Effect of Apnea Duration on Apnea Induced Variations in Cerebral Blood Flow Velocity and Arterial Blood Pressure

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***Abstract*— Obstructive Sleep Apnea (OSA), defined by shallow breaths or complete cessation of breathing for more than 10s, is a significant contributing factor for the developments of hypertension, myocardial infarction, stroke and neuropsychological impairments. In this study, we have investigated the relation between apnea duration and apnea induced variations in cerebral blood flow velocity (CBFV) concomitant with blood pressure changes in 9 sleep apnea subjects (8 male and 1 female; Age: 46.0±11.6 years; BMI: 34.5±7.8 kg/m^2; AHI: 81.6±41). As apnea duration increased from 10s to greater than 30s, the mean percentage rise in CBFV increased from 22% to 42% for amplitude and 22% to 33% for area respectively. For blood pressure, the values increased from 14% to 26% for amplitude and 14% to 23% for area respectively. The results suggest that the apnea duration has a measurable effect on the degree of rise in both cerebral blood flow velocity and arterial blood pressure during apnea episodes (p=0.0002).**

I. Introduction

Sleep plays an important role in maintaining longevity, cardiovascular health, learning, memory consolidation and overall central nervous system homeostasis [1]. Sleep fragmentation due to sleep disorders such as obstructive sleep apnea (OSA) can disrupt this sleep homeostasis and lead to multitude of major health consequences [2]. In OSA, due to repetitive occurrence of partial or complete interruptions in airflow resulting from upper airway occlusion, blood oxygen saturation can drop to dangerously low levels, eventually leading to arousals from sleep resulting in sleep fragmentation. It is estimated that about 5-25% of the adult population in Western countries are affected by OSA [3]. In U.S. alone, approximately 18 million adults are thought to be affected, with a prevalence of 24% men and 9% women [4].

OSA elicited events such as constriction of blood vessels due to increased sympathetic activity, metabolic dysregulation and systemic inflammation can lead to short term and long term rises in arterial blood pressure eventually leading to chronic hypertension [5-6]. Further, OSA mediates changes in cerebral blood flow which may cause cerebrovascular diseases such as stroke. Usually a consistent blood supply of about 50 to 54 ml of blood per 100 g of tissue per minute to the brain is maintained by the autoregulation mechanism. However, the increased oxidative stress due to repetitive hypoxia and hypercapnea during apnea episodes, concomitant with the elevated arterial blood pressure due to sympathetic vasoconstriction can lead to rapid rise and fall in cerebral blood flow [7-8]. Autoregulation may not be able to compensate for these frequent rises and falls either due to their abrupt nature or due to the fact that, abnormal vasodilation from hypoxia/hypercapnea may exceed the autoregulatory vasoconstriction [8]. All these will result in repetitive oscillations in cerebral blood flow throughout the night.

Several studies have reported the overall variations in cerebral blood flow and blood pressure during apnea episodes and found that there is a progressive increase during apnea episode followed by a rapid decrease below the baseline following apnea termination [9-11]. These observations suggest that the severity of hemodynamic changes due apnea may be correlated to the duration of apnea episodes. Even though apnea is defined as cessation of breathing for a minimum of 10 seconds, the duration of apnea episodes can vary anywhere from 10 seconds to over a minute. Further, the total number of apnea and hypopnea episodes per hour -- referred to as the apnea-hypopnea index (AHI) -- can vary from 5 in mild apnea to much greater than 30 in severe apnea. A study of the correlation of the severity of hemodynamic changes to the apnea duration may suggest that the duration of apnea episode is of significance. However, the relationship between the duration of apnea and severity of hemodynamic changes has not been adequately explored.

Hence, this study aims to investigate the influence of apnea duration on apnea induced changes in cerebral blood

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flow velocity and blood pressure during sleep.

II. Materials and Methods

A. Subject Demographics

Data was collected from 9 sleep apnea patients (8 male subjects and 1 female subject; Age: 46.0±11.6 years; BMI: 34.5±7.8 kg/m^2; AHI: 81.6±41.8) during an 8-hour overnight sleep study in an accredited laboratory (Sleep Consultants, Inc., Fort Worth, TX). The subjects were either previously diagnosed as having sleep apnea or were strongly suspected of suffering from OSA. Each subject was provided with complete instructions about the experiment and signed an informed consent that was approved by the institutional review board.

B. Polysomnography

An eight hour nocturnal polysomnography was performed on all the subjects. Electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), oral and nasal air flow pressure, chest and abdominal movement, leg movements, blood oxygen saturation and exhaled carbon dioxide concentration, blood pressure, cerebral blood flow and subject body position – using a video monitoring system – were recorded for the entire duration of study.

