Cardiac Related Parameters Are Not Reliable in Differentiating Central from Obstructive Sleep Respiratory Events

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***Abstract*— Sleep apnea can be broadly categorized as obstructive (OA) and central apnea (CA). The treatments for both are different and thus classifying them accordingly is important clinically. Cardiac derived parameters have shown their usefulness in detecting occurrences of sleep apnea. However, limited studies have been conducted to understand their potentials in differentiating CA from OA in sleeping children. 15 children (12 male) without overt cardiac disease aged 8.8 ± 3.0yr were recruited to undergo overnight diagnostic polysomnographic studies. Heart rate (HR) and its variability (HRV) were derived for assessment based on known criteria for OA and CA. 215 respiratory and 215 tidal breathing events that occurred in these children were recorded and analyzed. The results obtained indicated that HR and HRV can detect occurrences of these two types of respiratory events with moderately sensitivity (≥0.703) and specificity (≥0.815). However, no significant difference (p>0.05) between OA and CA can be observed in either HR or HRV. The findings herein suggest that both these cardiac parameters may be useful in identifying the episodes of respiratory events but are limited in differentiating their nature in accordance to standard sleep studies protocols.**

***Index Terms*— heart rate; heart rate variability; pediatric; respiratory; sleep apnea.**

I. Introduction

Studies have shown that there are two possible sleep-related processes that contribute to sleep-disordered breathing (SDB). Firstly, the brain activation level declines at sleep onset, particularly in the brainstem reticular formation that contains the neural oscillator that in turn controls breathing. The other process is the decline in the muscle tone throughout the body during sleep. This includes the muscle tone of the tongue, back of the mouth, throat and pharynx [1]–[2]. In order to understand the pathophysiology of these processes, respiratory events can be broadly categorized as obstructive (OA) and central apnea (CA). The accurate classification of these events is critical as this can determine the appropriate treatment [3]. CA is defined as a reduction in airflow proportional to breathing efforts while OA is a diminution of airflow in the presence of breathing efforts [4].

It is well-recognized that SDB are accompanied by concomitant cyclic variations in heart rate (HR). The pattern of tachycardia or bradycardia is closely associated to the time course of apnea. Thus, it has been used successfully to detect apneas in patients with clinical SDB symptoms [5]. Moreover, the physiology causing the cyclic variation of HR is being investigated in parallel with efforts to define evidence-based criteria for its utility as a simplified SDB diagnosis. Studies on sympathetic neural activity during the occurrence of apnea proved that sympathetic activation increases during its occurrence [6]. Currently, most clinical investigations are conducted to affirm the capability of HR in detecting OA in paediatric respiratory sleep studies. However, limited research has not been carried out to evaluate cardiac derived parameters in distinguishing CA from OA.

Hence, the objectives of this study were to: (1) assess the accuracy of these parameters in predicting CA or OA and (2) assess the potentials to differentiate them.

II. Materials and Methods

A. Polysomnography (PSG)

Overnight PSG study was performed in a sleep laboratory with monitoring that included electroencephalography (electrodes C3-A2 and O2-A1), left and right electrooculogram (LE-A2 and RE-A1), nasal airflow tracing (via pressure transducer), AC-coupled respiratory inductance plethysmography (RIP) recording of chest and abdominal movement (Respitrace Calibrator System, Ambulatory Monitoring Inc, Ardsley, USA), arterial blood oxygen saturation (SaO_2)and infrared photoplethysmography by a pulse oximeter (Novametrix Medical Systems Inc, Wallingford, USA), HR estimations from a single-lead electrocardiogram (ECG) monitor (S&W Medico, Teknik, Denmark). The studies were continuously observed and recorded by a PSG system (Uniquant system, LaMont Medical Inc, Wisconsin, USA). Standard PSG criteria for children were used in this study [7].

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An episode of OA was defined as a complete cessation of airflow with the presence of chest and/or abdominal wall movement. An obstructive hypopnea had similar characteristics except that airflow was reduced by at least 50% from its baseline. For the purpose of this study, it was classified as OA to simplify the comparison with the corresponding PSG scorings. Central hypopneic events were defined as a reduction of 50% or more in airflow proportional to the decrease in chest wall movement. For CA, it was the complete cessation in both airflow and respiratory drive. Similarly, they are regarded as CA in the context of this study.

