DYNAMICS UNDERLYING PATIENT-VENTILATOR INTERACTIONS DURING NOCTURNAL NONINVASIVE VENTILATION


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Noninvasive ventilation is a common procedure for managing patients having chronic respiratory failure. The success of this ventilatory assistance is often linked with patient’s tolerance that is known to be related to the quality of the synchronization between patient’s spontaneous breathing cycles and ventilatory cycles delivered by the ventilator. Thirty-four sleep sessions (more than 5000 ventilatory cycles each) were automatically investigated using a specific algorithm processing airflow and pressure time series. Four groups of patients were defined according to the interplay between asynchrony events and leaks. Different mechanisms that depend on sleep stages were thus evidenced. A Shannon entropy was also proposed as a new sleep fragmentation quantification methodology.

Keywords: Noninvasive ventilation; patient-ventilator interactions; sleep quality.

1. Introduction

When spontaneous breathing is no longer sufficient to maintain alveolar ventilation and subsequent gas exchanges, noninvasive mechanical ventilation may be applied to reduce the ventilatory work of breathing. It has become a standard procedure to relieve patients with acute or chronic respiratory failure [Ferrer et al., 2003]. One important dynamical feature involved in the patient discomfort is the lack of synchrony between patient’s spontaneous breathing activity and the output of the ventilator, that is, between the inspiratory effort and the air delivered by the ventilator. The quality of the so-called “patient-ventilator interactions” [Tobin et al., 2001; Kondili et al., 2003] is therefore one of the critical factors determining the success of noninvasive mechanical ventilation since it is widely accepted that patient tolerance depends on whether the patient feels comfortable or not [Carlucci et al., 2001]. But determining from noninvasive measurements whether patient-ventilator synchrony is optimal or not remains a research task. Recently, automatic algorithms for detecting asynchrony were developed [Achour et al., 2007; Mullqueeny et al., 2007; Cuvelier et al., 2010]. It is therefore now possible to investigate ventilation and, in particular, to estimate asynchrony rate during an entire night and not only for short period of time (30 min or so) during which patients were awake [Vignaux et al., 2009]. Such automatic analysis thus allows to assess
the quality of patient-ventilator interactions in conditions closer to what is applied for common nocturnal ventilation at patient’s home. Indeed, for mechanical ventilation sessions during whole nights, it was necessary to use automatic algorithms to investigate the large amount of cycles (around 5000 per night) at disposition [Curvello et al., 2010].

Patient-ventilator asynchronies and especially ineffective inspiratory triggering efforts are regularly encountered when performing mechanical ventilation [Nava et al., 1997]. Ineffective inspiratory efforts under pressure support mode are more frequent during sleep [Parthasarathy, 2005; Fanfulla et al., 2005] or when increasing the level of ventilatory assistance [Leung et al., 1997; Giannouli et al., 1999]. Patient-ventilator asynchronies including ineffective inspiratory efforts, may be clearly a cause of noninvasive ventilation intolerance and failure. Either in acute or chronic setting, the incidence of nontriggered respiratory cycles and their consequences on noninvasive mechanical ventilation efficacy was evidenced [Tassaux, 2005; Navalesi et al., 2007; Thille & Brochard, 2007] but the incidence on comfort remains uncertain. Moreover, if leaks can be more or less avoided during short sessions, it is not possible to control them during a whole night due to bodily motion, for instance. If leaks induce most of asynchrony events, it is still an open question whether leaks necessarily induce all asynchronies [Hotchkiss et al., 2001; Miyoshi et al., 2005; Haynes, 2008]. On the other hand, discomfort could be related to mouth leaks when nasal masks are used [Teschler et al., 1999]. One of our aims was therefore to assess whether all asynchronies were induced by leaks during nocturnal ventilation.

Among the natural rhythms that are relevant for life, breathing is certainly one of the most often perceived as fluctuations depending on various parameters. We always alternate inspirations and expirations but such cycling depends on our activity, our stress, etc. For short it depends on the surrounding world and on our behavior in this ambient world. Breathing is known for being not exactly periodic, but a decisive proof for its chaotic nature is still lacking [Small et al., 1999; Ahlstrom et al., 2006; Wysocki et al., 2006] in spite of works recently published [Samara et al., 2008], mainly because there is no conclusive technique for proving chaos from noisy time series. For instance, the noise titration technique (as used in [Samara et al., 2008]) was presented as a “simple litmus test for highly sensitive, specific, and robust detection of chaos in short noisy data” [Poon & Barahona, 2001]. But it was in fact unable to distinguish some stochastic dynamics from chaos, preventing a conclusive answer [Freitas et al., 2009]. But such features do not prevent the use of tools borrowed from the nonlinear dynamical systems theory to characterize the dynamics underlying ventilatory cycles.

Breathing patterns are necessarily noise contaminated in the sense that the ambient world always has an impact on the subjects through the emotions that affect the breathing rhythm [Elarholt & Bergland, 2008]. Moreover, performing a measurement, even in a noninvasive manner, necessarily affects the subjects and, consequently, the dynamics underlying the system — the patient coupled to his ventilator — under study. Such noise contamination can contribute to develop — to make more complex — the dynamics but, unfortunately, it cannot be avoided.

