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Coordination of respiratory muscles assessed by means of nonlinear forecasting of demodulated myographic signals

Joan F. Alonso^{a,b}, Miguel A. Mañanas^{a,b}, Mónica Rojas^{b,a}, and Eugene N. Bruce^c

^aDepartment of Automatic Control, Biomedical Engineering Research Centre, Universitat Politècnica de Catalunya, Barcelona, Spain

^bCIBER of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Spain

^cCenter for Biomedical Engineering, University of Kentucky, Lexington, KY, USA

1. Introduction

Pulmonary diseases such as chronic obstructive pulmonary disease (Mañanas et al., 2000) or obstructive sleep apnea syndrome (OSAS) (Alonso et al., 2007; Ryan and Bradley, 2005) affect respiratory muscle functioning. Whereas diaphragm is the main respiratory muscle, other accessory muscles such as the sternomastoid are active at higher levels of ventilatory effort associated with exercise or with pulmonary diseases (Hudson et al., 2007; Mañanas et al., 2000; Ratnovsky et al., 2003). The genioglossus muscle plays a special role in apnea generation, as it is considered the main muscle responsible for upper airways occlusion (Svanborg 2005). Individuals with OSAS experience intermittent collapse of the upper airways during sleep due to unbalanced forces generated by the contraction of the diaphragm and upper airway dilator muscles.

In OSAS, weak coordination of genioglossus and diaphragm is expected, and therefore also between genioglossus and sternomastoid because sternomastoid and diaphragm are activated in parallel in cases where both are active (Mañanas et al., 2000; Ratnovsky et al., 2003). In healthy subjects, on one hand, coordination of genioglossus and diaphragm might be stronger; however, on the other hand, coordination is less critical so it may be weaker. Thus, it is difficult to predict whether muscle coordination would be stronger or weaker in OSAS patients with respect to healthy subjects, but differences between both groups can be expected, particularly, in situations of increased respiratory effort. Some differences in levels of activity and coordination were found in previous studies (Alonso et al., 2007; Mañanas et al., 2003) but more studies are necessary to fully understand the patterns of respiratory muscle activities and their interactions.

Muscle function can be assessed from electromyographic (EMG) and mechanomyographic (MMG) signals (Merletti and Parker, 2004), which are related to electrical and mechanical

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Joan Francesc Alonso, Department of Automatic Control (ESAI), Biomedical Engineering Research Centre (CREB), Universitat Politècnica de Catalunya (UPC), C/Pau Gargallo 5, 08028 Barcelona, Spain, Telephone: +34 93 401 16 86, Fax: +34 93 401 70 45, joan.francesc.alonso@upc.edu.

Conflict of interest statement

The authors declare that there are no matters of conflict of interest arising in this study.

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muscle activity, respectively. Surface electromyography is widely used in the analysis of skeletal and also respiratory muscles whereas mechanomyographic signals are less common but they provide additional information on muscle activity to that obtained through electromyography (Esposito et al., 2009; Torres et al., 2010). Among the main advantages of these techniques it is noticeable that these measures are not invasive and allow a high temporal resolution that is very necessary to obtain information about the coupling between muscles within a respiratory cycle and between respiratory cycles. This requirement is not met by other advanced techniques such as fMRI and computerized tomography which are very useful to assess muscle mass and length changes during contraction (Legrand et al., 2003). Compared to intramuscular recordings, information recorded by surface electromyography is less focused and it may be affected by interfering signals such as cardiac activity and crosstalk from nearby muscles. In this study, these effects were minimized respectively using adaptive and singular value decomposition based filtering (Mañanas et al., 2001a), and recording signals from relatively distant muscles whose respiratory function was clearly different.

Overall activity of respiratory muscles during breathing can be evaluated by demodulated myographic signals (Bruce, 1984; Zhang and Bruce, 1998). Myographic signals are complex signals that can carry a considerable amount of information about muscular function. In some cases, only the global activity of the motoneuron pool is to be considered and thus, the total electrical activity reflecting the action of a muscle is measured. In these cases, it is common to process the EMG signal to obtain a waveform that tracks its envelope, performing the so called amplitude demodulation. The resulting demodulated signal is taken as a continuous indication of the entire electrical activity of a muscle.