B. Subjects

Children were eligible if they had a diagnostic PSG study following referral for investigation relating to sleep apnea. This study included 15 children (12 male) aged 8.8 ± 3.0yr. Their height and weight were 1.30 ± 0.24m and 36.9 ± 22.5kg respectively. Their resting systolic blood pressures were 106.8 ± 7.4mmHg; diastolic blood pressures were 63.5 ± 8.7 mmHg and HR were 85.9 ± 11.2 beats per minute (bpm). Verbal instruction and consent were obtained from the caregiver(s) and/or children. Institutional ethical approval was also given for the study. The data used in this study were collected previously and documented elsewhere [3].

C. Experimental Protocols

The accuracy of HR recordings in detecting respiratory events was verified by the corresponding readings of both the RIP and nasal airflow measure. In PSG scorings, these measures were used as sole criterion to identify CA and OA [7]. The RIP usually detected increased inspiratory efforts through the de-synchronization of chest and abdominal movements, while nasal airflow was determined by the pressure changes in relation to inspiration and expiration. Only respiratory events that fulfilled a predefined selection criterion were considered: (1) identified as valid event in PSG scorings by two blinded observers, (2) duration with at least 10 readings and (3) with no apparent motion artifact.

In this study, two cardiac derived parameters were assessed; HR and HR variability (HRV). For HRV, its examination needed to be determined by observing the fluctuations from its baseline history value. Documented criterion using HRV to classify respiratory events was applied [8-9]. In which, the classification was performed by using a minimum of 10 HRV readings associated with each event. For each valid event, HRV data was extracted for the event duration and for an equal duration of tidal breathing (as baseline value) directly prior to the event. This was to give an equal amount of data for both the baseline and respiratory events. Sensitivity (SE) is defined here as the probability of correctly identifying a true positive OA or CA event. Specificity (SP) is the probability of correctly identifying a true negative tidal breathing event. Positive predictive value (PPV) is the probability that a child with a positive test having OA or CA. Negative predictive value (NPV) is the probability that a child with a negative test not having OA or CA. Conversely, mean HR of each event was first compared to that obtained during tidal breathing. Thereafter, this parameter was compared between two types of respiratory events.

D. Data Analysis

This was performed using Matlab Release 14 (The Mathworks Inc, Natick, USA) package. For HRV analysis, their mean difference was tested with Student's *t*-test assuming equal variances. Since there may be a difference in the SE and/or SP between the CA and OA acquired, Chi-squared ($\chi 2$) test was used to test for its level of significance. For HR comparison, the same Student's *t*-test was applied to test the difference among OA, CA and tidal. A value of $p<0.05$ was considered as statistically significant.

III. Results

The recorded mean total sleep time was 6.98 ± 1.50hr, sleep efficiency was 85.4 ± 13.7% and apnea-hypopnea index (AHI) was 2.25 ± 1.93. From the 243 respiratory events identified by PSG protocol, only 215 (64 OA and 151 CA) were considered for comparison. The exclusion was due to: (1) events with motion artifact, (2) events with less than 10s apart (this proximity made distinction of each event difficult) or (3) scoring discrepancies between the two blinded observers. Another 215 tidal prior to each event were recorded as part of the analysis. With these 430 recorded events, the SE, SP, PPV and NPV were calculated for HRV for OA and CA as given in Table 1.

Events	SE	SP	PPV	NPV
OA	0.703	0.891	0.865	0.750
CA	0.715	0.815	0.794	0.741

Table 1: Statistical results of cardiac derived parameter in predicting occurrence of OA or CA from tidal breathing during sleep

Significant ($p<0.05$) difference was observed in HRV for OA when compared to its corresponding tidal event as in Figure 1. The former registered a mean HRV of 3.25 ± 1.00bpm while the latter had a mean value of 1.18 ± 0.31bpm. Similar results ($p<0.05$) were obtained for CA and its respective tidal with 3.34 ± 1.09bpm and 1.33 ± 0.57 correspondingly as in Figure 2.

However, no significant difference between CA and OA was observed ($p>0.05$). Moreover, the test of SE and SP difference shows that $\chi 2$ had a value of 0.032 and 1.908 respectively with the one degree of freedom. To be significance at the 0.05 level, $\chi 2$ should be at least 3.84, therefore both the distributions were considered not significantly different ($p>0.05$). The results obtained also did not show a distinct HR change trend for either type of respiratory events. For CA, mean HR varied by 9.44 ± 2.88bpm ($p<0.05$) while for OA, it changed by 9.49 ± 2.97bpm ($p<0.05$) when these were compared to mean HR of tidal. Similarly, no significant difference ($p>0.05$) was observed between CA and OA.