Noninvasive mechanical ventilation is commonly applied during night at a patient’s home. Consequently, patient-ventilator interactions may be influenced by sleep stages [Fanfulla et al., 2007; Guo et al., 2007] since breathing patterns can be affected by them [Smith et al., 1989; Ichimaru et al., 1990; Guilleminault et al., 2001]. Nevertheless, how breathing patterns are related to sleep stages is very rarely assessed due to technical difficulties. But it was found that the onset of patient-ventilator mismatch during sleep resulted in poor sleep quality, a high number of arousals and less effective noninvasive ventilation [Fanfulla et al., 2005]. In spite of this, patient-ventilator asynchronies during night were very rarely investigated too and never correlated to sleep stages [Fanfulla et al., 2007]. The aim of the present study is therefore to document and to investigate patient-ventilator asynchrony during nocturnal noninvasive ventilation for chronic respiratory failure. From our knowledge, no such data are available in the literature. The subsequent part of this paper is organized as follows. Section 2 introduces the main clinical characteristics of the patients and the measurements are actually achieved. Different estimators (asynchrony rates, leak) were automatically computed and investigated according to hypnograms. Section 3 is devoted to a new sleep fragmentation estimator using a Shannon entropy based on a close return plot built from a sleep stage scoring. Section 4 discusses the most important interplay between
the different quantities computed over the whole night (cross-covariance between ineffective efforts and out-of-phase cylings, and between leaks and ineffective efforts). Section 5 gives the conclusion.

2. Patients and Measurements

This retrospective, observational study was conducted in a medical university hospital Intensive Care Unit (Rouen). We selected 34 recordings from our sleep laboratory database. The corresponding time series were included in this study when they provided valid ventilatory (airflow and pressure) and polysomnographic time series for which reliable leak estimation was performed. All patients were ventilated with the bilevel ventilator ResMed VPAP III. These patients were long-term ventilated for chronic respiratory failure. Two types of respiratory failures were encountered in this study. The first type is named Obesity Hypoventilation Syndrome (OHS). It is a condition in which severely overweight people fail to breathe normally resulting in low blood oxygen levels and high blood carbon dioxide (CO$_2$) levels. Many people with this condition also have increased upper airways resistances during sleep (obstructive sleep apnea), resulting in many partial awakenings during the night, which leads to abnormal daytime sleepiness. The disease puts strain on the heart, which eventually may lead to the symptoms of heart failure, such as leg swelling and various other related symptoms. The second type is designated as Chronic Obstructive Pulmonary Disease (COPD). It refers to small airways obstructions and far emphysema, a pair of two commonly co-existing diseases of the lungs in which the airways narrow progressively. This leads to an airflow limitation causing shortness of breath. In contrast to asthma, the limitation of airflow is poorly reversible under bronchodilators and usually gets progressively worse over time. Although with severe health failure, all patients included in this study were in stable condition, as assessed by clinical examination and arterial blood gases. Only two of them were hospitalized for acute hypercapnic respiratory failure — for which a treatment is required in an intensive care service — during the three months before they were included in the protocol.

The main characteristics of the thirty-four patients corresponding to the selected recordings are reported in Table 1. Nineteen patients (56%) had OHS and 15 patients (44%) had COPD. Thirty patients (88%) presented obstructive sleep apnea syndrome (defined as more than 10 apneas per hour). Upon study inclusion, the patients were ventilated for few months. Nineteen patients (56%) were hypercapnic (PaCO$_2$ > 5.6 cmH$_2$O). The parameter settings for noninvasive ventilation were those made by the clinician in charge of the patient. Noninvasive ventilation was applied with facial or nasal masks, according to patients’ usage at home. In this study, the bilevel ventilator is used in a pressure support mode without backup frequency. No intervention whatsoever was made by the investigators. Pressure support ventilation is often qualified as a "physiological" ventilatory mode because it allows the patient to keep control over his respiratory rate, inspiratory time and tidal volume. It unloads the respiratory muscles and, consequently, decreases the respiratory work of breathing in stable patients with obstructive diseases like COPD [Nava et al., 1993] or restrictive diseases like OHS. Pressure support ventilation is often qualified as a "physiological" ventilatory mode because it allows the patient to keep control over his respiratory rate, inspiratory time and tidal volume. It is therefore not surprising that it has been found to be better tolerated than other ventilatory modes, especially when compared with volume-target ventilation [Fauroux et al., 2001; Vitacca et al., 1995]. However, it requires an adequately titrated and performing ventilator in order to correctly superpose mechanical breaths to spontaneous respiratory efforts [Brochard & Lellouche, 2006].

Table 1. Main clinical characteristics of the patients (n = 34).

