation. Our patients had the same fixed pressure assist, whereas flumazenil reversed benzodiazepine-induced sedation and inhibition of respiratory drive. The consequence was increased V_T, resulting in a well-tolerated increase in the patient's contribution to breathing and EAdi.

Effects of midazolam and flumazenil on diaphragm and respiratory patterns

Numerous studies have described midazolam-induced respiratory inhibition in healthy volunteers. The primary effect of midazolam in humans is to significantly decrease V_T.¹² This reduction in V_T of ~40% is associated with an increased RR and a reduction in minute ventilation.^{10 12} Wilkinson and colleagues¹³ found flunitrazepam binding sites in rat diaphragms, which could be receptors for the direct neuromuscular effect of benzodiazepines. It has been found, *in vitro*, that benzodiazepines inhibit diaphragm

contractility with 100% depression of twitch tension.¹⁴ Moreover, Fujii and colleagues¹⁵ found a significant reduction in transdiaphragmatic pressure in dogs that had been given benzodiazepines.

Molliex and colleagues¹⁰ investigated the effects of midazolam and flumazenil on intercostal, diaphragmatic, and abdominal muscle functions using the $\Delta Pga/\Delta Ppl$ index, and intercostal and abdominal electromyography in healthy volunteers. These authors reported decreased diaphragm contraction and increased contribution by accessory muscles to the load of the higher upper airway resistances caused by midazolam in these non-intubated patients. Interestingly, in this study, the injection of flumazenil allowed V_T to return to baseline values. It should be pointed out that these authors did not measure the diaphragm electromyography.

By measuring EAdi, which records electrical activation of the crural diaphragm, our study strongly suggests that midazolam inhibits intrinsic diaphragmatic contraction. Indeed, flumazenil induced a significant increase in EAdi and V_T. Interestingly, the increase in EAdi was significantly correlated with an increase in V_T when airway pressure remained stable. Of course, the contribution of the accessory muscle was not assessed, but none of the patients had any signs of respiratory distress from accessory muscle activation under PSV before an injection of flumazenil. Moreover, the work needed to breathe did not differ after flumazenil was injected: the patients were intubated and upper airway resistances remained stable.¹⁶ The contribution of the accessory muscle occurs essentially when the work of breathing increases significantly.¹⁷

The decrease in V_T with midazolam probably cannot be explained by alterations to the pulmonary mechanics, as no differences in functional residual capacity and dynamic pulmonary compliance have been found.¹² Therefore, in our

Table 2 Individual data of patients ($n=13$) before flumazenil and after bolus of flumazenil. Data are expressed as mean (SD) or median (IQR). RR, respiratory rhythm; EAdi, diaphragm electrical activity; V_T , tidal volume; CR, cardiac rhythm. * $P<0.05$ before flumazenil vs after bolus of flumazenil. All comparisons were performed by using a paired t-test for means and a Wilcoxon test for medians