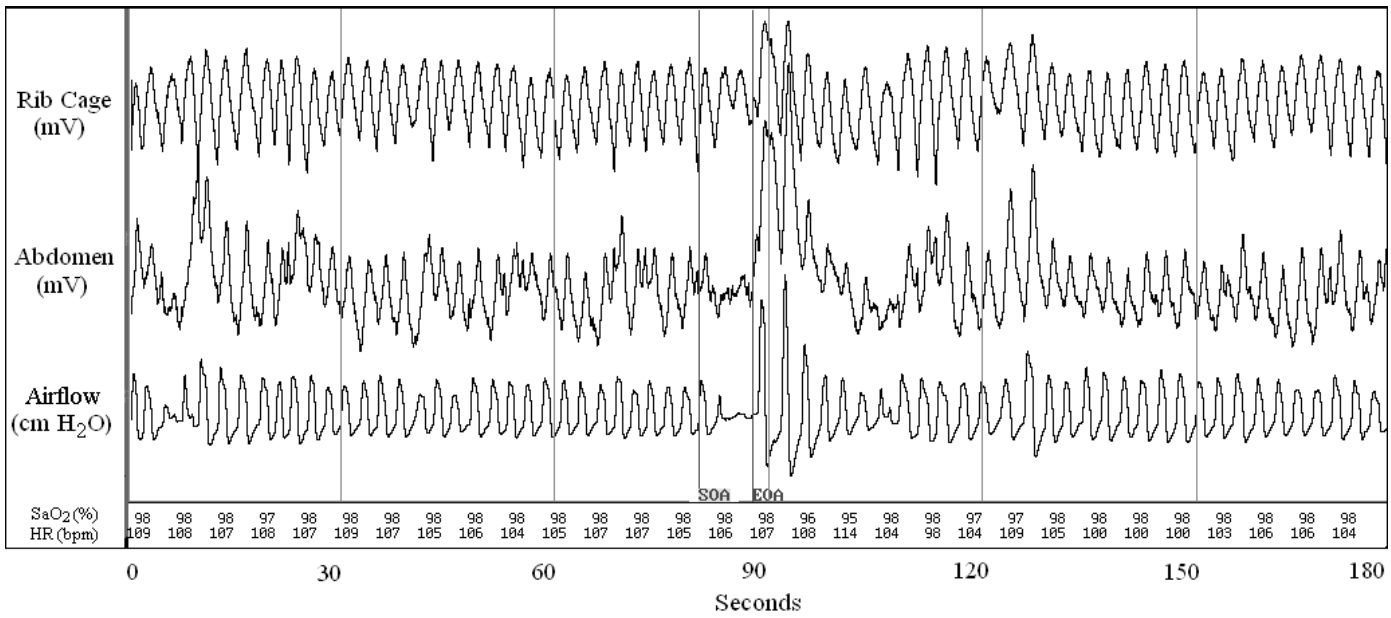

Figure 1: In this 180-second PSG recording, a 9-year-old female with an OA that led to significant cardiac variations when compared to the prior tidal breathing baseline can be observed. Legend: SOA and EOA denote start and end of OA respectively.