<table>
<thead>
<tr>
<th>Demographics and Respiratory Parameters</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>64.1 (11.8)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>24:10</td>
</tr>
<tr>
<td>Body Mass Index (kg·m$^{-2}$)</td>
<td>42.0 (10.8)</td>
</tr>
<tr>
<td>PaO$_2$ (cmH$_2$O)</td>
<td>9.5 (1.2)</td>
</tr>
<tr>
<td>PaCO$_2$ (cmH$_2$O)</td>
<td>5.8 (0.9)</td>
</tr>
</tbody>
</table>

Normal values: (10.7 < PaO$_2$ < 12.0) cmH$_2$O, PaCO$_2$ ≈ 5.3 cmH$_2$O, (18.5 < BMI < 25) kg·m$^{-2}$ and obesity is defined by BMI > 30 kg·m$^{-2}$.
A bilevel ventilator delivers pressure at the preset IPAP during inspiration and at the preset EPAP during expiration. The pressurization slope designates the time during which the ventilator increases the pressure delivered from EPAP (lower level) to IPAP (upper level). The ventilator used had control for adjusting the fraction of inspired oxygen (FiO\textsubscript{2}). This may be necessary in managing adequate oxygenation in patients who are critically ill. The FiO\textsubscript{2} in normal conditions is about 0.21. In our study, the mean oxygen delivery (Φ\textsuperscript{O}) leads to a FiO\textsubscript{2} around 0.30. Ventilator settings and respiratory parameters were summarized in Table 2. Expiratory cycling was set as the default parameter for all patients, that is, 30% of peak inspiratory flow. Characteristic time series of the various asynchrony events are shown in Fig. 1. A significant amount of ineffective efforts was present in 14 patients (41%) and out-of-phase cycling — that corresponds to a lack of phase synchronization between patients’ spontaneous respiratory cycle and the ventilatory cycle delivered by the ventilator — in 14 patients (41%). 12 patients (35%) presented both types of asynchrony events. All patients have less than 3% of double triggerings (35%) presented both types of asynchrony events. An asynchrony rate ρ\textsubscript{asyn} > 10%, indicating severe patient-ventilator asynchrony, was present in 17 patients (50%), in whom the 25–75 interquartile range was (20–48)%.

Breathing patterns, asynchrony events and leaks were assessed by an analysis of the flow evolution were measured. Anyway, the resulting cycle presents a pressurization period not synchronized with patient’s inspiration. There is therefore a lack of synchronization associated with a so-called auto-triggering. We thus choose to not distinguish “auto-triggering” from “late cycle”, and to designate them as “out-of-phase cycling” since in both cases, patients’ respiratory cycles are not synchronized to the ventilatory cycles. Premature cycling, that is, a too early expiratory phase, was identified with the help of EMG\textsubscript{a}, when an intensive unit care ventilator was used in a pressure support ventilation model [Thille et al., 2006; Vignaux et al., 2009]. In this study, they were not distinguished from out-of-phase cycling because they also resulted from a lack of synchronization between patient’s spontaneous breathing and ventilatory cycle delivered by the ventilator. In fact, this may be a side effect of an auto-triggering or a delayed triggering. Three asynchrony rates — global (ρ\textsubscript{asyn}), ineffective breaths (ρ\textsubscript{E}), and out-of-phase cycling (ρ\textsubscript{EP}) — were therefore computed. Only rates greater than 10% were considered as significant [Vitacca et al., 2004; Thille et al., 2006; Achour et al., 2007; Rabarimananitsosoa et al., 2007].

The asynchrony rate ρ\textsubscript{asyn} was correlated to the IPAP value (p < 0.002), that is, patients with less than 10% of asynchrony events were ventilated with an IPAP level (22.25 ± 1.15 mbar) smaller than those with more than 10% of asynchrony events for whom IPAP = (25.30 ± 3.10 mbar) as shown in Fig. 2. This is in agreement with previous results.

### Table 2. Ventilator settings and respiratory parameters during noninvasive ventilation (n = 34 patients).

<table>
<thead>
<tr>
<th>Ventilator Settings</th>
<th>Mean (25–75 IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPAP (cmH\textsubscript{2}O)</td>
<td>23.8 (20–26)</td>
</tr>
<tr>
<td>EPAP (cmH\textsubscript{2}O)</td>
<td>8.6 (7–10)</td>
</tr>
<tr>
<td>Pressurization slope (ms)</td>
<td>200 (150–250)</td>
</tr>
<tr>
<td>Φ\textsubscript{O} (l·min\textsuperscript{-1})</td>
<td>1.2 (0–2)</td>
</tr>
<tr>
<td>Facial mask/Nasal mask</td>
<td>10–24</td>
</tr>
<tr>
<td>Esophageal pressure Yes/No</td>
<td>13:21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Parameters</th>
<th>While on NIV</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (ms)</td>
<td>1125 (239)</td>
<td></td>
</tr>
<tr>
<td>VT (ml)</td>
<td>675 (162)</td>
<td></td>
</tr>
<tr>
<td>VT (ml·kg\textsuperscript{-1})</td>
<td>6.4 (1.9)</td>
<td></td>
</tr>
<tr>
<td>V\textsubscript{E} (l·min\textsuperscript{-1})</td>
<td>11.8 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Leak (l·min\textsuperscript{-1})</td>
<td>4.0 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Rate of cycles with leak</td>
<td>21.9 (26.3)</td>
<td></td>
</tr>
</tbody>
</table>

T\textsubscript{max} duration of pressurization; VT: expired tidal volume expressed in ml and ml·kg\textsuperscript{-1}; V\textsubscript{E} minute volume.
Fig. 1. Representative tracings of the three types of asynchrony distinguished in this study. $P_{aw}$, airway pressure; $Q_v$, instantaneous flow. Downward pointing arrows indicate relevant event. Auto-triggerings and double triggerings rates were less than 1.3%. (a) Ineffective efforts, (b) out-of-phase cycling, (c) double triggering, (d) auto-triggering.

