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Monitoring Ultradian Changes in Cardiorespiratory Control in Obstructive Sleep Apnea Syndrome

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Abstract— **Spectral analysis of heart rate variability (HRV) is commonly employed to track changes in autonomic nervous system and respiratory activity during sleep. However, conventional HRV spectral indices can be seriously confounded by inter-subject differences or intra-individual changes in ventilation and ventilatory pattern, especially in subjects with obstructive sleep apnea syndrome (OSAS). We highlight the approach we have undertaken to circumvent this problem by introducing "respiration-adjusted" spectral indices of HRV. Since fluctuations in sleep state also affect HRV considerably, we describe a method for combining the information derived from sleep staging and the information derived from cardiorespiratory measurements. We also introduce a new complementary index of autonomic function, BRS_{PTT}, based on measurements of heart period and pulse transit time. We demonstrate that this surrogate measure of baroreflex gain correlates well with the corresponding measures of baroreflex sensitivity based on noninvasive blood pressure measurements. Our experience to date suggests that BRS_{PTT}, along with respiration-adjusted spectral measures of HRV, are useful as clinical tools for assessing autonomic dysfunction in OSAS.**

I. INTRODUCTION

TO date, many epidemiological studies have provided compelling evidence linking OSAS to systemic hypertension, coronary artery disease, heart failure and stroke [1,2]. These retrospective studies in humans are supported by prospective animal studies, in which chronic exposure to nocturnal episodic hypoxia produced sustained daytime hypertension after several weeks [3]. Knowledge about the causal pathways linking OSAS to cardiovascular disease remains incomplete, but there is ample evidence that abnormal autonomic control is a prime factor [4]. If impaired autonomic control constitutes the primary link between OSAS and cardiovascular dysfunction, it would be ideal if abnormal autonomic function could be detected in subjects with OSAS prior to the development of frank manifestations of cardiovascular disease. In normal healthy subjects, parasympathetic activity peaks in the night and decreases to a nadir in the early morning hours; sympathetic activity essentially follows the opposite pattern of changes, peaking in the first few hours after waking [5]. In patients with coronary artery disease, however, circadian rhythmicity in heart rate variability (HRV) is highly attenuated [6]. Similar results have been found in another study on patients with angina pectoris [7]; as well, in the angina patients, the rate at which high-frequency power decreased in the early morning hours prior to awakening was slower than the corresponding rate of vagal withdrawal in normals. These findings speak to the importance of monitoring cardiac autonomic activity as a noninvasive and nonintrusive means of potentially predicting adverse cardiovascular events in advance of their occurrence.

Due to the ease and noninvasiveness of heart-rate monitoring, the spectral analysis of HRV has become widely employed as a means for continuously assessing cardiac autonomic function. However, the utility of HRV as a tool for measuring autonomic function dates back to the original study of Katona and Jih [8], which demonstrated in an anesthetized animal preparation a linear correlation between respiratory-related fluctuations in heart period and vagal firing rates, under conditions of tidal breathing. Subsequent validation studies in humans were also carried out under conditions in which respiration was controlled [9]. On the other hand, some studies have shown that changes in respiration within a given individual can substantially alter estimates of both high-frequency and low-frequency powers of the HRV spectrum [10]. In the present study, we highlight this issue in the context of autonomic monitoring during sleep, particularly in subjects with OSAS, where ventilation and respiratory pattern can change substantially with changes in sleep-wake state. As well, we present the approach that we have adopted to circumvent this problem.

The baroreflexes play a key role in influencing cardiovascular variability, and baroreflex sensitivity (BRS) has been shown to have strong prognostic value in predicting cardiovascular disease-related mortality [11]. However, standard BRS assessment requires either the introduction of an indwelling arterial catheter or the noninvasive monitoring of beat-to-beat blood pressure using expensive equipment. Moreover, even noninvasive continuous blood pressure monitoring can be relatively intrusive when carried out for long durations during overnight sleep. In this paper, we present an overview of our experience in employing a surrogate measure of BRS, based on the joint measurement of the R-R interval (RRI) and pulse transit time (PTT).

A final issue that this presentation will highlight is the way in which information derived from sleep staging is combined with information derived from the cardiovascular

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measurements. Current manual or automated algorithms for sleep staging still rely on the standardized scoring system established by Rechtshaffen and Kales [12] over four decades ago. Sleep stages are scored based on consecutive epochs that are each 30 s in duration. On the other hand, based on the recommendations of the HRV Task Force [13], ECG recordings of 5 min duration provide a good compromise between the requirements for signal stationarity and statistical reliability of the spectral HRV estimates.