Global muscular pattern during normal and increased respiratory effort can be measured by temporal interactions between muscles. Some of these interactions have already been assessed by means of different approaches: cross-spectrum between EMG (Mañanas et al., 2001a) signals and EMG-MMG signals, in order to evaluate mechanical-electrical coupling (Mañanas et al., 2001a, Orizio, 1993); magnitude squared coherence (Bruce and Ackerson, 1986); cross-correlation (Mañanas et al., 2001a) and cross mutual information function (Alonso et al., 2007). These techniques provide interesting information about couplings between different muscles, but only cross mutual information function evaluates nonlinear interactions. In general, nonlinear dynamics and complexity have usually been assessed with regard to one single time scale (correlation dimension, Lyapunov exponents and Kolmogorov entropy, among others), disregarding complex physiology organized in different time scales. This is an essential limitation with regard to complex multimatched control loops acting on different time horizons within the respiratory mechanisms. This drawback has been overcome by information transfer functions that take into account different time scales; see, for example (Alonso et al., 2007).

Correlations between data, either linear or nonlinear, can be expressed in terms of predictability. The most common and best-studied sources of predictability are linear correlations in time. Regarding linear dynamics, determinism and linear correlations are synonymous. This is not the case for nonlinear dynamical systems and therefore the construction of a deterministic model for prediction cannot rely on autocorrelations.

Nonlinear determinism means that equal states have the same future, and also that similar states will develop similarly, at least over short times. In other words, if points spread more or less along time are related with intrinsic underlying properties and provide similar information for future data, short-term forecasts exploiting a deterministic evolution law can be reasonable (Kaplan and Glass, 1995; Kantz and Schreiber, 1997). In contrast to relationships obtained by autocorrelation functions, those imposed by nonlinear

deterministic dynamics are only found by using nonlinear statistics. These usually called nonlinear correlations have to be detected employing new techniques, such as nonlinear prediction. If this prediction is calculated as a function of a prediction horizon, this approach can provide information about biological processes at different time scales.

Assuming that data are associated with an underlying dynamical system with a deterministic structure, a nonlinear prediction algorithm based upon a simple prediction layout can be used, given that the current state of the system is known and the future state is to be predicted. For this purpose, a certain number of past and already visited states is searched in order to select the closest state to the current one with respect to some distance measure. If the number of past states is large enough, that is, if the system has been observed for a long time, a good estimate is obtained. Direct application of this prediction algorithm is not strictly valid with real data but this prediction approach can be considered by taking into account only a few concerns (Kantz and Schreiber, 1997), for example applying an estimator on a certain number of nearest neighbors.

In (Caminal et al., 2004) nonlinear prediction methods were applied to find a set of indices that characterized the variability of a single time series: the respiratory volume. In this sense, only auto-prediction of the same signal was taken into account. Our study focused on the cross-prediction between demodulated myographic signals from respiratory muscles.

The aims of this work were: 1) to evaluate the use of locally linear models for fitting and predicting demodulated myographic signals from respiratory muscles; 2) to compare the prediction ability of nonlinear forecasting, based on these models, at low and moderate levels of respiratory effort; and 3) to evaluate the influence of OSAS on the muscular coordination by means of cross-prediction between myographic signals recorded from different respiratory muscles.

Prediction was expected to show different results when comparing OSAS patients and healthy subjects, since change in respiratory mechanics due to this disease may alter coordination patterns of muscles even during wakefulness and during normal breathing (Jeffery et al., 2006; Lydic et al., 1988; vanLunteren and Dick, 1991). The sternomastoid muscle and especially the genioglossus, which is the most critical muscle in OSAS, play an important role in the upper airway functionality (Ratnovsky et al., 2003, Svanborg 2005). Nevertheless, the mechanisms by which interaction between these muscles and the diaphragm may occur in patients with sleep apnea, even during wakefulness, are not well known. Traditionally, studies have focused on whether the increases of genioglossus activity during inspiration are lower than increases of diaphragm activity and whether this smaller response can lead to airway obstruction (Adachi et al., 1993; Carlson et al., 1995; vanLunteren and Dick, 1991; Worsnop et al., 1998). The aim of our work was different because it was focused on the coordination between respiratory muscles independently of their level of activity, and asking whether lack of coordination over multiple breaths was associated with OSAS. In this sense, cross-prediction was also studied to know how well the activity of one respiratory muscle can predict activity of another one, especially taking into account short term predictions, as well as predictions for several respiratory cycles later.