Fig. 2. Rate of ineffective inspiratory efforts, $\rho_{IE}$, and out-of-phase cyclings, $\rho_{OP}$, versus IPAP. The case of (a) non-significant ($\rho_{asy} < 10\%$) and (b) significant rates of asynchrony events were distinguished ($\rho_{asy} > 10\%$).
The ineffective triggering rate \( \rho_{\text{asyn}} \) was correlated with the leak \(( p < 10^{-5})\), that is, patients with no leak presented an ineffective triggering rate smaller than those with leak. The asynchrony rate was correlated to the presence of an esophageal pressure probe when a patient with \( \rho_{\text{asyn}} > 10\% \) were considered \(( p < 0.0012)\). This means that, when patients were near the required threshold to be able to trigger the ventilator, that is, near the minimal inspiratory pattern required to trigger the ventilator, applying an esophageal probe lead them to have many difficulties to trigger the ventilator, mainly because the probe was large enough to damp the inspiratory effort below the critical value required for triggering. But other respiratory parameters were not significantly correlated to the use of an esophageal probe (Table 3).

### 3. Estimating Sleep Fragmentation

For many years, sleep recordings were divided into discrete stages that were awake, stage 1, stage 2, stage 3, stage 4 and stage REM (Rapid Eye Movement) according to a widely accepted standard [Rechtschaffen & Kales, 1968]. Nevertheless, these rules may lead to subjective interpretation, that is, to a great variability in the visual evaluation of sleep stages [Danker-Hopfe et al., 2004]. Such inter-rater variability is illustrated in Fig. 3. Recently, the American Academy of Sleep Medicine (AASM) modified the standard guidelines for sleep classification and developed a new manual for terminology, recording method and scoring-rules for sleep-related phenomena [Iber et al., 2007]. In particular, stages 3 and 4 are no longer distinguished and merged into a single stage corresponding to the Slow Wave Sleep (SWS). Significant departures between these two standards seem to be evidenced by the time spent at each stage [Moser et al., 2009]. For this first study, we used a single rater for scoring sleep stages from EEG, airflow, chest movement, electromyogram and leg electromyogram.

If patient-ventilator interactions are relevant for patient’s comfort, it is still an open question to determine whether the quality of these interactions has an impact on the sleep quality or not. The main problem to address this question is to estimate the sleep quality from measurements. Usually, perceived sleepiness is estimated according to the Epworth’s sleepiness scale [Johns, 1991] that consists of a visual scale. But the sleep quality is thus estimated according to subjective evaluations by the patients, that is, there is one specific quantificator — his own appreciation — for each patient [Carskadon, 1993]. It is also possible to assess the sleep quality through the daytime sleepiness/alertness by using a physiological measure known as Multiple Sleep Latency Test (MSLT) [Carskadon & Dement, 1977]. Nevertheless, this

![Hypnograms scored by two different neurologists from the same ElectroEncephaloGrams. Case of patient #1 who had an OHS and received a nasal mask. Parameter values: IPAP = 23.0 cmH\(_2\)O, EPAP = 9 cmH\(_2\)O, \( \rho_{\text{asyn}} = 7.9\% \). (a) Scoring by neurologist A, (b) scoring by neurologist B.](image-url)
technique requires a full day of investigations, that is, it is therefore relatively time consuming for the patient and laboratory staff. But more importantly, results are not valid if the patient is ill or in pain [Carskadon, 1993] and MSLT only provides an estimation of the impact of the sleep quality on the daytime sleepiness but is not a direct estimation of sleep quality during a particular night. This could explain the relatively low correlation between arousal indices and daytime sleepiness [Bonnet & Arand, 2003]. It is therefore unreliable to correlate daytime sleepiness with patient-ventilator interactions during a single given night.