II. METHODOLOGY

The main lessons that this presentation will focus on are based on the findings derived from 3 separate studies:

Study 1: Polysomnograms from 288 participants in the Sleep Heart Health Study (1999-2004) [14] were analyzed. All subjects were free of known chronic cardiopulmonary disorders and chosen to achieve equal-sized samples of subjects in 4 categories of OSAS severity (apnea-hypopnea index: <5, 5-15, 15-30, >30 h^{-1}). Exclusionary criteria included history of lung disease (chronic obstructive pulmonary disease, asthma), cardiovascular disease, diabetes, hypertension (subjects taking anti-hypertensive medications were excluded) and current smoking. The recording of physiological signals from each participant was obtained through a single night, unattended polysomnography at home. The signals used from this study were the ECG and thoracic and abdominal respiration signals.

Study 2: Thirty one polysomnograms from the Cleveland Family Study were selected for analysis, with the following inclusionary criteria: (1) availability of a recorded channel of finger photoplethysmography (2) no previous diagnosis of chronic cardiac or pulmonary conditions, (3) subjects had not previously been on continuous positive airway pressure treatment for OSAS and (4) age >18 years. These particular recordings were also selected based on the availability of good quality signals in the ECG and photoplethysmograph (PPG) channels in all sleep/wake stages.

Study 3: Ten healthy adults (age: 26.2±2.2 yr), 10 children with OSAS (age: 11.4±0.5 yr; AHI: 21.0±5.3 h^{-1}), and 10 normal children (age: 11.5+0.3 yrs) were studied during wakefulness. Measurements of ECG and continuous blood pressure (Nexfin, BmEYE, Inc.) were recorded over periods of 10 minutes each, under the following conditions: supine rest, supine with cold face challenge (1 min), and standing.

Data Analysis

Beat-to-beat RRI were extracted from the ECG recordings from all 3 studies cited above. From the data collected in Study 2, the ECG and PPG signals were used to derive beat-to-beat sequences of PTT. PTT was defined as the duration between the each R-wave and the subsequent peak in the PPG signal. In Study 3, beat-to-beat values of systolic blood pressure (SBP) and diastolic pressure (DBP) were estimated from the continuous blood pressure waveforms. All signals were re-sampled at 2 Hz prior to further analysis.

The power spectra of RRI and PTT were calculated using the Welch method for each consecutive 5-min segment. From these, we obtained a value for each of the following autonomic indices at every 5-min interval: RRILF, low-frequency (0.04-0.15 Hz) RRI power; RRIHF, high-frequency (0.15-0.4 Hz) RRI power; LHR, the ratio of RRILF to RRIHF; and PTTLF, low-frequency (0.04-0.15 Hz) PTT power. From the blood pressure measurements in Study 3, we also computed successive 5-min values of the low-frequency (0.04-0.15 Hz) power of SBP, SBPLF. Baroreflex sensitivity for each 5-min interval was estimated as follows: $BRS=(RRILF/SBPLF)^{1/2}$. Similarly, the surrogate measure of baroreflex sensitivity using PTT was defined as: $BRS_{PTT}=(RRILF/PTTLF)^{1/2}$.

To compute respiration-adjusted indices of HRV, we first estimated, for each 5-min segment, the parameters of an autoregressive with exogenous input (ARX) model relating changes in respiration (V) to changes in RRI:

$$RRI(n) = -\sum_{j=1}^{p} a_j \, RRI(n-j) + \sum_{k=0}^{r} b_k \, V(n-k) + e(n) \qquad (1)$$

Having deduced the ARX model coefficients, the "respiration-adjusted" RRI were estimated in the following manner:

$$RRI_{ra}(n) = -\sum_{j=1}^{p} a_j(n) RRI_{ra}(n-j) + \sum_{k=0}^{r} b_k(n) V_b(n-k) + e(n) \qquad (2)$$

where V_b represents a baseline 5-min segment of the respiration signal during wakefulness. The respiration-adjusted HRV indices were subsequently derived from the power spectrum of RRI_{ra}:

$$S_{RRIra}(f) = \frac{\sigma_e^2 T}{\left| 1 + \sum_{j=1}^{p} a_j e^{-i2\pi f j T} \right|^2} \qquad (3)$$

Since scoring of sleep-wake state was carried out in consecutive segments of 30 s (epochs), while the autonomic indices were computed in segments of 5 min duration, we divided each 5-min segment into 10 consecutive sections, with each section having its own sleep state score but all 10 bearing the same autonomic index value. The median value for each autonomic index at a given sleep-wake state was deduced from all 30s epochs in the overnight study. Although there were periods after the start of each polysomnogram that were classified as "wake", we employed only the last 10 minutes of quiet wakefulness prior to sleep onset to represent "true wakefulness".

