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***Abstract*— Evaluation of the RR variability was carried out during the Cyclic Alternating Pattern (CAP) in sleep. CAP is a central phenomenon formed by short events called A-phases that break basal electroencephalogram (EEG) oscillations of the sleep stages. A-phases are classified in three types (A1, A2 and A3) based on the EEG desynchronization during A-phase. However, the relation of A-phases with other systems, such as cardiovascular system, is unclear and a deep analysis is required. For the study, six patients with Nocturnal Front Lobe Epilepsy (NFLE) and other six healthy controls patients underwent whole night polysomnographic recordings with CAP and hypnogram annotations. Amplitude reduction and time delay of the RR intervals minimum with respect to A-phases onset were computed. In addition, the same process was computed over randomly chosen RR interval segments during the NREM sleep for further comparison. The results suggest that the onset of the A-phases is correlated with a significative increase of the heart rate that peaks at around 4s after the A-phase onset, independently of the A-phase subtype.**

Keywords— **Heart Rate Variability, CAP, Sleep, NFLE, EEG**

I. Introduction

The Cyclic Alternating Pattern (CAP) is a sleep phenomenon that occurs during the NREM sleep in healthy conditions and is defined from the electroencephalographic signal (EEG) [1]. However, when noxious events occur during REM sleep (e.g. apneas), CAP is also found during REM sleep. CAP sleep is a central process that ensures autonomic and behavioral adaptation during sleep and participate in the dynamics of the sleep structure. CAP phenomenon is formed by phasic EEG events called A-phases, which appear super-imposed to the basal sleep stage oscillations observed on the EEG. A-phases are classified in three types A1, A2 and A3. Each A-phase type presents specific characteristics of frequency that allows its visual scoring. The general definition is [1]:

- A1-phase. It is characterized by delta burst (0.5-4 Hz), k-complex sequences, vertex sharp transients and polyphasic bursts with less than 20% of rapid activity.
- A2-phase. It has rapid EEG activity that cover between 20% and 50% of the A-phase duration.
- A3-phase. It is characterized by Alpha (8 Hz - 12 Hz) and Beta waves (12 Hz - 30 Hz), which cover more than the 50% of the A-phase duration.

The occurrence of the different A-phases changes across the sleep time and is related to sleep stages. For example, A1-phases are a common feature of deep sleep and accordingly are highly present during the first sleep cycles. A2-phases and A3-phases are closely related to sleep stage transitions and occur more frequently before REM onset and at the end of the sleep time. A-phases generally translate a condition of autonomic activation expressed by a transient heart rate acceleration. This phenomenon has been described in normal subjects and in pathologic conditions, especially during A3-phase (arousals from sleep) [2, 3], during other minor brain activations and during noxious events such as sleep apneas [2, 4]. However, no clear evidence has been collected on the autonomic changes during A1-phases and A2-phases because the effects of these A-phases on the cardiovascular system are more subtle and therefore more difficult to detect visually.

The aim of this study is to assess the behavior of autonomic system during the different A-phases types in both healthy subjects and patients with a sleep disorder. The evaluation of the autonomic system will be done through the analysis of the heart rate fluctuations (heart rate variability) obtained from the electrocardiogram (ECG).

II. Materials and Methods

A. Clinical Protocol

Polysomnographic data from six young adult patients (average age 25 years) diagnosed with NFLE were acquired at the Sleep Disorders Center at the University of Parma using international standard procedures. NFLE is a sleep disorder characterized by a percentage ratio of A1-phases, A2 and A3 similar to the percentage ratio of A-phases in normal subjects. Also, polysomnographic data from six healthy subjects (average age 33 years) were acquired as the control group.

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The sleep stages (hypnogram) and CAP A-phases were scored by sleep experts according to EEG inspection [1, 5]. And from the ECG, RR intervals were automatically detected and artifacts manually corrected. Finally, the signals were exported with a common sample rate of 128 Hz for further analysis. Although the number of subjects on each group is relatively small, the total number of A-phases for each A-phase type, as shown in Table I, is sufficiently large for a statistical analysis of the data.