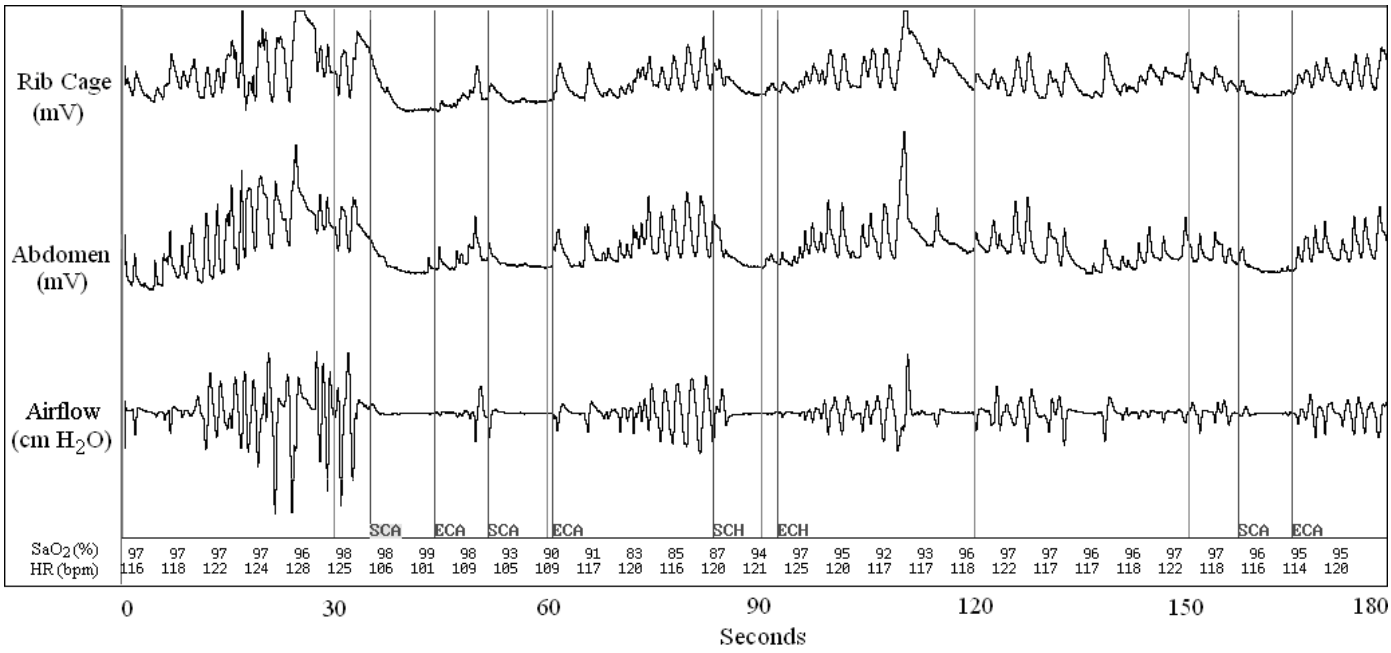

Figure 2: A 3-year-old male with mixture of central apneic and hypopnea events that has cardiac variations can be seen in this 180-second PSG recording. Legend: SCA and ECA denote start and end of CA respectively. SCH and ECH denote start and end of central hypopnea correspondingly.

IV. Discussion

The current study demonstrates that HR and/or HRV alterations can indicate the occurrence of sleep apnea in pediatrics without overt cardiac disease. There was a significant association observed between the respiratory events and cardiac parameters. However, the cardiac parameters are limited in distinguishing CA from OA. For the recruited children, they underwent ECG monitoring as part of the standard PSG study protocol, allowing a precise assessment of the cardiac autonomic function mirrored by these cardiac parameters. The physiology behind the cardiac changes during sleep has drawn significant attention and only few aspects of the heart-lung interactions had been clarified. It is interesting to investigate the time course of sleep apnea and following breaths [6]. It is also quite likely that sympathetic and parasympathetic activity increase at the end of each apnea and then decline during the short period of compensatory hyperventilation.

It is also known that HR changes with different sleep stages, with SDB and disorders affecting the heart. In order to

minimize such variability in the present study, they were collected within the sleep stage. In which, data were recorded immediately after the end of each apneic event and compared with those obtained prior to its onset. Thus, the recordings obtained are less dependent on the former factor and only children without coexisting cardiac disease were recruited. Moreover, the present limitation of stationary and non-stationary data analysis techniques does not allow cardiac derived parameters to be easily used as a marker of its autonomic function during sleep apnea [10-11]. Thus, comparison of absolute and relative fluctuations in the cardiac parameter to simplify the derivation of results was adopted here. From the results obtained, cardiac derived parameters are useful in detecting respiratory events. However, their assessment as a predictor of event type may not be as promising with current available techniques. As there are dissimilar characteristics for both types of apnea, distinguishing them from each other is essential [3]. Approach like a tracheobronchial stent is an important consideration when an upper airway obstruction due to narrowing of the tracheobronchial system leads to breathlessness and in more severe cases, death due to asphyxiation [12]. However, this may not be suitable for apneas with a central nature. The importance of classifying CA and OA is that the pathophysiology and pathogenesis of both respiratory events are distinctly different.

CA can be considered as a neurological condition. These apnea-terminating arousals may be less intense and cardiac arrhythmias can be less frequent [13]. They can cause the cessation of all respiratory efforts during sleep, usually with a decrease in SaO_2. CA arises as the central drive to respiratory muscles and airflow cease even when the summations of respiratory stimuli fall below a threshold level that is required to generate ventilation. This may be caused by the insensitivity of the chemoreceptors to the onset of such events [14]. Unlike its obstructive counterparts, there is generally no apparent physiological response even though hypoxemia can be observed. The onset of obstructive respiratory events may end with arousals to initiate of airflow; however arousals are usually absent at the termination of the central-oriented ones [15].

