Respiratory Muscle Effort during Expiration in Successful and Failed Weaning from Mechanical Ventilation

Jonne Doorduin, Ph.D., Lisanne H. Roesthuis, M.Sc., Diana Jansen, M.D., Johannes G. van der Hoeven, M.D., Ph.D., Hieronymus W. H. van Hees, Ph.D., Leo M. A. Heunks, M.D., Ph.D.

ABSTRACT

Background: Respiratory muscle weakness in critically ill patients is associated with difficulty in weaning from mechanical ventilation. Previous studies have mainly focused on inspiratory muscle activity during weaning; expiratory muscle activity is less well understood. The current study describes expiratory muscle activity during weaning, including tonic diaphragm activity. The authors hypothesized that expiratory muscle effort is greater in patients who fail to wean compared to those who wean successfully.

Methods: Twenty adult patients receiving mechanical ventilation (more than 72 h) performed a spontaneous breathing trial. Tidal volume, transdiaphragmatic pressure, diaphragm electrical activity, and diaphragm neuromechanical efficiency were calculated on a breath-by-breath basis. Inspiratory (and expiratory) muscle efforts were calculated as the inspiratory esophageal (and expiratory gastric) pressure–time products, respectively.

Results: Nine patients failed weaning. The contribution of the expiratory muscles to total respiratory muscle effort increased in the "failure" group from 13 ± 9% at onset to 24 ± 10% at the end of the breathing trial (P = 0.047); there was no increase in the "success" group. Diaphragm electrical activity (expressed as the percentage of inspiratory peak) was low at end expiration (failure, 3 ± 2%; success, 4 ± 6%) and equal between groups during the entire expiratory phase (P = 0.407). Diaphragm neuromechanical efficiency was lower in the failure *versus* success groups (0.38 ± 0.16 *vs.* 0.71 ± 0.36 cm $H_2O/\mu V$; P = 0.054).

Conclusions: Weaning failure (*vs.* success) is associated with increased effort of the expiratory muscles and impaired neuromechanical efficiency of the diaphragm but no difference in tonic activity of the diaphragm. **(ANESTHESIOLOGY 2018; 129:490-501)**

PROLONGED weaning from mechanical ventilation develops in 6 to 15% of mechanically ventilated patients and is associated with increased morbidity and mortality.[1–4] A major determinant of weaning failure is respiratory muscle dysfunction.[5–7] The respiratory muscles are profoundly affected by critical illness and mechanical ventilation.[8–15] The respiratory muscle pump is made up of a number of muscles, but research in weaning failure has mainly focused on the inspiratory muscles, in particular the diaphragm.[16–20] The role of the expiratory muscles including the internal intercostals and abdominal wall muscles during weaning failure is less well understood.

Recruitment of the expiratory muscles has been demonstrated in patients with chronic obstructive pulmonary disease (COPD) during a failed weaning trial.[21,22] Expiratory muscle recruitment may help inspiration because the active reduction in end-expiratory lung volume stores elastic energy, facilitating subsequent inspiration. In addition, active reduction in end-expiratory lung volume may help to limit hyperinflation.[23] However, recruitment of the expiratory muscles increases the energy expenditure of

What We Already Know about This Topic

- Inspiratory muscle weakness delays weaning from mechanical ventilation, but the contributions of expiratory muscles activity are less well understood.

What This Article Tells Us That Is New

- Twenty adult patients receiving mechanical ventilation (more than 72 h) performed a spontaneous breathing trial. Nine patients failed weaning (11 succeeded), and these patients exhibited increased effort of the expiratory muscles and impaired neuromechanical efficiency of the diaphragm but no difference in tonic activity of the diaphragm.

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breathing, although the relative contribution of expiratory muscle effort to total breathing effort in patients weaning the ventilator is unknown. Expiratory muscles effort can be quantified as the pressure–time product of gastric pressure during expiration.[24,25] Several studies have demonstrated that the diaphragm exhibits tonic activity during expiration.[26–31] Recently, Pellegrini *et al.*[32] have demonstrated in pigs with mild acute respiratory distress syndrome that the diaphragm acts as a brake during expiration to prevent lung collapse. In weaning-failure patients, tonic activity of the diaphragm during expiration might prevent airway closure and consequently limit intrinsic positive end-expiratory pressure (PEEP).

Accordingly, the aim of the current physiologic study was to quantify the expiratory pressure–time product and the expiratory activity of the diaphragm in weaning-success and weaning-failure patients. In addition, we studied respiratory muscle activity effort during inspiration. We hypothesized that expiratory muscle effort is higher in weaning-failure patients compared to successfully weaned patients.

Materials and Methods

Study Design and Population

This cross-sectional physiologic study was conducted in the intensive care unit of the Radboud University Medical Center, Nijmegen, The Netherlands. We recruited 20 adult patients invasively ventilated for at least 3 days and considered ready for a spontaneous breathing trial. *A priori* sample size calculation was not performed, but the number of required subjects was based on previous physiologic studies in mechanically ventilated patients.[33–36] The decision to extubate or resume mechanical ventilation was made solely by the clinical team, blinded to the study data. Exclusion criteria were a past medical history of neuromuscular disorders, upper airway or esophageal pathology (*e.g.*, recent surgery, esophageal varices, diaphragmatic hernia), and recent (less than 1 month) nasal bleeding.

The protocol was approved by the local ethics review committee (approval number 2010-058) and conducted in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained in patients that were not already instrumented with the dedicated nasogastric catheter.

Study Protocol

All patients were ventilated with the SERVO-i ventilator (Maquet Critical Care, Sweden). Per clinical protocol, sedatives were discontinued before the spontaneous breathing trial, and patients were verified to be responsive and adequate. If not already *in situ*, a nasogastric catheter with multiple electrodes and two balloons (NeuroVent Research, Inc., Canada) was inserted nasally. Catheter characteristics and positioning techniques have been described previously.[37–39] Baseline data were acquired while patients were ventilated in pressure support mode with an inspiratory support of 8 cm H_2O and a PEEP level of 5 cm H_2O for 10 min. Subsequently, a spontaneous breathing trial with T-tube and supplemental oxygen was performed for up to 60 min, according to our clinical protocol. The criteria for spontaneous breathing trial failure were tachypnea (more than 35 breaths/min), low peripheral capillary oxygen saturation (less than 90%), tachycardia (more than 140 beats/min), systolic hypertension (more than 180 mmHg), systolic hypotension (less than 90 mmHg), agitation, diaphoresis, and anxiety during the spontaneous breathing trial. Patients were extubated after a successful spontaneous breathing trial. Weaning failure was defined as a failed spontaneous breathing trial or reintubation within 48 h after extubation. Arterial blood samples were collected before disconnection from the ventilator and at the end of the spontaneous breathing trial before reinstitution of ventilator support.