III. RESULTS

Correcting for the effect of non-uniform ventilatory patterns and changes in sleep state during sleep in OSAS

Figure 1 shows an example of the sequential estimates of LHR (grey tracing) and LHR_{ra} (black tracing) deduced from the polysomnogram of a subject with OSAS (apnea-hypopnea index = 55 h^{-1}) displayed over the first 4 hours of the sleep study. While LHR_{ra} tracks LHR rather closely at the start of the study (when the subject is still awake), the

discrepancy between the respiration-adjusted and unadjusted index becomes quite substantial at various times during the overnight study. As expected, the size of this discrepancy is influenced largely by the degree of temporal nonuniformity in ventilation in the OSAS subject.

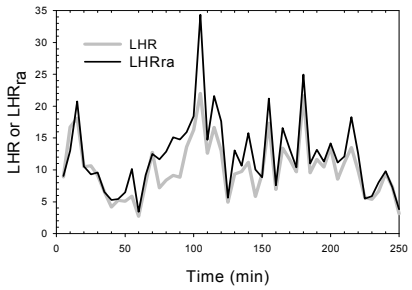

Fig.1: Comparison of the time-courses of LHR (thick grey) and LHRra (thin black) in an OSAS subject during the first 4 hours of a sleep study.

A broader comparison of the effect of "respiration adjustment" on HRV spectral indices, as assessed across 288 subjects in REM sleep, is shown in Figure 2. Here, the median LHR_{ra} deduced for each subject in Study 1 is plotted against the corresponding median LHR in the same subject. If respiration adjustment had no effect on LHR, then all the "data points" would lie on the line of identity. However, it is clear that LHRra tends to be larger than LHR in the same subject. The discrepancy becomes larger as median LHR increases. Again, this is consistent with the notion that differences in ventilation and ventilatory pattern exert a larger confounding influence on the estimation of autonomic indices as the severity of OSAS increases.

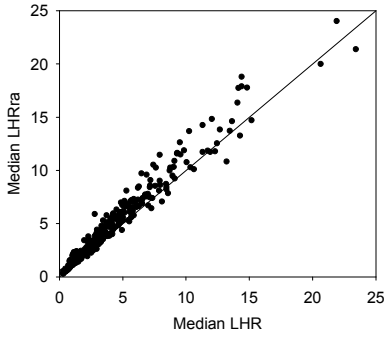

Fig.2: Plot of the median values of LHRra versus corresponding median values of LHR in 288 subjects during REM sleep. LHRra values lie above the line of identity, indicating that adjusting for respiration leads to generally higher values for LHRra compared to LHR.

Surrogate measure of baroreflex gain based on PTT

Figure 3 displays the results from the adult subjects in Study 3, in which estimates of BRS based on blood pressure measurements were compared with estimates of the surrogate measure of BRS based on PTT. BRS_{PTT} was linearly correlated with BRS_{SBP}, when these estimates were based on data collected during supine rest ($r = 0.76$, $p = 0.01$). The correlation became higher when the comparison was based on data collected during the cold face challenge ($r = 0.94$, $p < 0.0001$). However, during standing, there was a great deal of variability in the estimates, and as such, the correlation coefficient between BRS_{PTT} and BRS_{SBP} was not statistically significant ($r = 0.44$, $p = 0.21$).

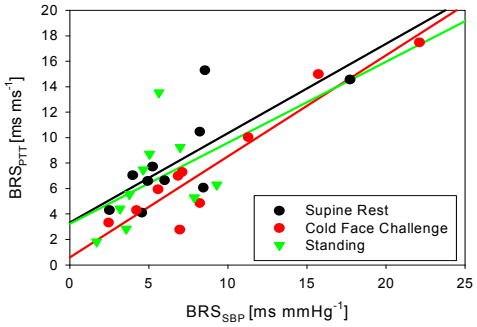

Fig.3: Comparison of the surrogate measures of baroreflex gain based on PTT with corresponding estimates of baroreflex sensitivity based on blood pressure measurements.

A comparison of BRS_{PTT} (panel A) and corresponding estimates of BRS_{SBP} (panel B), as well as how both measures respond to changes in posture from supine to standing, is displayed in Figure 4. These results are based on the measurements made on the pediatric OSAS subjects and their age-matched controls in Study 3. Both PTT and SBP derived measures of baroreflex gain, in both subject groups, show a decrease from supine to standing, reflecting a shift in sympathovagal balance towards greater relative sympathetic dominance. As well, both measures of baroreflex gain are lower in OSAS relative to their normal counterparts, consistent with the elevated sympathetic tone and reduced parasympathetic levels in OSAS that have been reported [1,4,10].