Previous finding suggested that a number of mechanisms have been identified by which central respiratory drive can be transiently inhibited [16]. These mechanisms include defects in the respiratory control system or muscles, transient instabilities in respiratory drive and reflex inhibition of the central respiratory drive. During sleep, breathing is mainly regulated by the metabolic respiratory control system that receives input from the peripheral and central chemoreceptors as well as mechanical ventilatory events in the airways and lungs. Disorders of this respiratory system may be compensated when awake. However, it becomes fully manifested during sleep. Secondly, if the central nervous system fluctuates between the “awake” and “asleep” state, there can be a difference in the stimuli threshold required to generate the respiratory rhythm. During these transient periods, fluctuations in the central respiratory drive can occur. Lastly, there are reflexes that are capable of transient abolition of the central respiratory drive. These include the pulmonary inflation reflex and inhibitory reflexes arising in the upper airway like the muscles surrounding it [14]–[16].

On the contrary, OA can be considered as anatomical or functional conditions [13]. Since the main difference between apneas and hypopneas is their relative degree of ventilatory, only the pathophysiology of OA is examined in this context. OA is characterized by repetitive pauses in breathing during sleep due to the obstruction and/or collapse of the upper airway. Diaphragmatic respiratory effort continues during the episodes of OA and is generally followed by an awakening to breathe [17]. Interestingly, OA is usually regarded to be clinically relevant if this happens more than five times per sleeping hour as it is quite likely for OA to occur occasionally in any healthy individual. In each obstruction, it can cause a fall in the blood oxygen level, which is followed by an increase in the sympathetic nervous activity. This can then produce an increase in HR and blood pressure thereby causing possible arousals [18]. Typically, the individual with OA can experience snoring, laborious breathing or profuse sweating during sleep. In short, the flow of air is restricted and cannot be ventilated through the lung tissues although breathing efforts can continue.

In addition to the effects experienced by adults, young children and infants with OA may also undergo breath-holding spells when they are awake. They may experience difficulty in breathing and have poor swallowing coordination during meal times. In severe cases, visible effects can occur in younger children and infants like delayed growth, abnormal weight and recurring ear infection [19]. However, the degree of these effects greatly depends on the child. The important thing is to detect these abnormalities so that proper treatments can be advised. In the midst of an OA episode, cessation to breathe continues until that individual wakes up from it. This arousal instantly increases the activities of the muscle in the tongue and throat that will then enlarge the airway. This individual will be able to breathe and to once again fill the lungs with the required oxygen as usual. This cycle may be repeated numerous times in a night while the individual has no idea that it is happening.

Anatomically, obstruction of the upper airway can occur in people who have a narrow upper airway or for those whose muscles around the throat behave abnormally. In the latter case, the tongue, the pharynx and other surrounding soft tissues relax against the throat during sleep [20]. This leads to a partially blocked upper airway thereby restricting the flow of air. Consequently, the body is unable to inhale sufficient oxygen and exhale excessive carbon dioxide. In particular, this causes a low level of oxygen or hypoxemia and high level of carbon dioxide or hypercarbia in the bloodstream [5]. This alerts the brain to coordinate remedial action to overcome the upper airway obstruction. The increase in BP or HR is the remedial response from the brain and this may lead to snoring or laborious breathing. Unknown to the person, the frequency and duration of these breathing pauses prevent the body from

getting a restorative as well as normal sleep.

It is acknowledged that there are some limitations to the present study. Firstly, as there can be differences in BP and vascular compliance in children, their corresponding cardiac parameters may vary. Thus, these parameters may only be useful when it was observed over a period of time on an individual basis. Secondly, variability in the cardiac parameters may not reflect true variations of inspiratory efforts in children with coexisting cardiac diseases. These diseases can affect the isometric contraction time in response to changes in inspiratory efforts causing false changes in the observed measurements. Lastly and most importantly, the major limitation is the effects of motion artifacts on the derived parameters. These may cause a shift in the baseline of these parameters and may be incorrectly regarded as an occurrence of abnormal variations in breathing efforts. However, artifacts of this nature can be detected or minimized with appropriate technological applications [21].

V. Conclusions

Cardiac derived parameters have shown their usefulness in detecting the occurrences of apnea in respiratory sleep studies. These parameters may be a simple and tolerable measure to be used on children, especially when prolonged clinical monitoring like nocturnal study is required. However, limited investigation has been conducted to understand its potential use to differentiate the nature of apnea as central from obstructive. From the findings herein, it can suggest that cardiac derived parameters with current analysis techniques can be useful in detecting the occurrences of respiratory event but not as an effective predictor of its respiratory event type.

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