It is therefore important to possess an estimator directly computed from data simultaneously recorded with those used to assess the mechanical quality of patient-ventilator interactions. One such quantifier contributing to impaired daytime function and sleepiness is the sleep fragmentation [Carskadon et al., 1982; Levine et al., 1987] that can be estimated by the number of micro-arousals [Bonnet et al., 1992]. The number of arousals was significantly correlated with nearly all sleep parameters in the direction indicating decreased quantity and quality of sleep as arousals increase [Stepanski, 2007]. As any EEG scoring, identifying micro-arousals is a time-consuming method that requires a trained observer and manual edition. It therefore presents a high inter-scorer variability [Loredo et al., 1999; Whitney et al., 1998; Drinnan et al., 1998]. Another measure of the sleep quality, the Sleep Fragmentation Index (SFI), was introduced as a crude estimate of sleep disruption [Morrel et al., 2000] presenting a good correlation with the rate of micro-arousals. Unfortunately, EEG estimated arousals do not uniformly provide robust correlations with daytime sleepiness [Bonnet et al., 2006], although sometimes this index seems to be an accurate estimator of sleep fragmentation in patients with sleep disorders [Haba-Rubio et al., 2004]. Consequently, the reliability of the sleep fragmentation index can be questioned.

The sleep fragmentation index is defined as the total sleep stage shifts plus the total number of awakening divided by the total sleep time [Haba-Rubio et al., 2004]. Consequently, this index does not take into account the time duration for each stage, a factor quite important since intervals of sleep must be 5-10 min to provide restoration, that is, to eliminate sleepiness [Levine et al., 1987; Downey & Bonnet, 1987; Norman et al., 2006]. In order to improve the sleep fragmentation index previously discussed, that is, to take into account the duration for each sleep stage, we used close return plots computed from hypnograms scored from EEG and EMG using 30 s-windows into sleep stages (Fig. 3). The EEG was thus converted into a symbolic sequence using six symbols according to

\[ \sigma_n = \begin{cases} 0 & \text{Awake} \\ 1 & \text{Stage 1} \\ 2 & \text{if signals} \\ 3 & \text{correspond to} \\ 4 & \text{Stage 3} \\ 5 & \text{REM sleep.} \end{cases} \]

The main characteristics for the sleep were reported in Table 4. Compared to the “norms” provided by [Bonnet & Arand, 2007], patients of the present study spent more time in the Slow-Wave Sleep by a factor of ten! Such abnormal time spent in slow-wave sleep can result from sleep deprivation as observed in old of insomniacs [Bonnet, 2000]. It can otherwise be a SWS rebound, that is, a compensatory increase in SWS following deprivation. For instance, patients noting a subjective improvement in sleep quality showed a SWS rebound [Verma et al., 2001]. But, since our patients presented a mean BMI denoting a significant obesity, it could also result from artifacts in EEG due to sweating. They had less numerous awakenings but the inter-sleep awake time is longer than what was observed in [Bonnet & Arand, 2007].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>This Study</th>
<th>Norms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG arousals (n)</td>
<td>158 ± 82</td>
<td>130 ± 42</td>
</tr>
<tr>
<td>Arousal index</td>
<td>33.2 ± 15.5</td>
<td>21.9 ± 6.8</td>
</tr>
<tr>
<td>Total Sleep Time (TST), min</td>
<td>367 ± 51</td>
<td>350</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Sleep Stages, Min</th>
<th>This Study</th>
<th>Norms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>28.5 ± 17.3</td>
<td>57</td>
</tr>
<tr>
<td>Stage 2</td>
<td>110.2 ± 48.0</td>
<td>161</td>
</tr>
<tr>
<td>Slow-Wave Sleep (SWS)</td>
<td>103.2 ± 51.2</td>
<td>11</td>
</tr>
<tr>
<td>Rapid-Eye Movement Sleep (REM)</td>
<td>43.2 ± 24.2</td>
<td>52</td>
</tr>
<tr>
<td>Awakenings, #</td>
<td>24.3 ± 15.2</td>
<td>42</td>
</tr>
<tr>
<td>Time in Bed (TIB), min</td>
<td>431.0 ± 20.3</td>
<td>—</td>
</tr>
<tr>
<td>Sleep Efficiency (SE), %</td>
<td>73.6 ± 14.5</td>
<td>80.7</td>
</tr>
</tbody>
</table>

*Norms were computed from the data provided by [Bonnet & Arand, 2007].
Fig. 4. Close return plots for two different hypnograms coded from the same electroencephalograms. In this case, neurologist A found sleep more fragmented than the one found by neurologist B. (a) Scoring by neurologist A: $S_A = 0.85$, (b) Scoring by neurologist B: $S_B = 0.62$, (c) Product between the two plots.

as revealed by the sleep efficiency, $S_E$, defined as

$$S_E = \frac{\text{Inter-sleep awake time}}{\text{Total Sleep Time}}$$  \hspace{1cm} (2)

Symbolic sequences $\{\sigma_n\}_{n=1}^N$ obtained according to Eq. (1) were converted into close return plots using

$$C_{ij} = \begin{cases} 1 & \text{if } \sigma_i = \sigma_{i-j} \\ 0 & \text{if } \sigma_i \neq \sigma_{i-j} \end{cases}$$  \hspace{1cm} (3)

where $j \in [0, 50]$. The close return plot shown in Figs. 4(a) and 4(b) encode the recurrence properties of hypnograms scored by neurologists A and B, respectively. Black segments indicate intervals of a given sleep stage. More jittery the close return plot, the more fragmented is the sleep. The common part shared by these two close return plots is obtained by the product

$$C_{A \otimes B,ij} = 1 - C_{A,ij} \times C_{B,ij}$$  \hspace{1cm} (4)

[Fig. 4(c)]. White points correspond to the parts of EEG that were scored by the same sleep stage shift by both raters. This third close return plot provides the sleep structure identified by both scorers.