Classical assessment of pulmonary function relies on respiratory variables related to flow, volume and respiratory pattern, but information associated with muscular activation can provide additional knowledge to be used during patients' treatment and monitoring. Even though it is an open research topic that needs further development, noninvasive myographic assessment of respiratory activity is a promising tool which could be used to improve respiratory therapies and to monitor their effectiveness.

Whereas differences between groups had been mainly found at high levels of effort in (Alonso et al., 2007), they have already been found at low and medium levels by using this nonlinear prediction approach. Thus, nonlinear prediction methodology could be considered as an additional technique for the evaluation of demodulated myographic signals in order to assess the interactions of respiratory muscles in OSAS patients with respect to healthy subjects, and more specifically when breathing at low and medium levels of effort. These findings could suggest that control mechanisms have been altered by disease, or maybe a different balance among activated muscles was achieved in OSAS patients.

Better prediction between muscles, which reached two consecutive respiratory cycles in patients with OSAS, and higher predictability between consecutive cycles for genioglossus muscle could be taken into account in therapies applied to the upper airways, such as CPAP treatment. Future studies should evaluate the functioning of muscles during previous respiratory cycles and how it could be used to adapt treatment and rehabilitation strategies in order to apply appropriate pressure during the current cycle.

2. Methodology

2.1. Signal acquisition and experimental protocol

Eight male patients on continuous positive airway pressure (CPAP) therapy with stable OSAS [age (yr.): 53.8 ± 10.5 ; height (cm): 177.0 ± 8.2 ; weight (kg): 96.4 ± 19.2] and eight male healthy subjects [age (yr.): 45.0 ± 7.0 ; height (cm): 177.2 ± 6.1 ; weight (kg): 80.5 ± 10.5] were studied. A Mann-Whitney test with significance level set to 5%, performed for all anthropometric variables, did not show any statistically significant differences between groups. The respiratory period was also analyzed and statistical differences between groups were not found.

Flow signal (F) was acquired with a pneumotacograph (Validyne-CD257). Three surface EMG and two MMG signals (Entran model EGA-25 accelerometers) were simultaneously recorded from three respiratory muscles: genioglossus (*GEN_EMG*, *GEN_MMG*), sternomastoid (*SMM_EMG*, *SMM_MMG*) and diaphragm (*DIA_EMG*). Each EMG signal was recorded with two pre-gelled Ag-AgCl electrodes with a diameter of 8 mm and with an interelectrode distance of 15 mm. The skin was always cleaned with abrasive paste. Genioglossus EMG signal was recorded on the submental zone (Bruce, 1996; Alonso et al. 2007). For the sternomastoid EMG, the innervation zone was detected by means of linear electrode arrays. This innervation zone is usually located around the mid-point of the muscle (Falla et al., 2002), so the electrodes were placed between this point and the mastoid process. Diaphragm EMG was recorded between the 7th and 8th interspace of the right ventrolateral surface of the rib cage midway between the clavicular and the axillary lines (Bruce, 1986). The accelerometers (Entran EGA-10) were placed as closest as possible to the electrodes to record the MMG signals. Myographic signals were bandpass filtered: 5–40 Hz (MMG) and 8–400 Hz (EMG). The sampling frequencies were 100 Hz for MMG and 1000 Hz for EMG signals.

During the experiment, subjects were awake in the supine position breathing through a nose mask connected to a low-resistance nonbreathing valve. The inspiratory port of the nonbreathing valve was connected to an external source of a negative pressure and the external pressure decreased 686.5 Pa (7 cm H₂O) at 90-second intervals from zero to the previously determined maximum maintained pressure (*MMP*) of each subject. The *MMP* was defined as the magnitude of the lowest external negative pressure below which the subject could no longer generate inspiratory airflow. For every subject, pressure in each step of this incremental protocol (IP) was expressed as a percentage of the individual *MMP*.

These studies were approved by the Institutional Review Board for Human Investigation of the University of Kentucky.

2.2. Data preprocessing and nonlinear prediction

The flow signal was utilized to detect inspiration onsets in order to obtain respiratory rate. EMG and MMG signals were processed to reduce cardiac activity from the recordings using adaptive and singular value decomposition valued filtering (Mañanas et al., 2001b). EMG and MMG signals were full-wave rectified and demodulated by means of a 400 ms moving average window (Alonso et al., 2007; Bruce, 1984). This demodulation integrated the contributions of all motor units in order to obtain a signal related to the whole muscle action. Then, resampling was carried out with a final sampling frequency of 20 Hz. Baseline trends along the 90-second interval of these myographic signals were also removed to support the assumption of wide-sense stationarity. These trends were related to skin-electrode contact and slow motions, among others, so that this trend removal along the 90-second interval affected neither the existing breathing rhythms nor linear or nonlinear couplings between signals during breathing.