Data Acquisition

Flow was measured with a Fleisch pneumotachograph (Hans Rudolph, USA) placed at the endotracheal tube or cannula. The pneumotachograph was connected to a differential pressure transducer (range ± 50 kPa; Freescale, USA).

The air-filled esophageal balloon and gastric balloon of the nasogastric catheter were connected to differential pressure transducers (range ± 50 kPa; Freescale). Pressure and flow signals were digitized (Porti 16, 22 bits, 1.4 μV/least significant bit; TMSi, The Netherlands) at a sampling frequency of 2 kHz. Transdiaphragmatic pressure was calculated as esophageal pressure subtracted from gastric pressure.

Electrical activity of the diaphragm recorded from the electrodes of the nasogastric catheter were amplified and digitized (Porti 16, 22 bits, 71.5 nV/least significant bit; TMSi) at a sampling frequency of 2 kHz. Signal processing of the electrical activity of the diaphragm was performed according to the method of Sinderby *et al.*[40–42] Details are provided in the Supplemental Digital Content (http://links.lww.com/ALN/B717).

Flow, esophageal pressure, gastric pressure, and diaphragm electrical activity were acquired synchronously (maximal 0.5-ms delay between mechanics and diaphragm electrical activity) using dedicated software (NeuroVent Research, Inc.) and stored on a hard disk for offline analysis in a software routine developed for Matlab (R2014b; Mathworks, USA).

Data Analysis

The data were analyzed on a breath-by-breath basis. For the period of mechanical ventilation, a 2-min epoch at the end was selected for analysis. The duration of the spontaneous breathing trial varied from patient to patient. Therefore, data were analyzed at seven points in time: the first and last minute and five epochs of at least 1 min taken at equal time intervals in between. The epochs were visually inspected for artefacts, such as movement and esophageal and gastric contractions. In the presence of artefacts, an adjacent

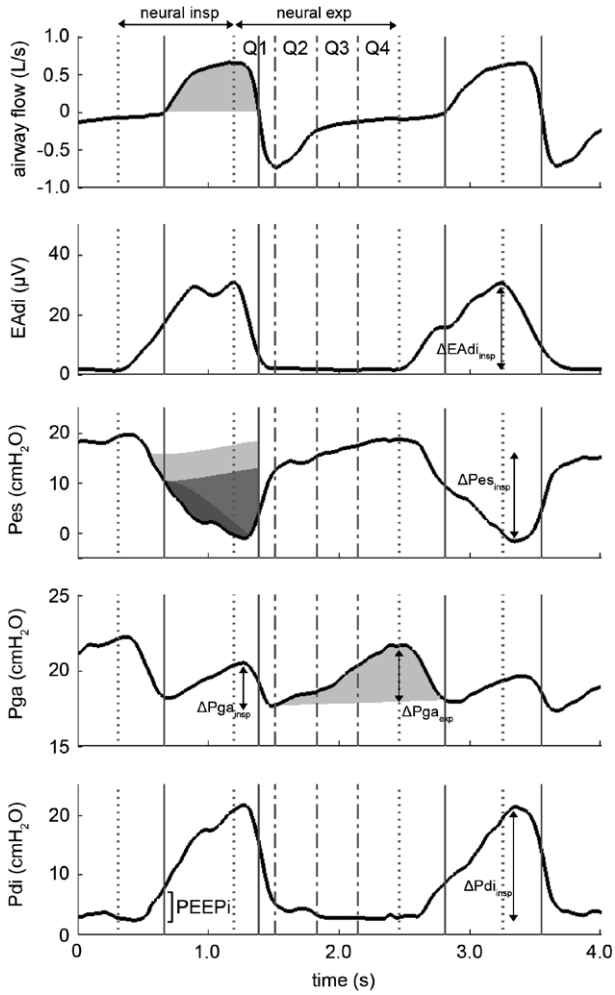


Fig. 1. Example of calculation of the different variables from the recorded signals from a weaning-failure patient during the end of the spontaneous breathing trial. The *dotted vertical lines* represent the start and end of neural inspiration, and the *solid vertical lines* represent the start and end of inspiratory flow. The neural expiratory phase was divided into four quartiles (Q1–Q4, *dotted and dashed lines*) to calculate the mean signal per quartile for diaphragm electrical activity (EAdi), transdiaphragmatic pressure (Pdi), and gastric pressure (Pga). Different areas under the curves are shown. The *gray area* in the flow signal represents tidal volume. The area with three shades of gray in the esophageal pressure (Pes) signal represents the different components of the esophageal pressure–time product during inspiration ($PTPes_{insp}$): intrinsic positive end-expiratory pressure (PEEPi: *light gray*), elastic (*medium gray*), and resistive (*dark gray*). The components of $PTPes_{insp}$ are defined by the recoil pressures of the chest wall and the lung. The *gray area* in the Pga signal represents the gastric pressure time product during expiration ($PTPes_{exp}$).

artefact-free epoch was selected. In figure 1, the acquired signals (flow, diaphragm electrical activity, esophageal pressure, gastric pressure, and transdiaphragmatic pressure) are shown with the calculated variables.

Mechanical inspiratory time, expiratory time, total breath cycle time, and respiratory rate were derived from the flow signal. Tidal volume (V_T) was calculated as the integral of inspiratory flow. Neural inspiration was defined as the period between the onset of diaphragm electrical activity and the peak of diaphragm electrical activity, and neural expiration was defined as the period between peak of diaphragm electrical activity and the onset of the next diaphragm electrical activity.[26,32]

The rise in expiratory gastric pressure (ΔPga_{exp}) was calculated as the difference in gastric pressure between end-inspiration and the start of decrease in esophageal pressure (*i.e.*, start of inspiration). As described previously,[26,32] expiratory diaphragm electrical activity ($\Delta EAdi_{exp}$) was calculated as the mean signal during ongoing neural expiration divided into four equally sized quartiles ($Q1EAdi_{exp}$, $Q2EAdi_{exp}$, $Q3EAdi_{exp}$, $Q4EAdi_{exp}$). The mean $\Delta EAdi_{exp}$ of each quartile was expressed as the percentage of the peak diaphragm electrical activity of that breath during inspiration after the subtraction of the noise level. Quartile 4 was considered the index closest to the tonic diaphragmatic activity. Details on the noise level calculation are provided in the Supplemental Digital Content (http://links.lww.com/ALN/B717). Analogous analysis was performed on the transdiaphragmatic pressure and gastric pressure signal, resulting in $Q1Pdi_{exp}$, $Q2Pdi_{exp}$, $Q3Pdi_{exp}$, $Q4Pdi_{exp}$, $Q1Pga_{exp}$, $Q2Pga_{exp}$, $Q3Pga_{exp}$, and $Q4Pga_{exp}$.