Concurrently, blood pressure (BP) was monitored continuously throughout the night using Nexfin HD monitor (BMEYE, Amsterdam, Netherlands). The monitor was equipped with an integrated heart reference system (HRS) which enabled accurate heart level blood pressure measurement without a need to restrict the free movement of hand and irrespective of its vertical height with respect to the heart.

Transcranial Doppler (TCD) has been widely used to non-invasively monitor and characterize the changes in the cerebral blood flow velocity (CBFV) during sleep apnea [3]. In this study, we measured cerebral blood flow velocity from the middle cerebral artery (MCA) using a Transcranial Doppler (TCD) monitor (DWL, Compumedics, Singen, Germany). CBFV was measured continuously throughout the night using transtemporal approach, by placing a 2MHz transducer on the temporal region of the volunteer's cranium, just in front of the ear.

C. Data Analysis

The analog outputs from the blood pressure and TCD monitors were transmitted to a computerized data acquisition system (DAQ). This study used a digital to analog converter board (DAQ 6024 E by National Instruments, Austin, TX) which has a maximum sampling speed of 200 kS/s, 12 bit resolution, and 16 analog input. A custom-designed program using Lab VIEW 8.3 software (National Instruments, Austin Texas) was implemented to control the DAQ. The digitized data from the DAQ was imported into MATLAB (Mathworks Inc. Natick, MA) for offline analysis.

Further, the identification of sleep stages and apnea scoring were performed by a certified sleep lab technician blind to objectives of this study. A custom-designed graphical user interface (GUI) was developed and programmed in the MATLAB environment (Mathworks Inc. Natick, MA) to visualize the data and clip it into segments containing apneas; referred to as apnea clips. In this study we have used a total of 309 apnea clips randomly selected from all the nine subjects.

Since, apnea episodes have variable duration, the apnea clips were sorted into 3 groups based on 10s duration intervals and named as Group1 (10-20s), Group2 (21-30s), and Group3 (≥30s). The number of apnea clips in each group was 110, 101 and 98 respectively.

A custom made program was developed to detect the peaks and troughs of recorded blood pressure and CBFV waveforms contained in each of the clips. The detection of the proper peaks and troughs were validated by visual inspection and any missed detection or erroneously detected points were corrected.

Following the peak and trough detection, the percentage rises in amplitude as well as the area for both BP and CBFV were calculated. Figure 1 shows a representative recording of the blood pressure waveform from an apnea clip along with peak and trough detection for amplitude and area calculation.

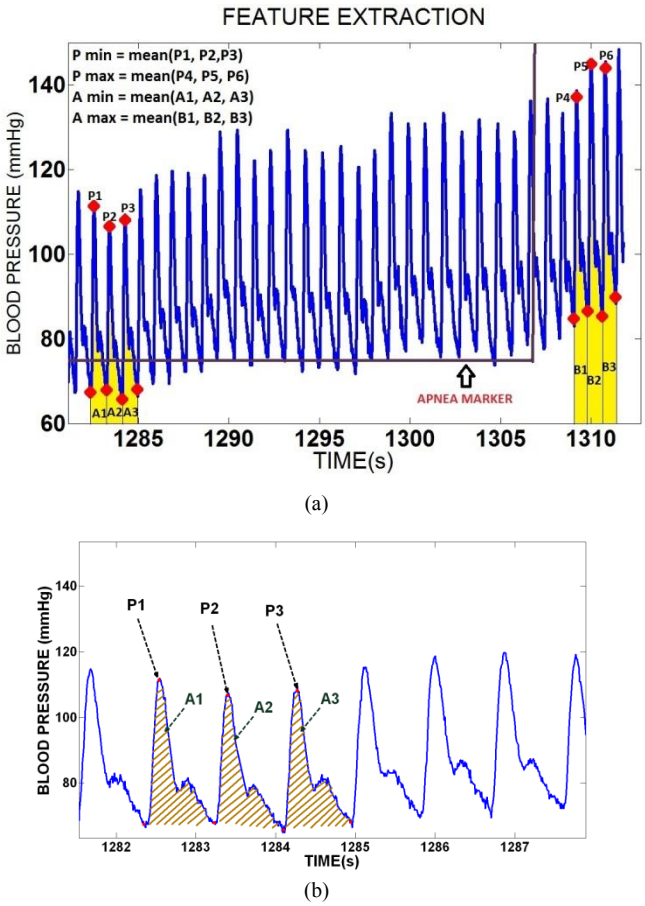


Fig. 1. Percentage Amplitude and Area Calculations. Shaded region shows the pulses used for area calculation.