In addition, prior to nonlinear prediction computation, 90-second demodulated myographic signals were also normalized in order to have zero mean and unit variance. This standardization was especially important for cross-prediction, because analysis of the dynamics of the signals and their relationships with the level of effort had to be independent of the amplitudes.

Nonlinear prediction (see the details of the algorithm in Appendix A) was used to carry out auto-prediction of each myographic signal available: *GEN_EMG*, *GEN_MMG*, *SMM_EMG*, *SMM_MMG* and *DIA_EMG*. Cross-prediction was applied to the following myographic signal pairs:

1. EMG-MMG from genioglossus muscle, and EMG-MMG from sternomastoid muscle.
2. EMG-EMG: from genioglossus to sternomastoid, from genioglossus to diaphragm, and from sternomastoid to diaphragm.

The reconstruction of the state of the system outlined in the introduction and necessary to perform the prediction was based on delay embedding (see appendix A). In our study, a delay time (*DT*) equal to the first zero of the autocorrelation of the signal was used (Kaplan and Glass, 1995). As this lag was approximately equal to a quarter of the mean respiratory period during the 90-second interval, with an embedding dimension (*ED*) equal to 4 the resulting embedding of the signal provided approximately 4 data points per respiratory cycle (see Fig. 2).

Regarding the selection of the number of neighbors, in (Sugihara and May, 1990) *ED*+1 neighbors were used to estimate locally linear models, but this value showed poor prediction performance with demodulated myographic signals. The number of neighbors was then increased until reasonably accurate forecasts were achieved, i.e., until mean error was lower than 10% of the signal variance. Ultimately, an evenly weighted average of 9 nearest neighbors was used as predictor, constructing an approximation to the tangent plane.

Prediction was computed for a prediction horizon (*PH*) ranging from 0 to 15 seconds, following a leave-one-out methodology. Prediction error was assessed by computing the residual with respect to the left-out data point. A set of residuals was obtained, and the median of the squared value of this set was calculated in order to provide an estimate of the prediction error of the model. The goodness of the prediction was also evaluated by means

of the calculation of the r^2 coefficient between predictions and the real data (Kaplan and Glass, 1995).

2.3. Variables and Statistics

The r^2 coefficient and the estimation of the residuals as functions of PH were obtained. Several variables were calculated to quantify and extract the essential information contained in these curves. Regarding the evolution of r^2 , the following variables were defined (see Fig. 3):

1. *Lowest PH whose corresponding r^2 value was lower than 0.7, and then the obtained PH value was divided by the respiratory period (PH07).* This normalization permitted avoiding the dependence on respiratory rhythm. Hence, prediction was evaluated along relative time horizon instead of absolute time (Alonso et al., 2007).
2. Maximum value of r^2 near the prediction horizon equal to the respiratory period (RP).
3. *Maximum value of r^2 close to prediction horizon equal to zero (R0).* This variable was totally related to short-term predictions.

With regard to the curves of the error estimate, the *value of the plateau (ErrorPT)* that was usually reached before PH equaled the respiratory period, was considered.

Statistics were carried out by means of two sample T-tests and ANOVA for repeated measures in order to compare healthy individuals and OSAS patients, and they were computed after assuring data normality by means of Kolmogorov-Smirnov tests. T-tests were applied to the average value of the variables at low and medium levels of respiratory effort, i.e. from 0% to 60% of *MMP* in each subject.

ANOVA for repeated measures was also performed for each variable at these low and medium levels of effort using a linear contrast. By doing so, the *effort-group* interaction was examined in order to distinguish the dependence on levels of effort between healthy subjects compared to OSAS patients. Statistical tests were applied taking into account equal and different variances of data and selecting the correct option according to Levene test. Significance level was set to 5%.

