

Variability of End-Expiratory Lung Volume in Premature Infants

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Key Words

Time-series analysis · Control of breathing · Mechanical ventilation · Neonatal respiratory distress syndrome

Abstract

Background: Analysis of breath-to-breath variability of respiratory characteristics provides information on the respiratory control. In infants, the control of end-expiratory lung volume (EELV) is active and complex, and it can be altered by respiratory disease. The pattern of EELV variability may reflect the behavior of this regulatory system. **Objectives:** We aimed to characterize EELV variability in premature infants, and to evaluate variability pattern changes associated with respiratory distress and ventilatory support. **Methods:** EELV variations were recorded using inductance plethysmography in 18 infants (gestational age 30–33 weeks) during the first 10 days of life. An autocorrelation analysis was conducted to evaluate the 'EELV memory', i.e. the impact of the characteristics of one breath on the following breaths. **Results:** In infants without respiratory symptoms, EELV variability was high, with large standard deviations of EELV. Autocorrelation was found to be significant until a median lag of 7 (interquartiles: 4–8) breaths. Autocorrelation was markedly prolonged in patients with respiratory distress or ventilatory support, with a higher number of breath lags with significant autocorrelation ($p < 0.01$) and higher autocorrelation coefficients ($p < 0.05$). Conventional assisted ventilation does not re-

establish a healthy EELV profile and is associated with lower respiratory variability. **Conclusions:** In premature infants, EELV variability pattern is modified by respiratory distress with a prolonged 'EELV memory', which suggests a greater instability of the control of EELV.

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Introduction

The breath-by-breath variability of the characteristics of respiratory cycle has been studied for years. In 1963, Priban [1] demonstrated that breath fluctuations were not purely random. Physiological breathing variability has been regarded as an indicator of good health [2] that reflects the adaptive capacity of the respiratory system. A lower variability has been associated with pathological conditions [3–5]. Excessive variability has also been reported as a sign of deleterious instability [6, 7], and an equilibrium is probably necessary [8]. Using time-series analysis, it has been shown that the magnitude of a component of one breath is positively correlated with the magnitude of the component of the preceding breath [9–12]. This observation that a given breath is followed by breaths with similar characteristics has been called 'short-term memory' [10], despite the fact that it does not necessarily originate from a neural mechanism. The short-term memory can be described by autocorrelation analy-

sis, which reflects the time necessary for the system to return to its baseline after a breath-by-breath change; it may be regarded as an indicator of the system stability [13]. Autocorrelation has been measured in adults for tidal volume (VT) and respiratory timing [10–12]. Autocorrelation is higher when a respiratory load is added [3] or in certain respiratory diseases [4, 5]. During infancy, VT, inspiratory time (TI), and expiratory time (TE) are also highly variable [14, 15], and presence of autocorrelation has been observed [6, 16].

Variability of end-expiratory lung volume (EELV) has been reported mainly in adults [17, 18]. Studies in animals suggest that EELV fluctuations may partly manifest autocorrelation [19]. In contrast to adults, infants actively maintain a level of EELV higher than the respiratory relaxation volume. Premature infants have a high risk of EELV reduction, with unfavorable prognostic impact [20, 21]. The complex EELV control involves the persistence of tonic diaphragmatic activity during expiration [22], a flow-braking action of the laryngeal adductor muscles [23], and a high respiratory rate with relatively short TE [24]. Tonic diaphragmatic activity has a high intrinsic variability [22], which can be modified by an external load [25]. Variability of TE is a major determinant for timing variability in infants [15]. The variations of these two key parameters suggest that resultant EELV likely presents fluctuations.

Latzin et al. [26] recently report that interindividual variability of EELV was more strongly related to the body weight in infants with more severe bronchopulmonary dysplasia, implying that the variability originating from neurorespiratory mechanisms had less impact. This suggests an activation of the mechanisms of EELV control, with a lower degree of freedom of the regulation system in patients with respiratory disease [26].

The aims of the present study were to characterize the variability of EELV in premature infants, and to evaluate the impact of respiratory distress with or without mechanical ventilation on the variability in EELV. Our hypothesis is that EELV variability is non-random, consistent with active central control, and that changes in the pattern of variability may be associated with respiratory distress.