During inspiration, the drop in esophageal pressure (ΔPes_{insp}) was calculated as the difference between the start of decrease in esophageal pressure and the negative peak value of esophageal pressure. ΔPga_{insp} was calculated as the difference between the start of increase in gastric pressure and the positive (or negative) peak value of gastric pressure during inspiration. ΔPdi_{insp} was calculated as the difference between the start of increase in transdiaphragmatic pressure and the positive peak value of transdiaphragmatic pressure during inspiration. ΔPes_{insp} and ΔPga_{insp} were corrected for ΔPga_{exp} in the preceding breath. The physiologic base for these corrections have been described in detail.[22,43,44] In short, expiratory muscle activity can increase the end-expiratory alveolar pressure, leading to an overestimation of the decrease in esophageal pressure during inspiration. In the case of expiratory muscle recruitment, part of the decrease in esophageal pressure preceding inspiration is actually due to relaxation of the expiratory muscles rather than contraction of the inspiratory muscles. Therefore, the amount of pressure due to expiratory muscle activity should be subtracted from the decrease in esophageal pressure. Intrinsic PEEP was calculated as the rise in transdiaphragmatic pressure until the start of inspiratory flow and thus corrected for a drop in gastric pressure at the start of inspiration. $\Delta EAdi_{insp}$, an estimation of neural respiratory drive, was calculated as the peak root mean square per 50 samples of the diaphragm electrical activity during inspiration. Neuromechanical efficiency of diaphragm during inspiration ($NMEdi_{insp}$) was computed as $\Delta Pdi_{insp}/\Delta EAdi_{insp}$.

The effort of the inspiratory muscles was quantified by calculating the esophageal pressure–time product ($PTPes_{insp}$).

$PTPes_{insp}$ was calculated as the time integral of the difference between esophageal pressure and the recoil pressure of the chest wall, as described previously.[45,46] $PTPes_{insp}$ was partitioned in resistive, elastic, and intrinsic PEEP components. A calculated theoretical value was used for the recoil pressure of the chest wall, as described previously.[47] Effort of the expiratory muscles was quantified by calculating the gastric pressure–time product ($PTPga_{exp}$) during expiration. $PTPga_{exp}$ was calculated as the time integral of the rise in gastric pressure during expiration, as described previously.[24,25] Total pressure–time product for the respiratory muscles was calculated as $PTPes_{insp}$ + $PTPga_{exp}$.

Dynamic compliance (C_{dyn}) and airway resistance of the lung and airways (R_{aw}) were calculated as described previously.[48] In short, C_{dyn} was measured as the ratio of the V_T to the change in transpulmonary pressure (difference in pressure between the esophagus and the mouthpiece) between instants of zero air flow. For calculation of R_{aw}, points were selected during the inspiratory phase and expiratory phase when lung volumes were identical and flow rates were about maximal. The ratio of the change in transpulmonary pressure between these points to the corresponding change in flow between these points represents an "average" flow resistance for inspiration and expiration.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp., USA), and the data were visualized using GraphPad Prism version 5 (GraphPad Software, Inc., USA). In response to peer review, we adapted the statistical analysis of our data by replacing a linear mixed model design with a two-way repeated measures ANOVA. Assumption of normality was tested using the Shapiro–Wilk normality test. Note that because of the limited sample size per group, this test may lack power to detect deviation from normality. First, to analyze the effects of removing ventilator assist, a paired Student's *t* test (pressure support ventilation *vs.* first minute of the spontaneous breathing trial) or its nonparametric equivalent, the Wilcoxon signed-rank test, was performed for the different variables per group (failure and success). Second, to analyze the effect of time and group on the different variables during the spontaneous breathing trial, a two-way repeated measures ANOVA with time as within-subjects factor (seven time points from minute one to the last minute) and group as between-subjects factor (success or failure) was performed. Third, to analyze respiratory muscle activity during the expiratory phase a two-way repeated measures ANOVA was performed with time as within-subjects factor (peak and quartile 1 to quartile) and group as between-subjects factor (success or failure). A fourth-order robust polynomial fit was calculated to visualize the trend of respiratory muscle activity during the expiratory phase. Mauchly's test of sphericity was used to test the homogeneity of variance for the mixed ANOVAs. Where Mauchly's test of sphericity was significant ($P \leq 0.05$), Greenhouse–Geisser corrections were applied. In the presence of a significant interaction or between-subject factor, *post hoc* pairwise comparisons between groups at each time point were performed by paired Student's *t* tests with Bonferroni correction. The correlation between the peak expiratory flow and ΔPga_{exp} for the average values per time point during the spontaneous breathing trial was calculated using a Pearson correlation for both weaning groups. The resulting Pearson correlation coefficients were transformed by performing the Fisher's r to z transformation and subsequently compared by determining the observed z test statistic. For all tests, a two-tailed $P \leq 0.05$ was considered significant. The data are described as means ± SD.

Results

Nine patients met the criteria for weaning failure, five patients failed the spontaneous breathing trial, and four were reintubated within 48 h after extubation. Eleven patients completed the 60-min spontaneous breathing trial and remained extubated for at least 48 h. Patient characteristics and ventilator settings at study inclusion are presented in table 1. Diaphragm electrical activity and transdiaphragmatic pressure signals of one patient in the weaning-success group were excluded from analysis due to dislocation of the catheter during the spontaneous breathing trial. From another patient in the failure group, diaphragm electrical activity was excluded from analysis due to electrode artefacts detected during offline signal analysis.