B. Extracted Features

From the signals containing the A-phases and RR intervals, the segments corresponding to each A-phase were extracted, starting 3.5s before the onset and ending 3.5s the A-phase offset. The 3.5s margin was chosen to be long enough to contain sufficient data to estimate the basal state prior to the A-phase, but short enough to ensure that it did not interfere with data from adjacent A-phases. Each segment was divided in two sub-segments: the first one, which we denote using sub-index *pre*, contains the first 3.5 seconds of the segment (i.e. — the basal state prior to the A-phase—), and the second sub-segment, denoted by sub-index *post* which contains the rest of the segment (from the A-phase onset to 3.5s after the end of the A-phase).

The premise of this work was to evaluate, qualitative and quantitatively, a possible decrease in the RR intervals (i.e., an increase in heart rate), which can often be observed after the onset of the A-phases. To do this, two features related to the magnitude and latency of the RR interval decrease were measured. For each segment, the average baseline of the RR intervals was computed, denoted by $\overline{H_{pre}}$, and the minimum RR interval during the *post* range was annotated. This minimum is denoted by H^*_{post}, and its latency with respect to the activation onset is written as T^*_{post}. From these values is obtained the change in the RR interval with respect to the basal state as $A^*_{post} = \overline{H_{pre}} - H^*_{post}$. These features are represented in Figure 1.

The hypothesis that motivated this work is that a reduction in the RR intervals can be observed during the A-phases; however, in a considerable number of cases, the RR interval does not show a noticeable change. There were also some segments where, due to ECG artifacts, the RR intervals could not be correctly estimated. Since these cases add uncertainty, was decided to exclude them from the study.

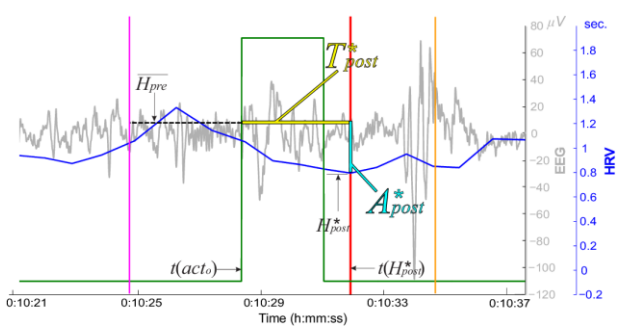

Figure 1. Representation of the features extracted from the RR intervals (blue trace): amplitude reduction with respect to the RR baseline (shown in cyan) and time delay (shown in yellow). The EEG signal is shown in grey, with a green window indicating the annotated A-phase. The vertical magenta and orange lines represents the analysis window (3.5 seconds before and after the A-phase, respectively).

TABLE I.
COUNT OF A-PHASES BY TYPE AND NIGHT PERIOD

	Patients			Controls		
	I	II	III	I	II	III
A1	617 (33.5%)	362 (19.6%)	250 (13.6%)	559 (30.0%)	365 (19.6%)	106 (5.7%)
A2	99 (5.4%)	121 (6.5%)	103 (5.6%)	165 (8.9%)	182 (9.8%)	115 (6.2%)
A3	71 (3.9%)	122 (6.6%)	98 (5.3%)	103 (5.5%)	119 (6.4%)	147 (7.9%)

Since sleep is a dynamic process of relatively long duration (with respect to the underlying systemic processes), the full sleep time was divided in three equally long periods, called I, II, and III, and analysis was performed independently for each period. Also the influence of each of the three types of A-phases on the autonomic system was analyzed separately. Table I shows the number of A-phases that were actually used for the analysis after removing those that showed artifacts due to errors in the R peak detection stage. For the patients, 1843 A-phases from a total of 2623 were considered suitable for analysis. For the controls, 1862 out of 2489 were taken into account.