3. RESULTS

3. A. Auto-prediction

RP and *ErrorPT* obtained from auto-prediction showed positive and negative linear trends, respectively, with increasing levels of respiratory effort only in *GEN_EMG* signal. This implied a better prediction at higher efforts in the genioglossus. These trends were statistically significant (p-value lower than 0.02 and lower than 0.05, respectively). Average value at low-medium levels for both variables revealed statistically significant differences between healthy subjects and OSAS patients (p-value lower than 0.05 in both cases). Average *RP* value was higher for patients, whereas *ErrorPT* was lower than in healthy subjects.

Variables obtained from MMG signals, as well as EMG signals from the other respiratory muscles, did not show any significant differences between the two groups.

B. Cross-prediction

Regarding the prediction between signals pairs where any MMG signal was involved, significant results were obtained only when *GEN_MMG* was used for the prediction. *RP* and *R0* variables obtained from *GEN_EMG* and *GEN_MMG* cross-prediction showed positive linear trends as the level of respiratory effort increased (p-value lower than 0.02 in any case), indicating a better prediction at higher levels. Both variables, averaged for low and medium levels of effort, also revealed significant differences between healthy subjects and OSAS patients (p-value lower than 0.03 and lower than 0.04, respectively): they were higher for patients than for normal subjects, that is, respiratory muscular coordination was more predictable in patients than in controls.

With regard to the prediction between demodulated EMG signals from different muscles, linear trends with respect to increasing levels of effort were found in all cases (p-value lower than 0.03 in any case): positive for *PH07*, *RP* and *R0*; and negative for *ErrorPT*. However, only cross-prediction when genioglossus was involved showed differences between groups (see Fig. 4 as an example).

Fig. 5 and Fig. 6 show the four variables (*PH07*, *RP*, *R0* and *ErrorPT*), as a function of % MMP, calculated from cross-prediction between *GEN_EMG* and *SMM_EMG*, and between *GEN_EMG* and *DIA_EMG* respectively, in mean and standard deviation for each population. *PH07*, *R0* and *ErrorPT* (averaged from low to medium levels of effort) showed statistically significant differences between the two groups (see Table 1). In addition, *PH07* showed significant differences when the linear contrast of interaction *effort-group* was assessed (see Table 1 and Table 2 for *GEN_EMG-SMM_EMG* and *GEN_EMG-DIA_EMG* cases, respectively).

In both EMG-EMG cross-prediction cases, variables from r^2 coefficient were always higher in OSAS patients than in normal subjects. On the contrary, *ErrorPT* was lower in the former than in the latter.

4. Discussion

It is already known that respiratory rhythm and pattern generation can be described via a nonlinear oscillator (Bruce, 1996) or two coupled oscillators (Vasilakos et al., 2005). The act of breathing requires coordination of multiple muscles, and hypotheses on the physiological control governing respiratory pattern variability are based on nonlinear dynamic interactions between pulmonary and airway afferent activities, and integrative central respiratory mechanisms. Variability can be produced either by a nonlinear respiratory pattern generator or by disturbance inputs nonlinearly related to the intrinsic variables of the pattern generator (Bruce, 1996; Vasilakos et al., 2005). Thus, feedback from airway and muscle mechanoreceptors may produce complex nonlinear interactions between different respiratory muscles which can only be assessed by means of nonlinear approaches. Results from Frasch et al. (2007) and Alonso et al. (2007) confirmed the relevance of time scale measures. Our current study followed the same strategy, focusing on the assessment of nonlinear auto and cross-prediction.

Nonlinear prediction methods based on locally linear models were applied to myographic signals from respiratory muscles, in order to assess predictability of muscle activities during an increased respiratory effort and to evaluate differences in respiratory muscular coordination between OSAS patients and normal subjects. The etiology of OSAS is not fully known, although many possible mechanisms are pointed out in the literature as causative of the disease. The role of specific genes that influence its development has not yet been identified and some studies suggest that several genetic systems may be important,

especially those responsible for obesity, fat distribution, cranial anomalies, and sleep regulation (Casale et al., 2009, Kaparianos et al., 2006). However, in many cases OSAS is a progressive disorder that outcomes after years of snoring, whose vibration may cause local nerve lesions which could induce morphological changes in upper airway muscles (Svanborg, 2005), and make muscles being less able to react to negative airway pressure events. Carrera et al. (1999) demonstrated that the structural and functional changes of genioglossus in patients with OSAS, which are associated with changes on the distribution of type I and II fibers, were a consequence of the disease rather than a primary cause and reasonably, the more rigid strategy of activation of respiratory muscles in patients could lead to changes in muscle composition. In general, OSAS may be a consequence of the interaction between genetic and environmental factors which obscure its pathogenesis.