Ventilation, Respiratory Timing, and Lung Mechanics

Variables of ventilation, respiratory time, and lung mechanics are listed in table 2. Immediately after the transition from pressure support ventilation to spontaneous breathing trial, V_T decreased in both groups but thereafter remained stable for the rest of the spontaneous breathing trial. In both groups, respiratory frequency and the ratio between respiratory frequency and V_T (*i.e.*, an index of rapid shallow breathing) increased after the transition to the spontaneous breathing trial. Only in the weaning-failure group, inspiratory time significantly decreased, and rapid shallow breathing index increased (borderline significant) during the spontaneous breathing trial. V_E did not change significantly during the spontaneous breathing trial and was not different between groups.

Respiratory Muscle Activity during Expiration

In figure 2 (A–F), activity of the diaphragm ($\Delta EAdi_{exp}$ and ΔPdi_{exp}) during the expiration (divided into four equally sized quartiles) together with peak activity during inspiration is shown during pressure support ventilation and during the first and last minute of the spontaneous breathing trial. Changes in expiratory gastric pressure are shown in figure 2 (G–I), together with peak activity of gastric pressure during expiration. At the end of the spontaneous breathing trial, expiratory gastric pressure increased in the failure group

Table 1. Patient Characteristics

Patient No. and Diagnosis		Age (yr)	BMI (kg/m^2)	Sex	Days on Ventilator	PSV Level (cm H_2O)	NAVA Level (cm H_2O/μV)	PEEP Level (cm H_2O)	FIO_2	Pao_2/FIO_2 (mmHg)	Time to Failure (min)
Failure group (n = 9)											
1	Cardiac arrest	88	24	F	24	-	2.3	6	0.40	268	60*
2	Pneumonia	64	22	F	49	10		6	0.30	328	52
3	Postoperative, CABG	72	27	F	83	10		8	0.40	194	60*
4	Multitrauma	45	28	M	4	10		5	0.30	318	24
5	Exacerbation COPD	58	25	M	14	8		10	0.30	405	60*
6	Postoperative, CABG	67	29	F	8	0		8	0.40	214	16
7	Postoperative, AAA	63	27	M	7	4		8	0.40	199	60*
8	Postoperative, papillary muscle rupture	80	24	M	8	0		8	0.45	132	13
9	Cardiogenic shock	76	23	M	21	-	0.4	10	0.30	228	23
Success group (n = 11)											
1	Tracheal stenosis, COPD	69	25	M	7	14		3	0.45	190	
2	Postoperative, aortoenteric fistula, COPD	71	26	M	8	5		6	0.40	†	
3	Sepsis	58	26	F	7	0		6	0.35	330	
4	Postoperative, CABG	73	29	M	14	10		10	-	†	
5	Cardiac arrest	76	29	F	17	6		6	0.45	248	
6	Postoperative, AAA	82	28	M	5	9		5	0.45	258	
7	Sepsis	73	29	M	24	8		6	0.25	306	
8	Multitrauma	46	25	M	9	0		5	0.30	†	
9	Sepsis	63	24	F	7	0		8	0.30	†	
10	Pneumonia	60	21	M	12	6		6	0.35	291	
11	Postoperative, CABG	78	30	M	3	4		10	0.40	358	

*Reintubation within 48 h. †Patient without arterial line.

AAA = abdominal aortic aneurysm; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; F = female; FIO_2 = fractional inspired oxygen tension; M = male; NAVA = neurally adjusted ventilatory assist; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation.

Table 2. Variables of Ventilation, Respiratory Timing, and Mechanics during PSV and the SBT for the Failure Group and Success Group

					P Value		
					Main Effect		
	Group	PSV	SBT Start	SBT End	Time	Group	Interaction (Time × Group)
V_T (ml)	F	535 ± 153*	384 ± 183	401 ± 214	0.901	0.830	0.670
	S	486 ± 233*	414 ± 205	413 ± 171			
Peak inspiratory flow (ml/s)	F	766 ± 232*	647 ± 213	801 ± 356	0.017	0.399	0.055
	S	714 ± 246*	637 ± 270	650 ± 257			
Peak expiratory flow (ml/s)	F	−618 ± 132	−556 ± 151	−651 ± 244	0.079	0.362	0.417
	S	−586 ± 193*	−525 ± 216	−547 ± 194			
Frequency (breaths/min)	F	22.1 ± 8.8*	26.9 ± 8.2	30.2 ± 8.4	0.128	0.743	0.171
	S	24.9 ± 8.2*	27.6 ± 9.1	28.0 ± 9.4			
Minute ventilation (l/min)	F	11.3 ± 4.0	10.0 ± 4.5	11.6 ± 6.4	0.247	0.985	0.385
	S	11.5 ± 4.8	11.1 ± 5.2	11.1 ± 4.6			
Inspiratory time (s)	F	1.01 ± 0.33*	0.87 ± 0.26	0.72 ± 0.20	0.024	0.126	0.033
	S	0.95 ± 0.22	0.96 ± 0.28	0.96 ± 0.32			
Expiratory time (s)	F	2.20 ± 1.16*	1.70 ± 0.87	1.52 ± 0.60	0.414	0.747	0.375
	S	1.76 ± 0.81*	1.48 ± 0.64	1.53 ± 0.16			
Inspiratory time/breath cycle time	F	0.29 ± 0.12	0.35 ± 0.08	0.33 ± 0.06	0.202	0.048	0.466
	S	0.37 ± 0.06*	0.41 ± 0.07	0.40 ± 0.06			
Frequency/V_T (breaths · min^{-1} · l^{-1})	F	46 ± 28*	83 ± 44	98 ± 55	0.182	0.437	0.057
	S	61 ± 29*	78 ± 34	78 ± 33			
PEEPi (cm H_2O)	F	2.7 ± 2.7*	4.9 ± 3.6	5.3 ± 4.5	0.621	0.160	0.649
	S	2.0 ± 1.5	2.8 ± 2.6	3.4 ± 3.0			
C_{dyn} (ml/cm H_2O)	F	39.5 ± 19.4*	31.9 ± 16.8	29.4 ± 24.2	0.464	0.529	0.695
	S	35.1 ± 12.6	40.8 ± 28.6	35.9 ± 23.5			
R_{aw} (cm H_2O · l^{-1} · s^{-1})	F	9.1 ± 7.4*	16.6 ± 8.6	17.2 ± 8.3	0.833	0.682	0.501
	S	7.3 ± 3.6*	14.4 ± 7.9	15.9 ± 10.3			

Note that only data at start and end of the SBT are shown and not the time intervals in between. The *P* values in table reflect results during the SBT (mixed ANOVA).

*$P \leq 0.05$ PSV *versus* SBT start.