In the context of the estimated characteristics, the hypothesis under study implies that A^*_{post} and T^*_{post} may be systematically influenced by the presence of an A-phase. To test this hypothesis, another set of segments was generated starting at random points of the EEG signal, and with uniformly random lengths in the same range as the segments corresponding to true A-phases. Just like true A-phases, these randomly generated segments are fully contained in NREM sleep. For these spurious segments the same features were computed: time delay, and amplitude reduction on the RR intervals with respect to the baseline, respectively denoted by T_{rand}, A_{rand}.

Therefore, the study aimed at determining whether there are significant differences in the distributions of the computed features corresponding to true A-phases, and the ones obtained from spurious, randomly-generated segments, for both patients and controls. The analysis of differences in the distributions of features between the control and patient groups was also accomplished. Statistical evaluation was carried out throughout the Kolmogorov-Smirnov test.

III. RESULTS

Figure 2 shows the histograms of amplitude reduction (A^*_{post}) and latency (T^*_{post}) of the RR intervals during true and spurious A-phases, for both groups (NFLE and controls). We can observe that the A^*_{post} histogram for spurious A-phases in controls (black line) is similar in all the plots; this means, at different sleep times and for different A-phases. Thus, this case is taken as reference point. For A1-phases during period III, it is possible to observe that histograms of true A-phases (red and blue lines) present a clear increase in

A^*_{post} (p-value < 0.01). For A2-phase on periods I and II, true A-phase histograms shows and increase in A^*_{post} (p-value < 0.01). A similar result is found in A3-phase (p-value < 0.01).

In the same figure, we can observe how the histograms of T^*_{post} are similar in the case of spurious A-phases (black and green lines) and this is independent of A-phase type and sleep period. The histograms tend to be uniform, which is expected since the spurious onset times were chosen randomly (within NREM sleep). However, histograms for true activations show a clear peak around 4 seconds and a significant difference with respect to the spurious A-phase histograms (p-value < 0.01). Note that this behavior is similar in normal and pathologic conditions, for all sleep periods and A-phases types.

IV. Discussion

The latency distributions showed clear differences between the true and spurious A-phases. While the latency distributions corresponding to spurious A-phases are highly entropic, the latencies for true A-phases concentrate around 4 seconds, regardless of the A-phase type and sleep time. This result could suggest that the autonomic system has a latency of 4 seconds with respect to the A-phase onset and this latency is not related to the sleep time and A-phase type. In addition, the amplitude reduction of the RR intervals (A^*_{post}) presents an increase during true A-phases with respect to spurious A-phases, supporting the hypothesis that the A-phase activation is reflected by the autonomic system. However, the change in A^*_{post} is related to the A-phase type and sleep time. This result is in agreement with previous studies [2, 4], in which only A3-phase (arousal from sleep) was analyzed since its influence on the autonomic system is visually clear. However, since autonomic changes related to A1-phases are not easily identifiable [2, 4], they have not been investigated and validation of its real existence was lacking. Our results confirm the existence of A1-phases and provide evidence of their influence on the autonomic system, which is found to be similar to the behavior of A3-phases.

One criticism to this study is the small sample size, thus is needed to increase the sample to obtain more conclusive results. Furthermore, in future studies, it will be included classical autonomic parameters computed from the RR intervals, such as the frequency components of the heart rate signal, to better characterize the autonomic response. Finally, to complete the analysis of the cardiovascular response, the assessment of the respiratory influence on the cardiovascular response in normal subjects and patients could be useful.

V. Conclusions

An evaluation of the cardiovascular system during different A-phases that build up CAP during sleep in NFLE patients and normal controls was carried out. Autonomic response was found to be similar for all types of A-phases as during the conventional arousal from sleep, i.e., CAP A3-phase. Moreover, it seems that all the activations present a similar latency (4 seconds) at the minimum of the RR interval with respect to the A-phase onset. These findings suggests that the CAP phenomenon has a real, measurable influence on autonomic system.