Methods

Patient Population

We investigated premature newborn infants during their first 10 days of life in the neonatal intensive care unit of Grenoble University Hospital from March 2005 to October 2006. Inclusion cri-

teria were: (1) gestational age from 30 to 33 weeks, (2) birth weight >1,000 g, and (3) postnatal age between 1 and 10 days. Patients were not eligible if they had one of the following conditions: hemodynamic impairment or need for inotropic treatment, cerebral hemorrhage, severe metabolic acidosis or alkalosis, or suspected neuromuscular disease. Presence of respiratory distress signs was clinically determined by the attending physician, using the Silverman score [27]. Three patient groups were predefined. Patients without respiratory distress signs, without oxygen supplementation, and with normal chest radiography constituted the control group. Patients with a Silverman score >1 or with supplemental oxygen were classified in the respiratory distress group. The ventilatory assist group included patients requiring any respiratory support, such as nasal continuous positive airway pressure (Infant Flow; EME Tricomed, Brighton, UK) or assisted ventilation (Babylog 8000; Dräger, Lübeck, Germany) with an endotracheal tube.

Study Protocol

Following morning nursing care, a respiratory inductance plethysmography (RIP) jacket was positioned. The infant was placed supine, with a 30° head elevation, and rested quietly for at least 5 min. RIP signals were then continuously recorded during 30 min. For the purpose of calibration, RIP signals and airflow (pneumotachograph) were simultaneously recorded for 60 s, when the infant was quiet [28, 29]. Oxygen saturation, heart rate, respiratory rate, and agitation episodes were monitored throughout the whole study. No modification of the respiratory support or of any treatment was done for study purposes. The protocol was approved by the local ethics committee. Written informed consent was obtained from the parents of all infants.

EELV Variation Measurement

RIP signals were recorded and calibrated using a standardized method, as previously described [28, 29]. The abdominal and rib-cage RIP coils were coated in a sleeveless jacket specially sized for preterm neonates. RIP signals were digitized at a 40-Hz sampling rate (Visuresp®; RBI, Meylan, France). The reference airflow was recorded by a calibrated pneumotachograph (PNT) with a flowmeter (dead space 1.9 ml, PN155500; Hamilton Medical, Rhäzüns, Switzerland) and a differential transducer (163PC01D36; Micro Switch) attached to a face mask (dead space 5 ml, Neonatal face mask; Ambu France, Le Haillan, France). In intubated patients, the flow signal was obtained from the ventilator (Babylog 8000; Dräger). Patients with air leak around the tracheal tube (measured by the ventilator) >10% were not eligible.

The 15 most regular (in duration) consecutive breaths of PNT signal were automatically identified and formed the calibration reference period. A least-squares method was used over this reference period to estimate α and β coefficients allowing to obtain a RIP volume signal (V_{RIP}) by combination of rib cage (RC) and abdominal (AB) RIP signals, in comparison to the integrated simultaneously recorded flow signal (V_{PNT}) [28, 29]:

$$V_{RIP} = \alpha \cdot RC + \beta \cdot AB$$

The derivative of V_{RIP} was then calculated by using centered divided differences [28]. A transfer function was calculated over the reference period between the V_{RIP} and V_{PNT} derivatives in order to take out an adjusted filter for each recording [28, 29]. This filter was then applied to the entire recording. Automatic detec-

Table 1. Patient clinical characteristics

	Control (n = 8)	Respiratory distress (n = 5)	Assisted ventilation (n = 5)
Age, days	5 (3–7)	6 (5–7)	3 (1–8)
Gestational age, weeks	31.6 (31.3–31.9)	32.0 (31.9–32.7)	31.0 (30.9–31.4)
Birth weight, g	1,350 (1,220–1,480)	1,560 (1,480–1,720)	1,570 (1,260–1,610)
Antenatal steroids, n	7	3	4
Exogenous surfactant, n	0	4	5
Ongoing sedation, n	0	0	2
Silverman score	0 (0–0)	2 (2–3)	–
Respiratory rate	66 (56–72)	72 (58–85)	70 (60–89)
PCO ₂ , mm Hg	35 (35–36)	36 (36–39)	38 (36–38)
SpO ₂ , %	99 (96–100)	97 (92–99)	93 (93–97)