C_{dyn} = dynamic compliance; F = weaning-failure group; PEEPi = intrinsic positive end-expiratory pressure; PSV = pressure support ventilation; R_{aw} = airway resistance; S = weaning-success group; SBT = spontaneous breathing trial; V_T = tidal volume.

compared to the success group. A significant correlation was found between peak expiratory flow and ΔPga_{exp} during the spontaneous breathing trial in the weaning-failure group ($R^2 = 0.90$, $P = 0.001$) but not in the weaning-success group ($R^2 = 0.10$, $P = 0.486$). The correlation coefficients were significantly different ($P = 0.039$).

Respiratory Muscle Activity during Inspiration

Figure 3 shows respiratory muscle activity during inspiration under pressure support and during the spontaneous breathing trial. Removal of ventilator assist caused immediate increases in ΔPdi_{insp}, ΔPes_{insp} and $\Delta EAdi_{insp}$ in both groups, whereas $NMEdi_{insp}$ did not change in the first minute after the removal of inspiratory support.

During the course of the spontaneous breathing trial, no significant interactions were found between time and group for ΔPdi_{insp}, ΔPes_{insp}, $\Delta EAdi_{insp}$, and $NMEdi_{insp}$. However, $\Delta EAdi_{insp}$ was significantly higher in the failure group compared to the success group during the entire spontaneous breathing trial. Consequently, $NMEdi_{insp}$ was lower in the weaning-failure group compared to the success group (fig. 3E). In the failure group, intrinsic PEEP increased after removal of ventilator assist, but during the spontaneous breathing trial, there were no differences between both groups (table 2).

Pressure–Time Product of the Respiratory Muscles

Figure 4 shows the pressure–time products of the expiratory muscle and inspiratory muscles during pressure support ventilation and the first and last minute of the spontaneous breathing trial. The transition from pressure support ventilation to spontaneous breathing did not affect $PTPga_{exp}$ but increased in $PTPes_{insp}$ in both groups. During the spontaneous breathing trial, there were no differences in $PTPes_{insp}$ between weaning-failure and weaning-success patients. In addition, there were no differences between the intrinsic PEEP and the elastic and resistive components of $PTPes_{insp}$ between groups. The apparent increase in $PTPga_{exp}$ in the failure group did not reach statistical significance ($P = 0.099$). However, the contribution of the expiratory muscles to the total pressure–time product significantly increased from 13 ± 9% at the start of the spontaneous breathing trial to 24 ± 10% at the end of the spontaneous breathing trial in the weaning-failure group but did not change in the weaning-success group (fig. 5).

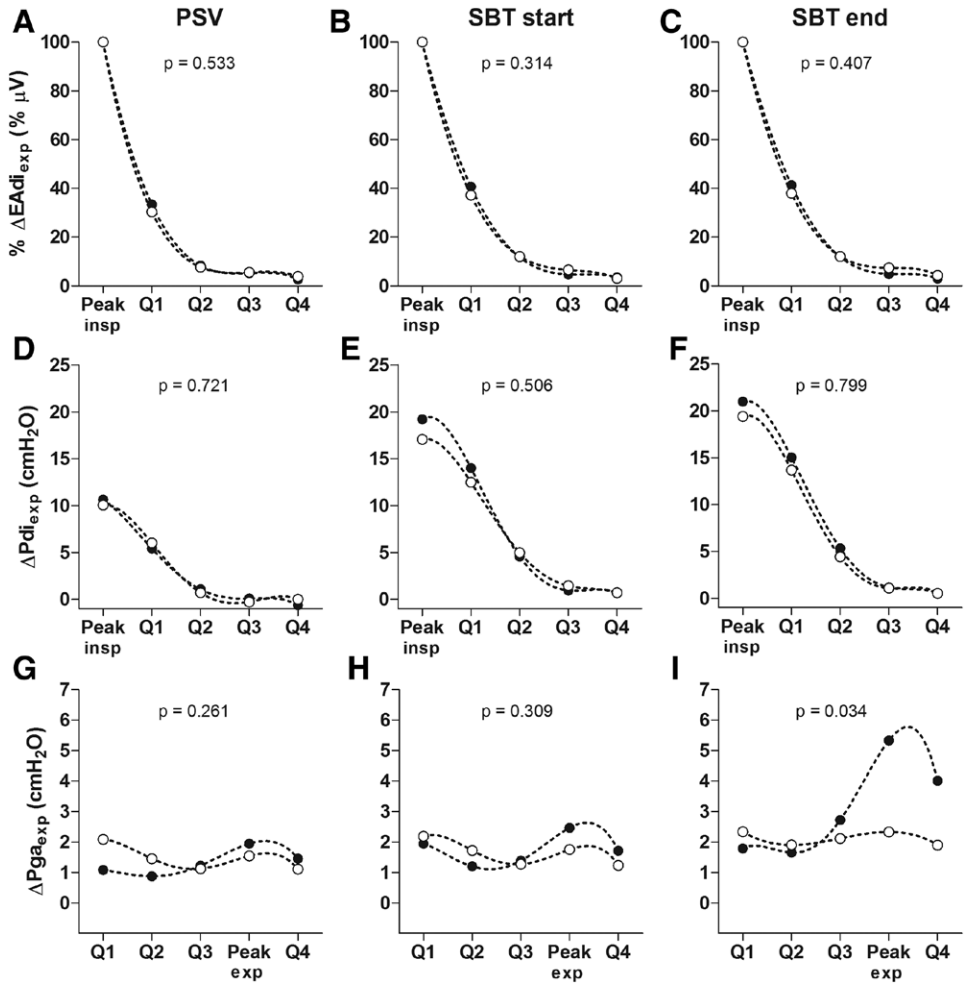


Fig. 2. Diaphragm electrical activity (EAdi), transdiaphragmatic pressure (Pdi), and gastric pressure (Pga) during expiration. Mean expiratory diaphragm electrical activity ($\Delta EAdi_{exp}$) values were normalized to the individual EAdi peak during inspiration (insp). Expiratory (exp) peak values of Pga were plotted between quartile (Q) 3 and Q4, the most common position of the peak during expiration (see fig. 1). There is no expiratory activity of the diaphragm in Q4 during pressure support ventilation (PSV) or during the spontaneous breathing trial (SBT). There is a significant increase in expiratory gastric pressure (ΔPga_{exp}) at the end of the SBT in the failure group compared to the success group. The *circles* in the figure represent the calculated mean values per quartile and the peak values (*white circles* indicate success, *black circles* indicate failure), whereas the *dashed curves* show the fourth order polynomial fit. SD ranged between 1.9 and 11.7%, between 0.6 and 8.8 cm H_2O and between 0.4 and 3.3 cm H_2O for % $\Delta EAdi_{exp}$, ΔPdi_{exp}, and ΔPga_{exp}, respectively. The reported *P* values in each panel represent the interaction term (time × group) of the two-way repeated measures ANOVA.