Pts	RR (cycles min^{-1})		Ti flow (s)		EAdi (μV)		V_T (ml)		V_T (ml kg^{-1})		V_T/EAdi ($\text{ml } \mu\text{V}^{-1}$)		CR (beats min^{-1})		SAP (mm Hg)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	15	26	0.95	0.80	1.8	4	780	950	11.1	13.5	433.3	237.5	115	130	110	140
2	17	13	0.98	1.04	2.0	3.2	450	652	6.8	9.9	225.0	203.8	72	80	127	139
3	22	22	1.00	0.9	2.2	10	420	490	7.6	8.9	190.9	49.0	85	85	119	161
4	12	13	1.38	1.26	3.2	7.1	560	741	11.3	14.9	175.0	104.4	100	110	100	110
5	31	30	0.61	0.57	4.9	26	310	555	4.4	7.9	63.3	21.3	120	130	133	140
6	29	35	0.64	0.60	8.4	9.2	500	520	7.6	7.9	59.5	56.5	89	95	148	155
7	27	29	0.68	0.69	7.0	12	400	450	6.1	6.8	57.1	37.5	114	108	109	121
8	31	35	0.54	0.48	11.0	16	471	481	8.8	9.0	42.8	30.1	91	115	126	163
9	32	40	0.64	0.59	26.0	40	340	440	4.5	5.8	13.1	11.0	73	85	133	155
10	30	29	0.65	0.70	12.5	28	340	450	6.7	8.9	27.2	16.1	90	85	107	120
11	34	38	0.64	0.60	38.0	52	504	506	7.1	7.2	13.3	9.7	85	90	130	145
12	28	33	1.05	0.66	46.0	59	533	593	8.8	9.8	11.6	10.1	100	117	130	166
13	25	25	0.86	0.92	59.0	110	600	690	10.5	12.1	10.2	6.3	79	83	130	150
	26 (7)	28* (8)	0.85 (0.27)	0.77 (0.24)	8.4 (3.2–26.0)	16.0* (9.2–40.0)	477 (127)	578* (147)	7.8 (2.2)	9.4* (2.7)	57.1 (13.2–175.0)	29.0* (9.2–40.0)	93 (16)	101* (18)	123 (13)	144* (18)

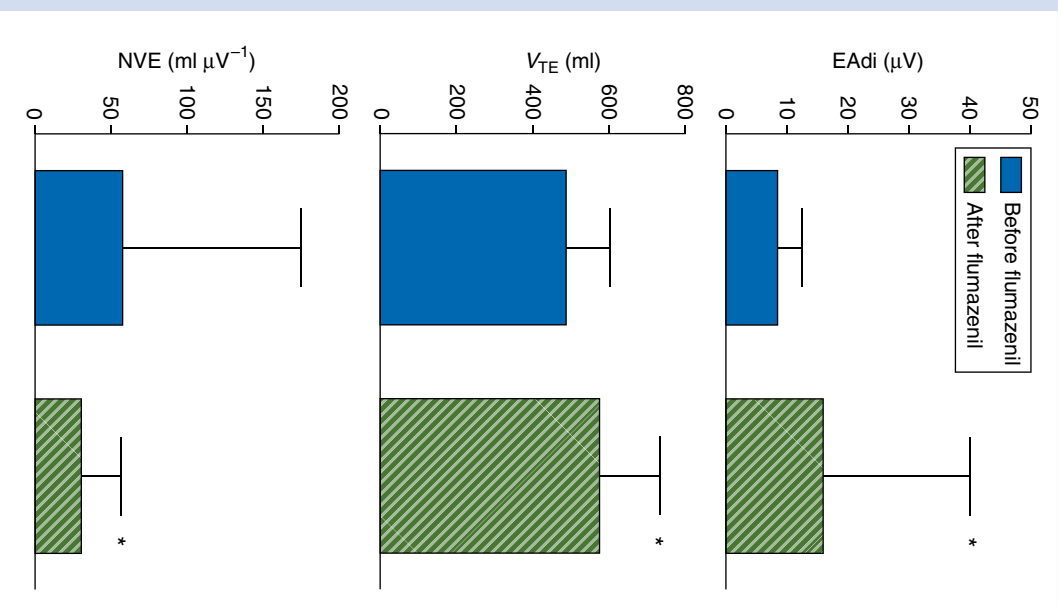
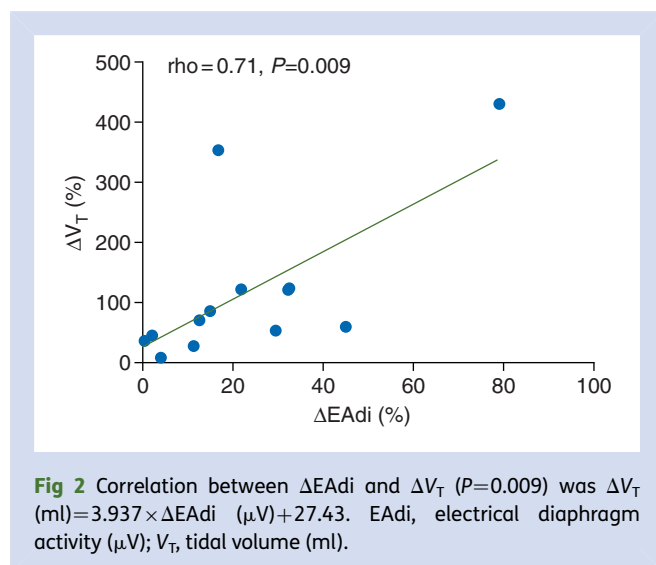