Continuous data are provided as median (25th–75th percentiles).

tion of individual breaths permits calculation of VT, TI and TE on a breath-by-breath basis. Variation in EELV was calculated for each breath as the difference between the EELVs of the breath as compared to the preceding breath. The cumulative sum of each breath EELV variation was used to establish the EELV time series. For easier comparison, EELV variations were expressed in ml/kg.

Data Analysis

For each recording, periods with artifacts due to agitation were carefully event-marked by the investigator who stayed at the bedside throughout the entire recording period, and were removed from the analysis. The quasi-stationary nature of EELV time series was verified by trending it with a least-square regression versus time (order 1) [5]. A given time series was rejected in the presence of a significant trend. The longest consecutive quasi-stationary and non-artifacted period was retained.

Respiratory variability was first evaluated for each subject using ‘classical’ statistical tools, namely the coefficients of variation (CV) for TI, TE, and VT. Standard deviations (SD) have been used for EELV rather than coefficients of variation, because the mean level of EELV was not measured, precluding calculation of the ratio. SD and CV were compared between the three groups using Kruskal-Wallis tests.

Second, an autocorrelation analysis was performed to evaluate the breathing ‘short-term memory’ [10], i.e. the impact of the characteristics of one breath on the characteristics of another one taken after a lag. Autocorrelograms were constructed based on autocorrelation coefficients, starting with a lag of one breath and continuing with a higher lag as long as autocorrelation coefficients remain significant ($p < 0.05$). Patient groups were compared using Kruskal-Wallis tests for the number of breath lags with significant autocorrelation, and using repeated measure ANOVA for the first 10 autocorrelation coefficients.

Any signal recording and processing methods can artificially introduce autocorrelation. In order to evaluate the influence of our acquisition method on autocorrelation results, we evaluated the EELV autocorrelation of a mechanical lung model. The RIP acquisition system was applied on a test lung 190 (Maquet AB,

Solna, Sweden) connected to a Servo Ventilator (Maquet AB). Seven recordings were conducted with various respiratory settings (respiratory rates 60–80 bpm, VT 20–30 ml). PEEP was also modified (5–15 cm H₂O) to evaluate different stretch status of the RIP jacket. In this bench condition, autocorrelation for EELV was absent in two experiments; a short-term autocorrelation limited to the first breath lag was observed in four experiments, and to the second breath lag in one experiment. Autocorrelation was never observed after the second breath lag.

Statistical Analysis

Data are reported as median (25th–75th percentiles) [30] unless otherwise specified. A p value < 0.05 was considered to be significant. When a significant difference was observed between the three groups with a Kruskal-Wallis test or with a repeated measure ANOVA, individual comparisons were conducted using the Mann-Whitney test or the Games-Howell test, respectively. The latter was chosen because of the sample size and of unequal variance [31, 32].

Results

Patients

Eighteen premature newborn infants 5 (3–8) days of age were investigated. The characteristics of the patients are reported in table 1. Five patients had clinical symptoms of respiratory distress, and 5 infants had ventilatory support. All these 10 patients had respiratory distress syndrome. One patient in the respiratory distress group also had a group B streptococcal infection, and 1 patient in the ventilatory support group had a pneumothorax which was completely drained prior to the study. The remaining 8 patients constituted the control group. The

Table 2. Variability of the breath components described using standard deviations or coefficients of variation

	Control (n = 8)	Respiratory distress (n = 5)	Assisted ventilation (n = 5)	p value
SD of EELV, ml/kg	6.7 (2.3–8.0)	5.0 (3.2–7.9)	2.1 (0.7–2.2)	0.09
CV of VT, %	73 (56–95)	72 (51–82)	46 (34–51)	0.10
CV of TI, %	30 (26–52)	34 (34–44)	28 (27–35)	0.55
CV of TE, %	109 (91–123)	110 (71–144)	40 (40–56)*	<0.05

CV = Coefficient of variation; EELV = end-expiratory lung volume; SD = standard deviation; TI = inspiratory time; TE = expiratory time; VT = tidal volume. Data are provided as median (25th–75th percentiles).