Arterial Blood Gas Measurements and Hemodynamics

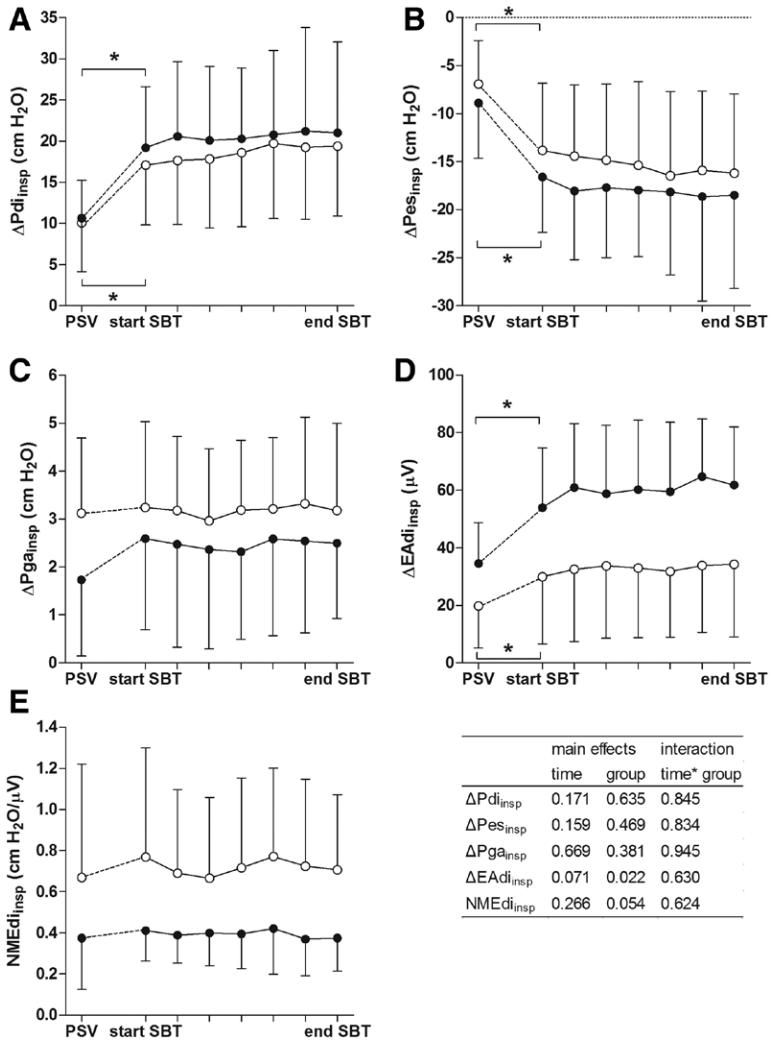
In table 3, the blood gas values and hemodynamic variables are presented. There were significant effects of time and group on $Paco_2$, such that $Paco_2$ increased over time during the spontaneous breathing trial and was higher in the failure group. However, the interaction between the effects of time and group were not significant, indicating that the increase in $Paco_2$ was not different between both groups.

Discussion

The present study provides new insights in the recruitment and effort of the respiratory muscles during expiration in a heterogeneous group of patients weaning from mechanical ventilation. First, we found that in weaning-failure patients, expiratory muscles recruitment is as high as 24% of the total respiratory muscle effort at the end of the trial. Second, we found no difference in tonic activity of the diaphragm during expiration between weaning-failure patients and weaning-success patients. Finally, neuromechanical efficiency of the diaphragm is lower in weaning-failure patients compared to weaning-success patients, both during pressure support ventilation and during a spontaneous breathing trial.

Respiratory Muscle Effort during Expiration

The pressure–time product has been used to quantify breathing effort.[45,46] Experimental studies have demonstrated that changes in inspiratory PTPes are correlated with changes in



	main effects		interaction
	time	group	time* group
ΔPdi_{insp}	0.171	0.635	0.845
ΔPes_{insp}	0.159	0.469	0.834
ΔPga_{insp}	0.669	0.381	0.945
$\Delta EAdi_{insp}$	0.071	0.022	0.630
$NMEdi_{insp}$	0.266	0.054	0.624

Fig. 3. Changes in transdiaphragmatic pressure (ΔPdi_{insp}), esophageal pressure (ΔPes_{insp}), gastric pressure (ΔPga_{insp}), diaphragm electrical activity ($\Delta EAdi_{insp}$), and neuromechanical efficiency ($NMEdi_{insp}$) during inspiration for pressure support ventilation (PSV) and during the spontaneous breathing trial (SBT) in the weaning-success (*white circles*) and weaning-failure (*black circles*) groups. After removal of ventilator assist ΔPdi_{insp}, ΔPes_{insp}, and $\Delta EAdi_{insp}$ increased in both groups. During the SBT, data were analyzed at seven points in time: the first minute (start SBT) and last minute (end SBT) and five epochs of at least 1 min taken at equal time intervals in between (ticks in between). A *P* value table is inserted with the results of the repeated measures ANOVA for each variable during the SBT. *$P < 0.05$ PSV *versus* start SBT.

diaphragmatic energy expenditure.[49,50] In the present study, we found an increase in PTPes during inspiration with the transition from mechanical ventilation to unassisted breathing, with no differences between the success group and the failure group. At first sight, this seems surprising, but under conditions of increased loading and/or impaired diaphragm function, the expiratory muscles could be recruited.[23] Indeed, in the present study, expiratory muscle activity, as indicated by an expiratory rise in gastric pressure, was found in the weaning-failure group during the spontaneous breathing trial. This expiratory rise in gastric pressure is consistent with previous findings in patients weaning from mechanical ventilation with COPD.[21,22] Expiratory muscle recruitment may increase the energy expenditure of respiration. In exercising healthy subjects, expiratory pressure generation is a significant contributor to the perception of dyspnea.[51] Therefore, muscle effort during expiration should be taken into account when calculating respiratory muscle effort. To this end, we calculated the expiratory pressure–time product from the gastric pressure curve. In the weaning-failure group, the contribution of the expiratory muscles to total respiratory muscle effort progressively increased during the spontaneous breathing trial, whereas it remained stable in successfully extubated patients. Whether the increase in expiratory muscle effort resulted from activation of the abdominal muscles, expiratory rib cage muscles, or a combination of the two is unknown; the relative contribution of each muscle group during expiration cannot be derived from the expiratory rise in gastric pressure.[22]