From these close return plots, a Shannon entropy was computed (see Appendix) to estimate the sleep fragmentation. Note that the time duration of each sleep time is naturally taken into account in a Shannon entropy. Larger the entropy, the more fragmented is the sleep. In the case shown in Fig. 4, the Shannon entropies resulting from the two close return plots differ by around 15%. Here, scorer A estimated that the sleep was more fragmented than scorer B.

Such Shannon entropy was computed for each of the 34 patients and plotted versus the rate of micro-arousals $\rho_{\mu\text{-arousals}}$. The linear regression

$$S_{\text{Sleep}} = 0.41 + 0.008 \rho_{\mu\text{-arousals}}$$  \hspace{1cm} (5)

was obtained with a regression coefficient $r$ equal to 0.42, leading to a significant correlation ($p \leq 0.007$) between Shannon entropy $S_{\text{Sleep}}$ and the rate of micro-arousals $\rho_{\mu\text{-arousals}}$. Similar computations were performed with the Sleep Fragmentation Index. The linear regression

$$\text{SFI} = 0.52 + 0.00016 \rho_{\mu\text{-arousals}}$$  \hspace{1cm} (6)

was obtained with a regression coefficient $r$ equal to 0.009, that is, there is no significant correlation ($p = 0.048$) between SFI and $\rho_{\mu\text{-arousals}}$. Shannon entropy $S_{\text{Sleep}}$ is therefore significantly ($p < 0.05$) better correlated to $\rho_{\mu\text{-arousals}}$ than SFI.
The lack of significance of SFI mainly results from the large departure between the linear regression obtained for patients with esophageal probe (n = 13) and without (n = 21). Without esophageal probe, a nonsignificant correlation (r = 0.09, p = 0.35) was obtained between SFI and \( \rho_{\mu}-\text{arousals} \) [Fig. 5(b)] but an anti-correlation (r = −0.41, p = 0.08) was obtained for patients with an esophageal probe [Fig. 6(b)]. The Shannon entropy was significantly correlated to \( \rho_{\mu}-\text{arousals} \) for patients without esophageal probe [Fig. 5(a)]. The linear correlations were nearly the same for patients with and without esophageal probe [Figs. 5(a) and 6(a)]. But the correlation obtained for patients with an esophageal probe was not significant due to the small number of data sets investigated (n = 13). Shannon entropy \( S_{\text{Sleep}} \) is thus more robust than SFI to assess sleep fragmentation.

Such features result from the fact that \( S_{\text{Sleep}} \) takes into account how the stage switches are distributed over the night. Further investigations with a larger population is currently in progress. These results also suggest that the esophageal probe could affect the sleep dynamics (if not the quality).

4. Cross-Covariance

One of the key questions about noninvasive ventilation is to assess (i) the impact of asynchrony events on the sleep quality and (ii) how asynchrony
events are related to leaks. In order to propose a first attempt to address such issue, we investigated the interplay between:

- The hypnogram corresponding to the sleep stages, scored by a neurologist using 30-s-windows.
- The micro-arousals defined as abrupt changes in frequency content of the EEG that persist at least during 3 sec. The change in frequency can include α-waves (8–12 Hz), θ-waves (4–7 Hz) and frequencies greater than 16 Hz (β-waves), but not including the spindle band (12–14 Hz). Moreover, micro-arousals need particular criteria in the preceding and following states as well as submental EMG activity [SDATF, 1992].
- The rate of ineffective inspiratory efforts estimated during a sliding 10-cycles window.
- The rate of out-of-phase cycles estimated during a sliding 10-cycles window.
- The nonintentional leak that mainly occurs at the interface between the face skin and the mask. They can be estimated from the nonlinear conductance \( G \) equal to the low pass filtered airflow \( Q_v \) divided by the low pass filtered square root of the pressure \( P \). The leak flow \( \Phi_L \) is then

\[
\Phi_L = G\sqrt{P} \tag{7}
\]

where \( P \) is the unfiltered pressure [Berthon-Jones, 2000].

All these times series are shown in Fig. 7 for one nocturnal session of mechanical ventilation.

In order to investigate interplays between these time series, cross-covariances were computed among them. Cross-covariance is a measure of similarity shared by two time series. It is a function of the relative time between two time series. For discrete time series \( x_i \) and \( y_i \), the cross-covariance is defined as

\[
R_{xy}(j) \equiv \frac{1}{N-\tau_w} \sum_{i=1}^{N-\tau_w} (x_i - \overline{x})(y_{i+j} - \overline{y}) \sqrt{\sigma_x^2 \sigma_y^2} \tag{8}
\]

where \( \overline{x} \) and \( \overline{y} \) are the mean values of \( x \) and \( y \), \( N \) the number of points, \( j \) the considered delay and, \( \sigma_x^2 \) and \( \sigma_y^2 \) are variances of \( x \) and \( y \), respectively.