* Significant difference as compared to both other groups.

three groups had similar perinatal characteristics, except for the Silverman score, which was higher in patients with respiratory distress ($p < 0.01$), and the absence of surfactant treatment in the control group ($p < 0.01$).

In the ventilatory support group, 1 patient had nasal CPAP, and 4 patients were intubated and ventilated in assist control ventilation mode, with a PEEP of 4 (4–4) cm H₂O, inspiratory pressure of 18 (17–18) cm H₂O, and FiO₂ of 0.25 (0.21–0.33). The respiratory rate was set at 48 (44–53) breaths per minute, with TI 0.32 (0.30–0.34) s and TE 0.95 (0.84–1.05) s, but the patients had a higher respiratory rate (70 (60–89) breaths per minute), with 44 (15–51)% of the breaths that were spontaneous, resulting in a shorter actual TE (0.43 (0.40–0.68) s).

Breath-by-Breath Variability

The number of breaths in the patient breath series was 344 (293–455) in the control group, 311 (301–445) in the respiratory distress group, and 494 (243–744) in the assisted ventilation group ($p = 0.68$). The TI was 0.34 s (0.32–0.36) in the control group, 0.31 s (0.30–0.45) in the respiratory distress group, and 0.28 s (0.28–0.33) in assisted ventilated patients; TE was 0.59 s (0.48–0.70), 0.53 s (0.43–0.61), and 0.43 s (0.40–0.68) in the same order, respectively. Standard deviations of EELV and coefficients of variation of TI, TE, and VT are presented in table 2. EELV variations were high in control patients and in patients with respiratory distress symptoms, as illustrated by standard deviations of 6.7 ml/kg (2.3–8.0) and 5.0 ml/kg (3.2–7.9). No clear differences in SD or CV were observed between control group and respiratory distress group for EELV, VT, TI, and TE. Lower SD and CV were observed for each breath characteristics in assisted ventilation group, which reached significance for TE ($p < 0.05$).

Table 3. Number of breath lags with significant autocorrelation for each breath component