Pellegrini *et al.*[32] have recently demonstrated that in lung-injured pigs, decreasing extrinsic PEEP increases diaphragm

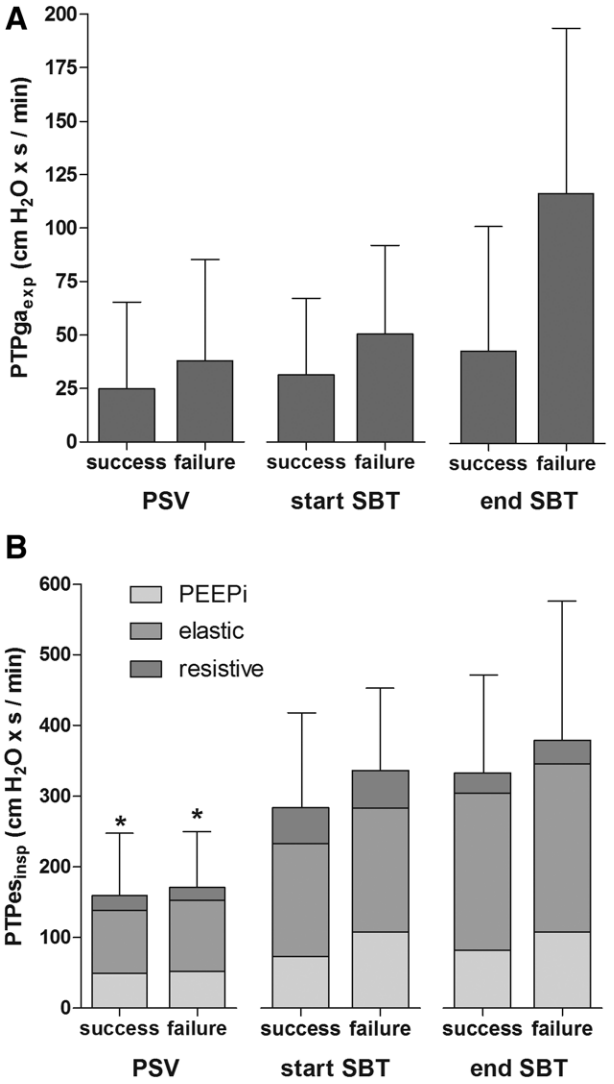


Fig. 4. Expiratory muscle pressure–time product (*A*) and inspiratory muscle pressure–time product (*B*) for pressure support ventilation (PSV) and during the spontaneous breathing trial (SBT) in the weaning-success and weaning-failure groups. After removal of ventilator assist, esophageal pressure–time product during inspiration (PTPes$_{insp}$) increased in both groups. During the SBT, there were no effects of time and group on PTPes. The apparent increase in gastric pressure–time product during expiration (PTPga$_{exp}$) did not reach statistical significance for the interaction term of the mixed ANOVA ($P = 0.099$). Note that only data at start and end of the SBT are shown and not the time intervals in between. *$P < 0.05$ PSV *versus* start SBT. PEEPi = intrinsic positive end-expiratory pressure.

activity during expiration. Diaphragmatic contraction during expiration will affect ΔPga_{exp} and $PTPga_{exp}$ in patients weaning from mechanical ventilation. In the current study, there was negligible low tonic diaphragmatic activity in the last quartile of the expiratory phase during the spontaneous breathing trial. However, in the first expiratory quartile, diaphragm activity was approximately 40% of its peak value. In our opinion, it is debatable whether the electrical

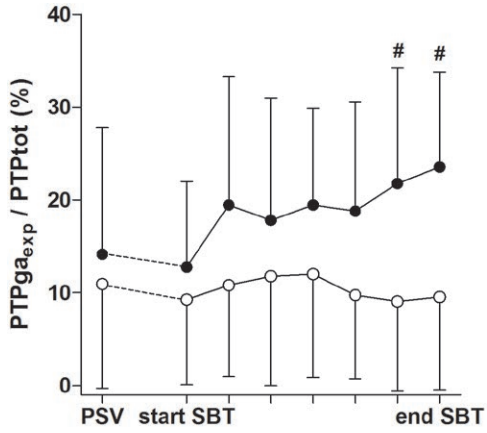


Fig. 5. The contribution of the expiratory muscles to total respiratory muscle effort for pressure support ventilation (PSV) and during the spontaneous breathing trial (SBT) in the weaning-success (*white circle*) and weaning-failure (*black circle*) groups. During the SBT, there was a significant interaction between the time and group ($P = 0.049$) on the ratio between the expiratory gastric pressure–time product and the total respiratory pressure–time product (PTPga$_{exp}$/PTPtot). #$P \leq 0.05$ pairwise *post hoc* comparison between success and failure group.

activity of the diaphragm in the first expiratory quartile should be defined as persistent activity of the diaphragm in expiration[26,32] or should be regarded as the termination of the inspiratory activity. Regardless, in our study there was no difference in activity of the diaphragm (diaphragm electrical activity and transdiaphragmatic pressure) between weaning-failure patients and weaning-success patients for all expiratory quartiles during the spontaneous breathing trial. Therefore, it is reasonable to assume that cyclic expiratory changes in gastric pressure at the end of the spontaneous breathing trial in weaning-failure patients are the result of expiratory muscle activity. In addition, the rise in gastric pressure was correlated with peak expiratory flow in the weaning-failure group, consistent with increased expiratory muscle activity.

It has been reasoned that an important goal of expiratory muscle recruitment is to assist the inspiratory muscles by decreasing end-expiratory lung volume.[23,52] A decrease in end-expiratory lung volume places the diaphragm at a more optimal position of the length-tension curve. However, intrinsic PEEP (corrected for the expiratory rise in gastric pressure) in the current study, a surrogate of end-expiratory lung volume, was not lower in the failure group compared to the success group. On the contrary, intrinsic PEEP tended to be higher in the failure group. In addition, we found no improvements in NMEdi$_{insp}$ in the failure group as a result of increased expiratory muscle recruitment. In line with these findings, it has been demonstrated that expiratory muscle recruitment does not increase NMEdi$_{insp}$ in COPD patients.[52] Thus, it is questionable whether expiratory muscle recruitment assists the inspiratory muscles in weaning-failure patients. Whether expiratory muscle recruitment aids weaning patients should be addressed in future studies.