Demodulated EMG and MMG signals were used to model muscle dynamics and the accuracy of forecasts was analyzed. Auto and cross-prediction, following a leave-one-out methodology, were computed to evaluate nonlinear determinism as a function of prediction horizon. Several variables calculated from changes of the prediction accuracy with increasing prediction horizon provided information about changes in predictability of myographic signals, and therefore muscles functioning, as respiratory effort increased during an incremental protocol.

Both auto and cross-predictions evidenced an almost linear dependence on the level of effort. When this respiratory effort increased, all signals became more predictable (and cross-predictable) in both groups, independently of the appearance of statistically significant differences between them. This was shown by the increasing trend of the r^2 related variables (*PH07*, *RP* and *R0*) and the decreasing trend of the *ErrorPT* variable (see Fig. 5 and Fig. 6). These linear trends were found to be significant for all variables obtained from cross-prediction between EMG signal pairs, and also between EMG and MMG from the genioglossus muscle.

Regarding differences between the two groups, they were found at low and medium levels of effort when genioglossus signals were used for cross-prediction of signals from other respiratory muscles. Thus, results from cross-prediction showed a different interaction of respiratory muscles because of OSAS.

In (Alonso et al., 2007), variables obtained from another nonlinear technique (cross mutual information function) had indicated different nonlinear couplings of respiratory muscles between the two groups; but only at higher levels of respiratory effort whereas differences could have been also expected to be found even during normal breathing or low levels of respiratory effort. These differences were obtained by this other technique based on nonlinear prediction. This demonstrates the need of using different approaches in order to analyze any biological process, because of the specificity of the techniques and their related variables.

In addition, results from auto-prediction of EMG signals from genioglossus muscle also showed differences between groups, but such differences were not found for the other muscles. These disparities were obtained with *RP* variable, and they meant that a better prediction for two consecutive respiratory cycles was found in the behavior of genioglossus muscle of patients with respect to healthy subjects' behavior. All these differences, which were obtained only when genioglossus was involved, reflect the role of this muscle during breathing, and they were consistent with its importance in OSAS patients (Blumen et al., 2004; Svanborg, 2005). These patients have little flexibility in the way genioglossus is used, so it has to be activated more regularly on every breath and even more coupled with other muscles, probably because the airway pathology could lead to collapse if this activation is

too far from optimal. This behavior might reflect the dominance of one control mechanism, similarly to the increased regularity of heart rate variability with aging or in disease which is assumed to indicate a modification of autonomic balance toward sympathetic, restricting the reactivity of the system to adjust to different demands (Boettger et al., 2010).

On average, demodulated EMG signals from OSAS patients were more predictable than from healthy subjects because variables associated with correlation (namely *PH07*, *RP* and *R0*) showed higher values than variables from healthy subjects. Moreover, *ErrorPT* was always lower for patients. Patients with obstructive sleep apnea often exhibit fatigued or inefficient upper airway dilator muscle activity which can be related to the increased regularity pointed out by the results found in our study indicating that demodulated myographic signals of OSAS patients are more easily predictable than those of healthy subjects'. In the event of a respiratory challenge, patients do activate muscles in a more regular or uniform way and hence the results suggest that OSAS patients have a less flexible strategy in adapting to different respiratory efforts, even at low and medium levels.

Previous results based on cross mutual information function as well as changes in predictability found in this study suggested that these control mechanisms showed a clear dependence on the level of respiratory effort. In (Alonso et al., 2007), although OSAS patients presented a loss of nonlinear coordination at short time scales, this coordination persisted along the respiratory cycles longer in patients than in healthy subjects. This remaining coordination could have been the source of increased predictability that was found for the group of patients.

In this work, normalization of the *PH07* variable permitted us to observe that a relatively good cross-prediction between muscle functioning (i.e. r^2 coefficient higher than 0.7) remained until 50% of a respiratory period in healthy subjects. However, this good prediction remained on average much longer in patients, even more than two respiratory cycles, from 40% to 60% of *MMP* (see Fig. 5 and Fig. 6). These results confirmed the necessity of methods that use information transfer functions and that take into account different time scales, such as the nonlinear prediction approach used in this study. Also, the greatest differences between populations were found at long time scales, which could be interpreted as providing less flexibility of response to disturbances, and thus a sign of disease.