The cross-covariance \( R_{xy}(j) \), for a given delay \( j \), corresponds to a simple covariance between \( x \) and \( y \) delayed by \( j \). Values of \( R_{xy}(j) \) were computed for

\[-\tau_w \leq j \leq \tau_w\]

where \( \tau_w \) equals 20 ventilatory cycles. When the null hypothesis is rejected (with \( p < 0.05 \) the cross-covariance is denoted by “+” (“−”) when the maximal value is positive (negative).

After many trials, we identified two discriminating cross-covariances, namely \( R_{IE-OP} \) between the ineffective effort rate and the out-of-phase cycling rate, and cross-covariance \( R_{\Phi_L-IE} \) between the nonintentional leak and the ineffective effort rate. Patients can thus be grouped into four classes as reported in Table 5. The most discriminating indicator is cross-covariance \( R_{IE-OP} \). In most cases (\( n = 23, 68\% \)), ineffective efforts are positively correlated to out-of-phase cyclings. This means that there is a strong relation between the occurrence of
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Table 5. Four groups of patients were defined according to cross-covariances $R_{IE-OP}$ and $R_{\Phi L - IE}$. Patients were associated with group IV when they did not belong to group I, II or III. All patients in group IV had less than 10% of asynchrony events.

<table>
<thead>
<tr>
<th>$R_{IE-OP}$</th>
<th>Negative</th>
<th>$\emptyset$</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\Phi L - IE}$</td>
<td>Negative</td>
<td>9, 14, 31</td>
<td>12</td>
</tr>
<tr>
<td>$\emptyset$</td>
<td>Patients 2, 16</td>
<td>Patient 8</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Group III</td>
<td>Patients</td>
<td>Group I</td>
</tr>
<tr>
<td>$n = 2$ (6%)</td>
<td>1, 35</td>
<td>$n = 17$ (50%)</td>
<td></td>
</tr>
</tbody>
</table>

ineffective efforts and out-of-phase cyclings. Then the 23 patients were split into two groups according to cross-covariance $R_{\Phi L - IE}$: 17 patients had a positive cross-covariance $R_{\Phi L - IE}$ (group I) and for six patients, ineffective efforts were anti-correlated to leak $\Phi L$ (group II). In this latter case, ineffective efforts mainly occur when there is no nonintentional leak. Group I corresponds to what is commonly observed, that is, to patients having asynchrony events correlated to nonintentional leak. Group III is associated with patients presenting the two types of asynchrony events anti-correlated, that is, asynchrony events occurred rarely together, but rather by bursts of ineffective efforts excluding out-of-phase cyclings, or vice versa. Group IV corresponds to patients with other possibilities (see Table 5). All patients belonging to group IV had less than 10% of asynchrony events, that is, events that did not significantly affect the comfort and the sleep quality.

From this first investigation, it appears that asynchrony events were not necessarily related to nonintentional leak $\Phi L$. More surprisingly, they were sometimes anti-correlated to nonintentional leak. Depending on the patient, we observed that ineffective efforts can be correlated (68%) or anti-correlated (21%) to out-of-phase cyclings. One has therefore to note that there is not a unique mechanism underlying patient–ventilator interactions and a better understanding of the interplay between asynchrony events and leaks would require not only a deeper investigation of the procedure that drives the ventilators but also how patients manage their ventilator.

Only one patient with more than 10% of asynchrony events presented a nonintentional leak correlated to the awake stage. All other patients with significant rate of asynchronies had leak associated with sleep stage, and deeper the sleep stage was, greater the leak was (see, for instance, Fig. 8). When the sleep fragmentation — estimated by the Shannon entropy $S_{sleep}$ — is plotted versus the group index (Fig. 9), there is no particular feature, that is, it is not possible to exhibit a correlation between asynchronies and leak, and the sleep quality.

Group I seems to represent what is most often encountered in our patients as well as what is the most commonly evoked scenario to explain the interplay between sleep and asynchrony events [Guo et al., 2007]. Both types of asynchrony events mainly occurred during Slow-Wave Sleep [Fig. 10(a)]. Ineffective efforts also often observed during REM sleep but out-of-phase cyclings was nearly reduced by 2. During stages 1 and 2, both types of asynchronies were less often identified.

![Fig. 8. Cross-covariance $R_{\Phi L - sleep}$ for each sleep stage. Case of patients belonging to group II.](image1)

![Fig. 9. Shannon entropy versus the group index.](image2)
When patients were awake, they were able to manage their ventilator in a better way and, consequently, to reduce significantly the rate of asynchrony events below 10%. The main characteristic of group II was (i) a rate of out-of-phase cyclings decreasing with deeper sleep [Fig. 10(b)] and (ii) ineffective efforts during sleep were observed twice more often than during awake stage. Contrary to what is observed for patients belonging to group I, patients in group III presented a large amount of out-of-cyclings ($\rho_{OP} = 35\%$) during the awake stage, an amount that was reduced to about 10% during sleep stages. These two patients could be good examples of patients fighting with their ventilator. Apart from that, these two patients presented their highest rate of ineffective efforts during Slow-Wave Sleep.