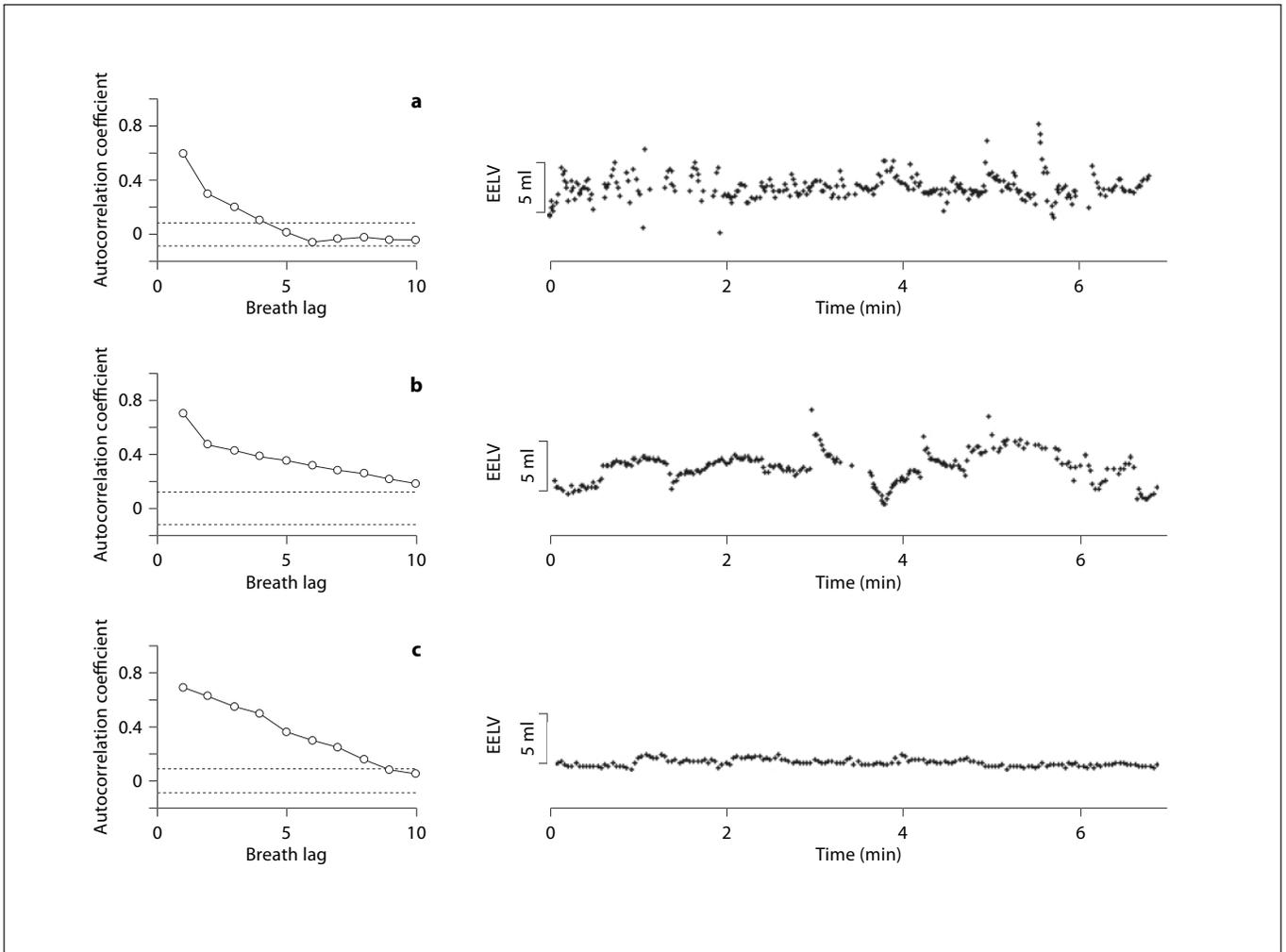
	Control (n = 8)	Respiratory distress (n = 5)	Assisted ventilation (n = 5)	p value
EELV	7 (4–8)*	13 (12–13)	20 (9–25)	<0.01
VT	1 (1–2)	1 (1–21)	4 (2–4)	0.31
TI	3 (1–8)	1 (1–11)	0 (0–2)	0.70
TE	1 (0–1)	2 (1–3)	8 (1–9)	0.46

EELV = End-expiratory lung volume; VT = tidal volume; TI = inspiratory time; TE = expiratory time. Data are provided as median (25th–75th percentiles).

* Significant difference as compared to both other groups.