Whereas differences between groups had been mainly found at high levels of effort in (Alonso et al., 2007), they have already been found at low and medium levels by using this nonlinear prediction approach. Thus, nonlinear prediction methodology could be considered as an additional technique for the evaluation of demodulated myographic signals in order to assess the interactions of respiratory muscles in OSAS patients with respect to healthy subjects, and more specifically when breathing at low and medium levels of effort. These findings could suggest that control mechanisms have been altered by disease, or maybe a different balance among activated muscles was achieved in OSAS patients.

Significant differences between the two groups were only found when myographic signals from genioglossus muscle were involved in prediction procedures. These results reinforced the major role of the genioglossus muscle in upper airway stability, apnea generation and OSAS diagnosis. It is known that, in OSAS patients, the more the genioglossus contracts, the less need there is for forceful contractions of other respiratory muscles (Lydic et al., 1988). This mechanism can be explained by compensation due to the higher coordination between respiratory muscles as results from nonlinear prediction methodology showed in this work. This coordination represents the effective interaction of contractions. This study was based on normalized demodulated EMG signals and hence the results were independent

of signal amplitudes. Therefore, this coordination and prediction was only associated with signal waveforms and muscle pattern generation, and not directly related to levels of muscle activity.

It should be noted that signals obtained by surface EMG can be affected by the activity of nearby muscles or crosstalk (Merletti and Parker, 2004) although the electrodes were placed obtaining the maximum EMG level during specific contractions for each muscle. Possible crosstalk could exist between scalene and sternomastoid, which are very close, and to a lesser extent between genioglossus and sternomastoid because of the larger distance between them. The scalene is another accessory muscle close to the upper airways (Chiti et al., 2008; Hug, 2010) whose respiratory function can be considered similar to that of the sternomastoid in spite of having a different threshold of activation (Hudson et al., 2007). Even though crosstalk can influence the recordings, it would appear in all records of both groups, and the results obtained with muscles that interfere each other should be similar. Thus, it can be concluded that the differences in muscular coordination, even if due to crosstalk, reflect changes in respiratory muscle activation pattern between patients and healthy subjects.

Hence, conclusions derived from the differences found between the two groups of individuals under study remained valid because this study was not focused on the analysis of three specific muscles but the coordination in the respiratory muscular system by means of muscles or groups of muscles with different roles during breathing.

Better prediction between muscles, which reached two consecutive respiratory cycles in patients with OSAS, and higher predictability between consecutive cycles for genioglossus muscle could be taken into account in therapies applied to the upper airways, such as CPAP treatment. Future studies should evaluate the functioning of muscles during previous respiratory cycles and how it could be used to adapt treatment and rehabilitation strategies in order to apply appropriate pressure during the current cycle.

Finally, it can be concluded that nonlinear forecasting based on locally linear models, and its related variables, provides a useful diagnostic assessment in order to show different predictability of signals from respiratory muscles signals for OSAS patients with respect to healthy subjects.

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Biographies

Appendix A

A.1. Underlying dynamics of a system and delay embedding

The underlying dynamics and variables of the system controller are usually neither available nor measurable when recording myographic signals from respiratory muscles. In practice, only some signals which depend on these states can be measured, and then these signals can be used to build a model of this dynamics. The delay embedding technique, also called lag embedding, can be used to represent these state variables. This method depends on two parameters: delay time (DT) and embedding dimension (ED). DT is usually considered either as the lag until the first zero of the autocorrelation function of the signal, or as the lag where this function is equal to $1/e$ (Kaplan and Glass, 1995), but usually DT and ED depend on the application.

Thus, by embedding a scalar time series $x = x_1, \dots, x_N$, the following vector time series is obtained (x_t is the measurement made at time t):

$$\mathbf{x}_t = (x_t, x_{t-DT}, \dots, x_{t-(ED-1)DT}) \Big|_{t=1 \dots M}$$

Each $\mathbf{x}_t$ is a point in the ED -dimensional embedding space, and the embedded time series can be regarded as a sequence of points, one point each time t . Each point represents the state of the system at that time (Kaplan and Glass, 1995; Kantz and Schreiber, 1997). Note that if time series is of length N , $M = N - ((ED-1) \cdot DT)$ different points are obtained. Fig. 7 shows some examples of this kind of delay embedding.