5. Conclusion

Noninvasive ventilation may often be applied during night in patients having chronic respiratory failure. It is therefore required to investigate its quality on a long-term basis since breathing patterns are known to depend on sleep stages. Nevertheless, to address patient-ventilator interactions, it is necessary to use automatic analysis with the help of specific algorithms to process the data set as airflow and pressure time series. In this retrospective study, 34 sleep sessions with noninvasive ventilation were investigated by computing cross-covariances. It appeared that patients can be split into four groups as summarized in Fig. 11. The first three groups correspond to different dynamics underlying patient-ventilator interactions. Group I roughly corresponds to the most common situation, that is, ineffective...


Fig. 11. Flowchart for identifying the four groups of patients according to two cross-covariances, namely $R_{IE-OP}$ and $R_{OP-IE}$.


of physiologic variables and subjective comfort under different levels of pressure support ventilation," Chest 126, 851–859.


Appendix A. Close Recurrence Plots

Recurrence plots were introduced by Eckmann et al. [1987] and some quantifiers were later introduced to convert recurrence plots into a statistical analysis [Trulla et al., 1996]. Among these quantifiers, it is possible to properly define a “Shannon entropy” which was found to be correlated to the largest Lyapunov exponent [Letellier, 2006].

A recurrence plot $R_{ij}$ is built as follows. Every point of the phase space trajectory $\{x_i\}_{i=1}^N$ is tested whether it is close to another point $x_j$ of the trajectory, that is, whether the distance between these two points is less than a specified threshold $\epsilon$. In this case, the point is said to be recurrent and is represented by a black dot. Otherwise, the point is not recurrent and is represented by a white dot. This can be described as a $N \times N$ array

$$R_{ij} = \theta(\epsilon - ||x_i - x_j||)$$

where $\theta(x)$ is the Heaviside function. When built using this definition, recurrence plots are symmetrical with respect to the diagonal and, consequently, they used twice the same information. In order to optimize the representation, Mindlin and Gilmore used a so-called “close return plots” defined as a $N \times \tau$ array

$$C_{ij} = \theta(\epsilon - ||x_i - x_{i+j}||)$$

where $j \in [1, \tau]$ with $\tau$ defining the size of the window over which close returns are checked. These plots present the advantage to have horizontal and vertical lines as the main structuring axes which are, compared to diagonals, slightly easier to use for computations and interpretations. Thus, close return plots were used by Gabriel Mindlin and Robert Gilmore for extracting periodic orbits from experimental data recorded in a Belousov-Zhabotinski reaction [Mindlin & Gilmore, 1992] and by Claire Gilmore for showing that there is no obvious signature of deterministic chaos in financial data [Gilmore, 1993]. Two examples of these close return plots are shown in Fig. 12 for the Logistic map

$$x_{n+1} = \mu x_n (1 - x_n).$$

Periodic behaviors are easily identified by parallel horizontal lines spaced by the period of orbits [a period-4 limit cycle in the case of Fig. 12(a)]. Chaotic behaviors present more jittery close return plots with few recurrent horizontal segments as a signature of the deterministic nature of the underlying dynamics [Fig. 12(b)].

As for the usual recurrence plots, it is possible to compute a Shannon entropy according to

$$S_{RP} = - \sum_{n=1}^{H} P_n \log(P_n).$$

where $P_n \neq 0$ corresponds to the number of non-recurrent horizontal segments with length $n > 0$ divided by the total number of recurrent points. If the number of recurrent points is not included in this definition, the entropy provides more or less a
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Fig. 13. Comparison between the Shannon entropy computed from the close return plots and the largest Lyapunov exponent for the logistic map versus parameter $\mu$. A close return plot of 3000 × 150 data points was used for computing the Shannon entropy for each $\mu$-value. (a) Shannon entropy $S_h$, (b) Largest Lyapunov exponent $\lambda_{\text{max}}$.

yes-or-no estimator [Letellier, 2006]. With this definition, the Shannon entropy quantifies the complexity of the dynamics and is correlated to the largest Lyapunov exponent (Fig. 13). Such a feature suggests that such a Shannon entropy can behave as a

Kolmogorov–Sinai entropy known to be correlated to the largest Lyapunov exponent as stated by the Pesin conjecture [Pesin, 1998]. As for the recurrence plots, a working Shannon entropy can be defined and used as an estimation of the largest Lyapunov exponent.

As any estimation of a Shannon entropy or other dynamical invariants, computations may depend on some parameters. In the present case, estimations of the Shannon entropy depend on the number of points retained for computing the close return plots. Nevertheless, with a maximum time delay $\tau$ equal to 100 (the smallest reasonable value for $\tau_{\text{max}}$), it is found that the Shannon entropy value does not depend too much on the number of points until this number is greater than 500 (Fig. 14). This feature tells us how long must be the data set to have a rather safe estimation of the Shannon entropy.