Fig 1 Comparison of expired tidal volume, diaphragm electrical activity, and NVE before and after an injection of flumazenil. Data are expressed as the mean (SD) of expired tidal volume (V_{TE}) or the median (IQR) of diaphragm electrical activity (EAdi) and NVE; * $P<0.05$ before flumazenil vs after a bolus of flumazenil. All comparisons were performed using a paired Student's t-test.

study, the increase in V_T after flumazenil, for the same airway pressure, cannot be explained by improved pulmonary mechanics.

Conflicting results have been found regarding the reversal effect of flumazenil.^{18–22} The fact that these studies had different protocols, doses and timings of injections, and measurements could partly explain these variations. Additionally, it may be difficult to demonstrate the effects of flumazenil when residual sedation includes opioids. Opioids induce respiratory depression with a significant decrease in RR through μ - and δ -receptors.^{23–24} Gross and colleagues²⁵ found that, in the presence of concomitant opioid-induced depression of ventilatory drive, flumazenil only reversed the benzodiazepine-induced component of ventilatory depression.



In our study, flumazenil increased RR and decreased inspiratory time. Consequently, the increased V_T under PSV cannot be explained by an increased inspiratory time.

With the rapid reversal of midazolam-respiratory inhibition, V_T increased significantly and three patients had, transiently, a V_T of $> 12 \text{ ml kg}^{-1}$ predicted body weight. The rapid increase in EAdi and diaphragmatic muscle function with flumazenil was responsible for the increased transpulmonary pressure, as airway pressure was fixed. This highlights the risk of overdistension when patients awake under PSV.²⁶ It would have been interesting to transiently reduce the level of pressure assist under flumazenil in order to keep V_T constant and to quantify the reduction in driving pressure for a given increase in EAdi. These three patients had V_T around 10 ml kg^{-1} predicted body weight, before flumazenil injection. It is possible that the assist level chosen by the attending physician was too high for them. This illustrates the dependency of V_T on the assist level with PSV and the possible uncoupling between inspiratory effort and V_T . This might have been different with proportional assist.²⁷

Neuroventilatory efficiency

The consequence of injecting flumazenil in this population of patients was a decrease in NVE. The patients' conditions did not worsen with this reduction in NVE. We only found a significant correlation between NVE and RR after injection of flumazenil. Arterial blood gases and levels of pressure support were not correlated to NVE before or after an injection of flumazenil. The range of NVE values, for our patients, was large. Some patients had very low or high NVE values under PSV; the level of assist was chosen by the attending physician, and none of the patients had any clinical signs of respiratory distress, otherwise PSV would have been stopped. EAdi can sometimes be affected by interindividual anatomical differences, such as an increased distance between the electrodes in the oesophagus and/or because the crural diaphragm lowers the amplitude of EAdi.¹⁵ It is therefore possible that, in this situation, its variation

is more clinically relevant than its value. NVE reflects volume-generated determinants, that is, respiratory drive, diaphragm function, and respiratory load. Respiratory drive determinants may explain why patients had increased EAdi and V_T with flumazenil. Respiratory drive was inhibited by the presence of residual sedative drugs, which were still present during the weaning process. In our study, patients were maintained in a sedated state under controlled mechanical ventilation for at least 4 days before initiating the weaning-off process, this was done to inhibit respiratory drive.