A.2. Leave-one-out nonlinear prediction

The resulting ED -dimensional time series is used to model the dynamics and then this model is used to predict other signal epochs, taking into account a certain value of prediction horizon (PH). To predict the future of a point in the embedding space, the image (i. e., predicted value after time PH) of its closest neighbor can be taken as a predicted value of the current point of interest.

However, searching only the single closest state is not appropriate, due to the uncertainty introduced by quantification error associated with signal recording. Theoretically, all points in the phase space within a hypersphere of radius equal to the resolution have to be considered equally good predictors. Taking these neighbors into account, this method solves the linear system that maps present images to future ones. In this way, a nonlinear regression model can be implemented by stitching smoothly together a large number of locally linear models. The collection of all these locally linear models constitutes a model of nonlinear dynamics. Moreover, the single local models are interpreted as the linearization of the global nonlinear dynamics at the considered points in the phase space (Kantz and Schreiber, 1997; Kaplan and Glass, 1995; Sugihara and May, 1990; Porta et al., 2007). Fig. 8 shows an example of prediction with ED equal to 2 and with 2 neighbors: if the image of point 6 is to be predicted, its two closest neighbors (2 and 3) and their corresponding images are used to predict its “future” location.

In this work, nonlinear prediction was applied following a leaving-one-out approach: a vector time series $\mathbf{x}_t$ ($t = 1$ to M) obtained from the 90-second demodulated myographic signal, was modeled M different times and a single data point was left out each time. The model was then obtained using the images of the neighboring points as explained above.

Figure 1. Examples of surface EMG (upper traces) and MMG signals (lower traces) of the sternomastoid. Gray traces represent filtered myographic signals and black lines correspond to their demodulated counterparts.

Figure 2.

Example of cross-prediction for two demodulated EMG signals along time. Different respiratory cycles are indicated by different background shadings. Black and gray traces correspond to two demodulated EMG signals from different muscles, and circles indicate the samples of one cycle that are used by locally linear models to predict another sample located a respiratory period ahead. DT and PH indicate delay time and prediction horizon respectively.

Figure 3. Examples of r^2 coefficient and error estimation (as functions of prediction horizon) and their associated variables calculated on data corresponding to a single patient.

Figure 4. Time course of the r^2 coefficient and the error estimation for a typical patient and a typical healthy subject at low level of effort.

Figure 5.

Mean and standard deviation of *PH07*, *RP*, *R0* and *ErrorPT* corresponding to cross-prediction between GEN_EMG and SMM_EMG, shown as a function of %MMP. Gray solid lines represent healthy subjects and black dotted lines refer to OSAS patients. Symbols on the upper left corner of each plot indicate statistically significant differences between patients and healthy subjects (* refers to the linear contrast of the *effort-group* interaction, and † refers to the average variable at 20–60% of MMP).

Figure 6.

Mean and standard deviation of *PH07*, *RP*, *R0* and *ErrorPT* corresponding to cross-prediction between *GEN_EMG* and *DIA_EMG*, shown as a function of %MMP. Gray solid lines represent healthy subjects and black dotted lines refer to OSAS patients. Symbols on the upper left corner of each plot indicate statistically significant differences between patients and healthy subjects (* refers to the linear contrast of the *effort-group* interaction, and † refers to the average variable at 20–60% of MMP).

Figure 7.

Examples of delay embedding for a time series of length $N = 20$. Three different embeddings with $ED = 3$ are depicted: $DT=1$, $DT=2$ and $DT=3$. Some samples of the time series are gray-shaded to act as reference points when looking at the embedded matrix.

Figure 8.

Graphical example of local linear prediction using $ED = 2$ and 2 neighbors. Five points (1 to 5) with known images in the future are shown, whereas image of point 6 after a certain prediction horizon is unknown. Using images of the 2 nearest neighbors (points 2 and 3), forecast for point 6 is obtained.

Table 1

P-values for cross-prediction of SMM_EMG from GEN_EMG.

	PH07	RP	R0	ErrorPT
Effort · Group	< 0.01	N. S.	N. S.	N. S.
Average Variable	< 0.01	N. S.	< 0.03	< 0.04

Table 2

P-values for cross-prediction of DIA_EMG from GEN_EMG.

	PH07	RP	R0	ErrorPT
Effort · Group	< 0.03	N. S.	N. S.	N. S.
Average Variable	< 0.03	N. S.	< 0.05	< 0.03