Table 3. Blood Gas Values and Hemodynamic Variables before and after the SBT for the Failure Group and the Success Group

				P Value		
				Main Effect		
	Group	PSV*	SBT End	Time	Group	Interaction (Time × Group)
Pao_2 (mmHg)	F	91 ± 26	101 ± 18	0.225	0.127	0.595
	S	102 ± 21	99 ± 26			
$Paco_2$ (mmHg)	F	46 ± 11	50 ± 14	0.014	0.045	0.128
	S	38 ± 4	40 ± 5			
pH	F	7.42 ± 0.07	7.39 ± 0.08	0.015	0.261	0.427
	S	7.45 ± 0.04	7.44 ± 0.04			
MAP (mmHg)	F	88 ± 20	92 ± 23	0.621	0.707	0.157
	S	96 ± 25	94 ± 21			
Heart rate	F	87 ± 17	91 ± 21	0.194	0.312	0.425
	S	81 ± 11	82 ± 9			

*Blood gas values were drawn just before start of the SBT.

F = weaning failure; MAP = mean arterial pressure; PSV = pressure support ventilation; S = weaning success; SBT = spontaneous breathing trial.

Neuromechanical Efficiency of the Diaphragm during Inspiration

As expected, removal of ventilator assist increased ΔPdi_{insp} and $\Delta EAdi_{insp}$ in both groups. $NMEdi_{insp}$ was lower in weaning-failure patients compared to the success group. The neuromechanical efficiency of the diaphragm in weaning-failure patients and weaning-success patients in our study were approximately 30 and 50% of the values we reported for healthy subjects, respectively.[37] To the best of our knowledge, our study is the first to continuously measure $NMEdi_{insp}$ during a T-tube trial using diaphragm electrical activity and transdiaphragmatic pressure. Previously, $NMEdi_{insp}$ has been calculated intermittently during a 30-min weaning trial as the decrease in airway pressure divided by $\Delta EAdi_{insp}$ during an inspiratory occlusion.[18] In the latter study, the weaning trial was performed with 5 cm H_2O of continuous positive airway pressure. The addition of 5 cm H_2O of continuous positive airway pressure decreases the work of breathing by as much as 40% in ventilated patients.[46] Nevertheless, the reduced ability of the diaphragm to convert neural respiratory drive into pressure in weaning-failure patients is a consistent finding among studies.[17,18]

Numerous studies have demonstrated that diaphragm weakness develops in critically ill patients.[9–14] Reduced pressure-generating capacity of the diaphragm may result from structural modifications but also from the development of muscle fatigue, altered force-velocity relation, or altered force-length relation of the muscle. These factors may play a role in the development of weakness during a spontaneous breathing trial. However, previously it was demonstrated that a 1-h spontaneous breathing trial did not cause long-lasting fatigue of the diaphragm.[19] Increased end-expiratory lung volume may place the diaphragm at a less favorable position on a length-tension curve. An increase in lung volume from functional residual capacity to total lung capacity reduces transdiaphragmatic pressure by 60% for a given $\Delta EAdi_{insp}$.[53] Although we did not directly measure end-expiratory lung volume, corrected intrinsic PEEP and lung mechanics were not significantly different between groups during weaning, suggesting no major differences in lung volume. Accordingly, reduced neuromechanical efficiency in the failure group may largely be explained by structural modifications, such as diaphragm atrophy, but we cannot completely rule out impaired respiratory mechanics.

In contrast to a previous study by Jubran and Tobin,[45] we did not find a difference in $PTPes_{insp}$ between weaning-success and weaning-failure patients. This difference may be explained by patient selection and weaning failure criteria. In Jubran and Tobin's study, only patients with COPD were included. This provides an explanation for the fact that the higher $PTPes_{insp}$ resulted from higher resistance and intrinsic PEEP. Furthermore, we defined weaning failure as failing the spontaneous breathing trial or reintubation within 48 h after extubation, whereas in their study, weaning failure was defined as failing the spontaneous breathing trial.

In the present study, increased respiratory muscle effort (including expiratory muscle effort) and reduced neuromechanical efficiency of the diaphragm appear to play a role in failure to wean from mechanical ventilation. However, it is important to note that cardiac dysfunction, cognitive dysfunction, and metabolic disorders are recognized causes for weaning failure as well[6,7] and may have contributed to weaning failure in the current study.

Limitations

In the present study, raw EAdi signals were recorded and processed according to the methods of Sinderby *et al.*[40–42] Today, many studies record electrical activity of the diaphragm not in its raw format but as a processed signal *via* the SERVO-i (Maquet Critical Care) ventilator. Differences between algorithms to process EAdi can lead to differences in absolute values of $\Delta EAdi_{insp}$. Therefore, absolute values of $\Delta EAdi_{insp}$ (and $NMEdi_{insp}$) obtained in our study cannot be directly compared to values obtained with recordings from the SERVO-i (Maquet Critical Care) ventilator.

We did not record electrical activity of the abdominal wall muscles. However, we are confident that ΔPga_{exp} reflects expiratory muscle recruitment in our study. First, we excluded the possibility of expiratory diaphragmatic activity contributing to ΔPga_{exp}. Second, we found a strong correlation between peak expiratory flow and ΔPga_{exp} in weaning-failure patients. Third, a strong correlation has previously been demonstrated between ΔPga_{exp} and electrical activity of the abdominal wall muscles.[54]

In conclusion, the expiratory muscles significantly contribute to respiratory muscle effort in a mixed group of weaning-failure patients. Therefore, the expiratory pressure–time product should be measured when estimating energy expenditure of the respiratory muscles during weaning from mechanical ventilation. We did not find evidence of increased expiratory tonic diaphragmatic contraction during weaning failure. In addition, our findings confirm that impaired pressure-generating capacity of the diaphragm, regardless of its origin, plays a role in failure to wean from mechanical ventilation.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Heunks: VU University Medical Center Amsterdam, Department of Intensive Care Medicine, Postbox 7057, 1007 MB Amsterdam, The Netherlands. L.Heunks@VUmc.nl.

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