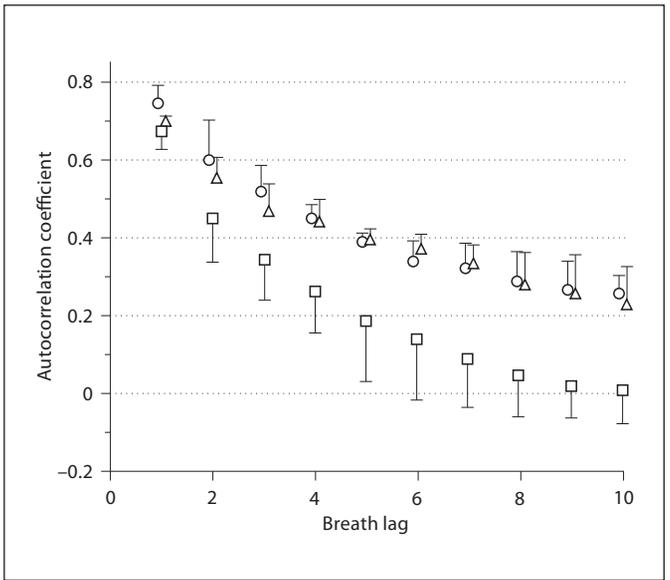
Autocorrelation Analysis

The autocorrelograms of EELV variations in 3 representative subjects are presented in figure 1, with their corresponding time-series plots of EELV. The numbers of breath lags with significant autocorrelation for all patients are presented in table 3. Significant autocorrelation persisted after high-order lags for EELV, whereas it was limited to a few breath lags for VT, TI, and TE. The number of lags with significant autocorrelation for EELV was higher in the patients with respiratory distress, with or without assisted ventilation, compared to control patients ($p < 0.01$). Figure 2 illustrates the median values of autocorrelation coefficients for EELV for the first 10 breath lags in each group. Whilst comparing the first 10 breath-lag autocorrelation coefficients for EELV, a significant difference was observed between the groups ($p < 0.01$; rmANOVA), with higher autocorrelation in patients with respiratory distress or with ventilatory assistance, com-



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Fig. 1. Autocorrelograms of EELV (left) and corresponding time-series plots of EELV fluctuations (right) in 3 representative patients: control (a), with respiratory distress (b), and with ventilatory assist (c). In the autocorrelograms, points lying outside the pair of dotted lines are statistically different from zero ($p < 0.05$). **Fig. 2.** Autocorrelation coefficients of EELV for the first 10 breath lags in control group (squares), respiratory distress group (circles), and ventilatory assist group (triangles). Autocorrelation is higher in patients with respiratory distress and with ventilatory assist, as compared to control group ($p < 0.05$). Data presented as median and interquartile difference.



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pared to control patients ($p < 0.05$; Games-Howell test). The first autocorrelation coefficient (lag 1) did not differ between the groups ($p = 0.92$).

Regarding VT, TI, and TE, autocorrelation coefficients were not different between the groups ($p = 0.60$, 0.23 and 0.28, respectively; rmANOVA).

Discussion

Principal Findings

This study shows the existence of a high breath-by-breath variability of EELV in premature infants of a gestational age from 30 to 33 weeks. This variability is not purely random as the EELV of each breath depends on the characteristics of the preceding breaths, as shown by significant autocorrelation coefficients. In the presence of respiratory distress or ventilatory support, different variability patterns are observed, with longer breath lags exhibiting significant autocorrelation coefficients and with higher autocorrelation coefficients.

Critique of the Methods

We used RIP to measure EELV variability. As regards EELV measurements, gas dilution methods cannot measure cycle-to-cycle variation. Whole-body plethysmography permits this kind of recording; however, this could not be used in fragile patients requiring intensive care. RIP is currently the most widely used method for the measurements of respiratory volumes in infants. As regards the measurement of variability, RIP has long been used in adults [11] and in infants [6]. Fiamma et al. [33] recently confirmed that the ventilatory flow signal obtained from the RIP acquisition device that we used gives access to valid estimates of respiratory variability and complexity. In order to optimize RIP accuracy in these small patients, we used a specific and individualized calibration method, which remains adequate even in infants with thoraco-abdominal asynchrony or ventilatory assist [29].

We have used an autocorrelation analysis to characterize variability. This method permits one to accurately distinguish different variability patterns [11, 12]. Certain segments of the recordings were impossible to analyze because of artifacts induced by agitation. Only consecutive periods free of artifacts were retained for the time series, in order to avoid potential bias created by discontinuities. Autocorrelation can be artificially introduced by the signal acquisition system or the signal processing method. The bench studies conducted on a mechanic lung model at various stretch statuses and with the same

data processing and analysis method have only generated brief and limited autocorrelation. This may have affected part of our results, but this does not explain the importance of the autocorrelation that was observed in patients nor the difference of patterns found between the groups. Autocorrelation is also sensible to baseline drift. These drifts may arise from real lung volume changes or may follow an equipment drift. We choose to analyze only quasi-stationary time series, excluding time series with a significant trend. This method probably limited the influence of drift due to recording method, but the results may not be applicable to situations in which drift is due to physiological changes.