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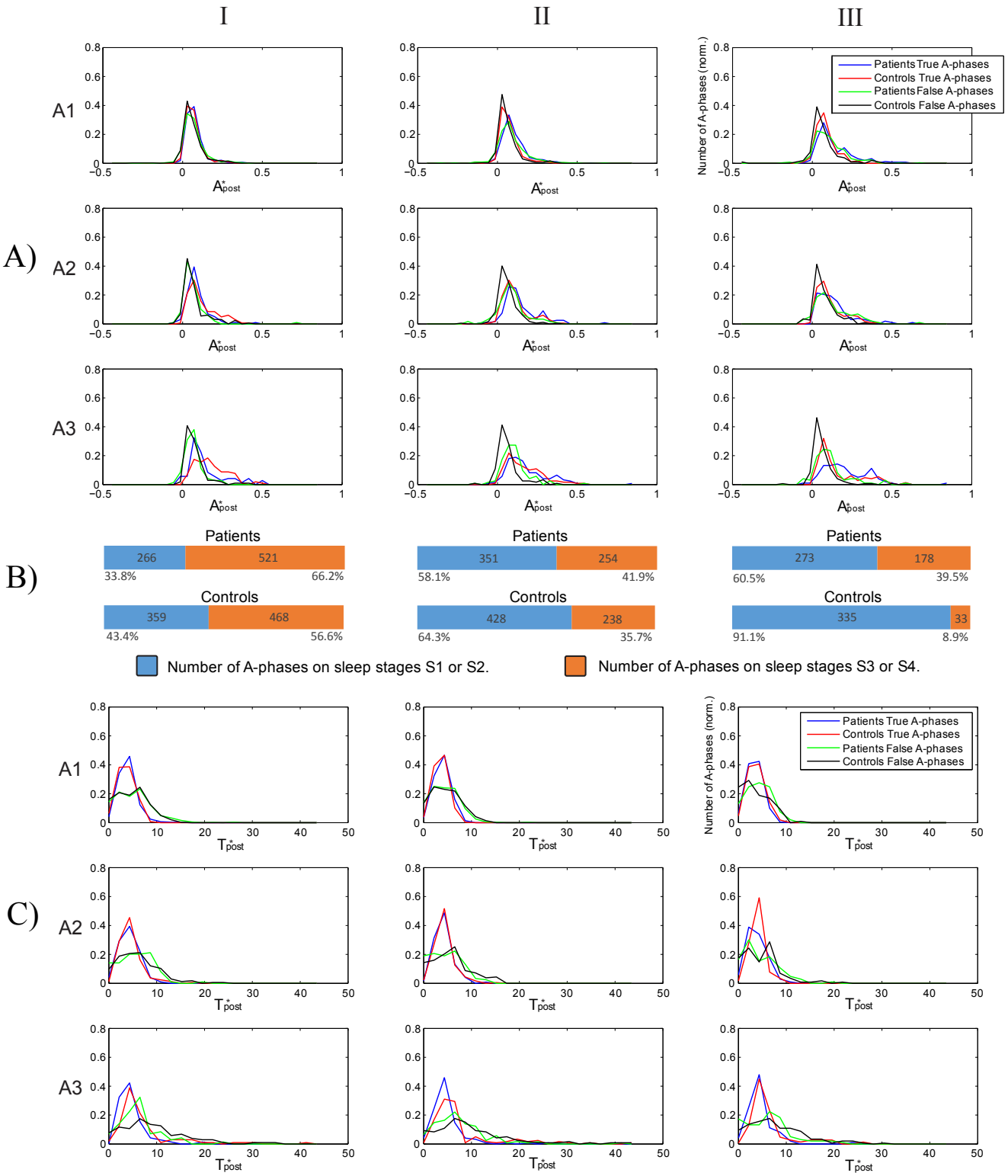

Figure. 2: (A) Distributions of the RR amplitude reduction (A^*_{post}) for each A-phase type (A1, A2, A3) and sleep period (I, II, III). (B) Percentages of light (S1/S2 – shown in blue) vs deep sleep (S3/S4 – shown in orange) for each sleep period (I, II, III). The number inside each bar represents the number of A-phases found during these sleep stages and used in the present study. (C) Distributions of the latency of the RR-minimum respect to A-phase onset (T^*_{post}) for each A-phase type (A1, A2, A3) and sleep period (I, II, III).