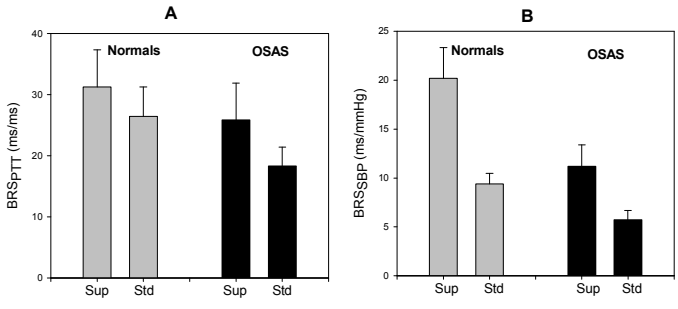

Fig.4: Estimates of BRS_{PTT} (Panel A) and BRS_{SBP} (Panel B), and how they are altered by postural changes. These estimates were derived from measurements made during wakefulness in pediatric OSAS subjects and their age-matched controls in Study 3.

Detecting differences in baroreflex gain during sleep and between subject groups

In Figure 5, the median values of BRS_{PTT} for each sleep-wake state (W=wake, R=REM sleep, N1= Stage 1 sleep, N2 = Stage 2 sleep, N3 = Stage 3 sleep) were first calculated in each of the subjects from Study 2. Subsequently, the means and standard errors of BRS_{PTT} were calculated from these individual subject-medians in the various sleep-wake stages.

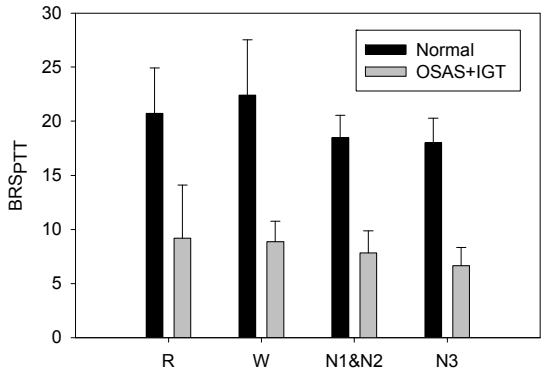

Fig. 5: Group-averaged estimates of BRS_{PTT} in normal controls compared to corresponding estimates in subjects with both OSAS and glucose intolerance across different sleep-wake states.

The plots in Figure 5 compare BRS_{PTT} in normal controls with BRS_{PTT} in subjects who had OSAS and who were also found to be glucose intolerant. BRS_{PTT} in the OSAS subjects was on average less than half the values of BRS_{PTT} in the controls ($P = 0.01$).

IV. Discussion

A key limitation of using HRV to monitor autonomic nervous system activity during sleep is the strong influence that ventilation and ventilatory pattern can exert on beat-to-beat fluctuations in heart period. Hypopnea, for instance, will increase arterial P_{CO2} and lower P_{O2} levels, in turn activating the chemoreceptors, which then act to increase ventilator drive and alter autonomic input to the heart. On the other hand, the consequent increase in breathing increases vagal feedback from the lungs, and this has been shown to exert an inhibitory influence on sympathetic activity. Against this backdrop of dynamic autonomic activity, it is unclear whether the popularly used spectral indices of HRV, which were validated under relatively stable conditions of respiration either in wakefulness (in humans) or anesthesia (in animals), truly reflect autonomic state. The simple solution that we have advocated has been to adopt a "compare apples with apples" approach. We select a segment of tidal respiration prior to sleep, assume that it is representative of the ventilation level and respiratory pattern during "quiet wakefulness", and use that segment as the baseline breathing pattern against which other segments during sleep are compared. We see this form of computational "respiration adjustment" as being analogous to the standard practice of adjusting for confounding factors in statistical analysis. This approach is admittedly simplistic and does not completely address the more complex aspects of the physiological effects of non-uniform ventilatory patterns during sleep. However, the inclusion of noninvasively-derived measures of autonomic function, such as BRS_{PTT} or peripheral arterial tonometry [16], could be useful in complementing the information derived from HRV. Thus, more extensive validation of BRS_{PTT} over a larger sample of subjects and in overnight studies should be useful in advancing the search for improved noninvasive methods of monitoring autonomic activity during sleep.

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