The three patient groups were defined according to the presence of respiratory distress or ventilatory assistance. The Silverman score used to quantify respiratory distress symptoms is a validated score [27], routinely employed in our neonatal intensive care unit. Moreover, the two groups appeared well delineated, as all the patients in the respiratory distress group had a score of 2 or more, whereas in the control group, the score was zero except for 2 patients who only presented intermittent nasal flaring. The size of the three groups permitted to detect differences in EELV pattern but may have been insufficient to show other differences between the groups.

The sleep state influences respiratory variability, with a lower variability observed in quiet sleep as compared to REM sleep [14, 34]. Polygraphic recordings have not been done in the present study. However, all the patients were studied following morning nursing care and recordings began after a few minutes when the patients were calm to limit the movement artifacts; the sleep state was probably rather similar between the patients.

Respiratory variability is influenced by sighs. Baldwin et al. [35] have shown in infants that short-term autocorrelation of VT diminished during the 50 cycles preceding the sigh, while coefficients of variation of VT increased. In the present study, the impact of sighs on EELV autocorrelation has not been evaluated due to the limited number of cycles between the sighs. Sighs may have influenced short-term autocorrelation results. However, the incidence of sighs did not differ between the groups (data not shown). Moreover, long-range correlation seems to be unaffected by sighs [35], so the difference observed in the autocorrelation patterns cannot be attributed to sighs.

EELV Variability in Normally Breathing Patients

In adults, two studies [17, 18] have shown that the EELV level fluctuates around its mean value, with cycle-by-cycle differences which may reach 360 ml [17]. Low-frequency

oscillations were suspected in a 4-patient study [18]. In animals, a positive long-term correlation of EELV was found in anesthetized rats, suggesting that EELV had fractal properties [19]. In infants, variability of EELV has not been reported previously, whereas variability of respiratory timing and amplitude has been shown to be greater in premature infants in comparison to older infants or adults [15]. Breathing variability is not purely random; a long-range correlation that follows a power-law distribution has been demonstrated for VT and respiratory timing in infants [6, 16]. In the present study, we have found that EELV also presents non-random fluctuations in premature infants. In addition to the respiratory control mechanisms classically described – implying vagal afferent inputs, chemoreceptors, non-respiratory systems influences (hemodynamic status, sleep state, or cerebral blood flow), which all act on the respiratory generator within different time scales [36] and gains [37], favoring the occurrence of variability – particular mechanisms in infants may contribute to EELV variability. A large number of mechanisms are involved in the regulation of EELV during the first months of life. The active control of EELV implies the flow-breaking action of the larynx [23] and of the diaphragm by its tonic activity [22], and the respiratory timing pattern with relatively short TE [24]. Both tonic diaphragmatic activity and TE have high intrinsic variability [15, 22]. In the present study, important variations of TE and VT were also observed, which may have favored EELV fluctuations. The EELV variability we observed in these premature infants may also be due to immaturity. Irregular breathing pattern is common in preterm infants and has been attributed to brainstem immaturity [38, 39]. However, active maintenance of EELV has been demonstrated not only in premature infants, but also throughout the entire first year of life [40]. EELV fluctuations have been observed also in adults [17, 18]. It seems unlikely therefore that immaturity is the only explanation for the high EELV variability in preterm infants.

Breathing variability has been reported as a sign of good health [2]. The presence of variability may be considered as a reflection of the high number of degrees of freedom of the respiratory regulation system [41], and of its capacity for responsiveness and adaptability to a perturbation [16]. An abnormal respiratory condition may decrease the degree of freedom of the respiratory control system, and result in reduced variability [41].

EELV Variability in Infants with Respiratory Distress

The impact of pathology on breathing variability has seldom been studied in infants. Patzak et al. [34] have ex-

plored the frequency spectra of breathing in infants with bronchopulmonary dysplasia and in controls, but their findings did not suggest a modification of breathing complexity [34]. In adults, experimental studies have demonstrated that a mechanical load of respiration or hypercapnia may induce a decrease in variability and an increase in autocorrelation of ventilatory timing and amplitudes [3, 42–44]. This has also been observed in patients with restrictive lung disease [4]. A prognostic impact has been suggested by Wysocki et al. [5], who found a lower breathing variability and higher autocorrelation in mechanically ventilated patients who failed weaning trials in comparison to those patients who succeed [5]. Kobylarz et al. [25] have shown that in healthy adults a mechanical respiratory loading decreases the variability of tonic diaphragm activity [25]. As tonic diaphragm activity is involved in EELV regulation, this may facilitate also a decrease in EELV variability.