In a recently published report, there was no improvement in NVE during SBTs, but there were progressive and significant increases in V_T and EAdi between the first failed and then successful SBTs.⁷ This suggests an increased degree of wakefulness. Elimination of sedation decreases ventilatory depression and increases EAdi, and the consequences on NVE depend on the ability of EAdi to generate V_T when the same level of pressure assist is used. Long periods of sedation for severe respiratory failure may have complex effects on the control and efficiency of breathing, and can alter the coupling between respiratory drive and motoneuron activation, which will generate a specific V_T .

NVE involves a complex set of interactions between the respiratory centres that feed signals to a central control mechanism, which, in turn, provides output to the effector muscles.¹⁷ For example, in exercising chronic obstructive pulmonary disease (COPD) patients, dynamic hyperinflation reduces the transdiaphragmatic pressure for a given EAdi.⁸ It would also be interesting to study the effects of other factors, other than sedation, such as acidosis and thoracopulmonary compliance, on NVE with NAVA.

It is important to consider the following points when considering the clinical relevance of our study. Patients were sedated with benzodiazepine: the effect induced by other sedative drugs on EAdi and NVE could be different. A combination of benzodiazepine and an opioid was used during controlled mechanical ventilation. The ventilator-depressant effects of opioids are known to potentiate those of benzodiazepines;²⁸ consequently, the interaction of opioids could have limited the effect of flumazenil reversal in ventilatory depression and, thus, affected EAdi, V_T , and NVE. No opioid antagonists were given to patients. The study population was specific and consisted of intubated patients after prolonged controlled mechanical ventilation for acute respiratory distress syndrome.

Results are probably different with COPD patients in terms of the effect of midazolam²⁹ and NVE, as these patients have reduced pressure-generating capacities for a given drive because of disadvantageous diaphragmatic configuration.³⁰ NVE is also probably more efficient under proportional-assist modes (NAVA), as assist is delivered in synchrony and in proportion to EAdi. Indeed, the limitation of V_T observed with increasing NAVA levels in humans could suggest that the Hering–Breuer reflex is operative and reduces output from the respiratory controller at the same V_T level, irrespective of the NAVA level.^{27 31} The same study with NAVA would be interesting, as flumazenil might have different effects on patients' control of V_T . Moreover,

with NAVA, synchrony is improved as the flow is synchronized to EAdi, thus making NVE easy to measure.³² PSV asynchrony, especially regarding the trigger for expiratory flow, will not always allow correct measurement of NVE changes.

Clinical interest

This study highlights the effects of residual midazolam (for sedation) on EAdi, V_T , and NVE: these effects need to be taken into account at the bedside when interpreting the evolution of a patient's respiratory parameters during weaning from mechanical ventilation. EAdi could be an interesting tool at the bedside to assess and limit the deleterious effects of midazolam on the functioning of the diaphragmatic muscle.

Conclusion

During weaning from mechanical ventilation after respiratory failure, the effects of receiving prolonged mechanical ventilation and sedation with midazolam may cause residual midazolam-induced ventilator depression, which may contribute to a decreased diaphragmatic contribution to the breathing process. The increase in EAdi induced by reversal of residual sedation (using flumazenil) was associated with a proportional increase in V_T and a reduced NVE. Thus, residual sedation should be taken into account by the attending physician when interpreting daily EAdi and NVE changes at the bedside during weaning from mechanical ventilation.

Authors' contributions

Study concept and design: H.R.; acquisition of data: H.R., A.G., V.P., O.J.B., A.D., and C.F.; analysis and interpretation of data: H.R. and A.O.; drafting of the manuscript: H.R. and A.O.

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Declaration of interest

H.R. received honoraria for public speaking from Maquet.

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