In the present study, the global amplitude of EELV variability (as evaluated by SD) was not modified by the presence of respiratory distress symptoms, whereas autocorrelation was markedly prolonged, suggestive of different profiles of EELV variability, as illustrated in figure 1. In infants without respiratory distress, EELV seems highly variable around the baseline but the latter is quite stable, and after a deviation, EELV returns to the mean level after only a few cycles. In the case of respiratory symptoms, deviations of EELV from its baseline level are slowly corrected, thus corresponding to a ‘prolonged memory’. The higher and more prolonged autocorrelation in the pathological groups may reflect an increased instability of the EELV control [13]. This instability is not surprising in patients with respiratory distress syndrome. The surfactant deficiency makes the control of EELV more difficult in preterm infants. Both atelectasis and overdistension are present [45], which may favor changes in EELV following small changes in mechanical inputs. The increased activation of the laryngeal contraction (grunting) to regulate the EELV [23] may also result in a prolonged EELV memory due to a lower degree of freedom of the EELV control.

In contrast with the results found in adults [3, 5, 42–44], the autocorrelation patterns for TE, TI, and VT were not different in infants with respiratory distress; a difference in autocorrelation pattern was only found for EELV. The group sizes may have been too small to detect differences for these other parameters; nevertheless, EELV variability seems to be more influenced by pathological conditions than the variability of respiratory timing or amplitude in these infants.

EELV Variability in Infants with Ventilatory Support for Respiratory Distress

Infants under ventilatory assistance present an autocorrelation profile similar to the respiratory distress group in this study. The CV of TE was lower in this group, and there was a trend of a lower variability of TI, VT, and EELV. This decreased variability may be due to the impact of the ventilatory assist and/or to the severity of the respiratory disease. The ventilator settings certainly influenced the respiratory timing; the lower variability of TI and TE in this group is not surprising, even if a large proportion of the breaths were spontaneous. Mandatory breaths are also known to induce the Hering-Breuer reflex [46]. The quasi-continuous activation of this reflex could have lowered the variability of TE, which can partly explain our findings. The setting of the TI and inspiratory pressure in assist control ventilation has probably limited the fluctuations of VT as well, even if a certain variability occurred, mainly explained by the variable respiratory efforts of the patients.

The presence of the endotracheal tube suppresses the laryngeal expiratory breaking action. The loss of EELV may be prevented by the application of PEEP and by the activation of tonic diaphragmatic activity [22, 47]. The loss of activity of the larynx and the continuous activation of expiratory breaking by the tonic diaphragmatic activity may explain that the EELV variability is particularly low in this condition, due to the low degrees of freedom of the EELV control.

The mechanical properties of the respiratory system are also directly related to EELV, which may affect the respiratory control. As the absolute EELV was not mea-

sured in the present study, it is difficult to establish a direct relationship between the EELV level and its variability pattern. However, this observational study shows that different patterns can be observed, that may reflect different EELV control behaviors. Future studies relating these patterns with EELV measurements would help to further approach the EELV control understanding.

In assisted ventilated adult patients, Wysocki et al. [5] reported that low variability was associated with weaning failure. Experimental studies on animals or with a mathematical model have suggested that the restoration of some of the physiological variability in the ventilatory settings can be beneficial for patients [48, 49]. We may speculate that ventilation modes with non-constant settings (e.g. biologically variable ventilation [49], or neurally adjusted ventilatory assist [50]) would favor the restoration of physiological variability pattern.

In conclusion, the breath-by-breath EELV variability is high in premature infants, in control patients as well as in patients with respiratory distress. The autocorrelation analysis of EELV time series showed different patterns, with more prolonged 'short-term memory' of EELV in premature infants with respiratory distress with or without ventilatory support. The EELV variability pattern may reflect the instability of the control of breathing with lung disease.

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