Minimum peak (P2) within the first 3-5 seconds after the start of apnea was obtained. The average value, P_{min} was calculated as

$$P_{min} = \frac{P1+P2+P3}{3} \quad (1)$$

where P1 and P3 are the preceding and succeeding peaks respectively. Further, area under each of these three pulses (A1, A2 and A3) was evaluated as the cumulative integration of waveform between two troughs as shown in Fig 1 (b). Average area (A_{min}) was calculated similar to that of P_{min}. Similarly the highest peak P5 occurring at the end or ± 5s after the apnea termination, was obtained. Using P4, P5 and P6, average max value of amplitude P_{max} and the area A_{max} were calculated similar to P_{min} and A_{min}.

The percentage change in amplitude and area were calculated as follows

$$\%\, Amplitude = \frac{P_{max}-P_{min}}{P_{min}} x100 \quad (2)$$

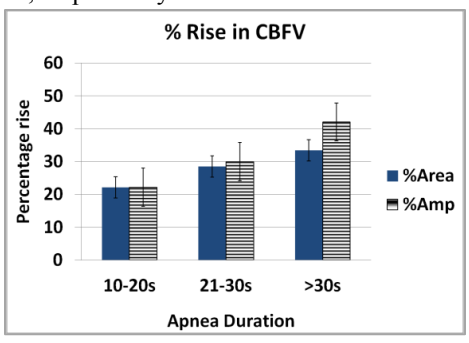
$$\%\, Area = \frac{A_{max}-A_{min}}{A_{min}} x100 \quad (3)$$

The above equations were used to calculate the percentage rise in amplitude and area for both CBFV (% Amp CBFV and % Area CBFV) and blood pressure (% Amp BP and % Area BP). Further, for each subject, the percentage rise in amplitude and area of BP and CBFV for all the apnea episodes, were grouped into three duration intervals and average values were obtained, respectively. Statistical analysis was performed on these average values using one way ANOVA followed by Bonferroni multiple comparison test.

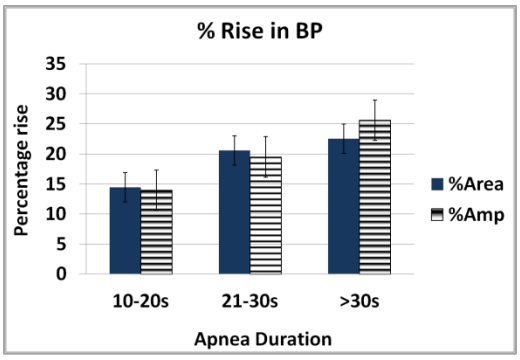
III. Results

A. Effect of Duration of Apnea on Blood Pressure and Cerebral Hemodynamics

The percentage rise in amplitude and area for each duration interval were averaged across all the subjects and the results are as shown in Fig 2. As the apnea duration increased from 10s to greater than 30s, the mean percentage rise in CBFV increased from 22% to 42% for amplitude and 22% to 33% for area respectively. For blood pressure, the values increased from 14% to 26% for amplitude and 14% to 23% for area, respectively.



(a)



(b)

Fig. 2. Percentage Rise in amplitude and area for (a) Cerebral Blood flow Velocity and (b) Blood Pressure for Different Duration Intervals.

B. Statistical Analysis

In order to test whether the duration of apnea has any effect on the magnitude of the rise in CBFV and BP, one way ANOVA was performed on the average values of the proposed metrics obtained from all the subjects, for each duration interval. This result is shown in Table 1. Since the ANOVA demonstrated that the proposed metrics are sensitive to the duration of apnea, a pair-wise comparison of the metric means was conducted using Bonferroni post hoc analysis. Table II summarize the result of the analysis.

TABLE I
P-VALUES FOR EFFECT OF APNEA DURATION ON PERCENTAGE RISE OF CBFV AND BP

Features	p-value
% Amp CBFV	<0.0001
% Amp BP	<0.0001
% Area CBFV	0.0002
% Area BP	0.0001

α = 0.05 is considered to be the significance level

TABLE II
BONFERRONI POST HOC ANALYSIS

Features	Group Comparison		
	1vs 2	1vs 3	2vs 3
% Amp CBFV	0.0003*	< 0.0001*	0.0103*
% Amp BP	0.0005*	< 0.0001*	0.0001*
% Area CBFV	0.0734	< 0.0001*	0.1528
% Area BP	0.0139*	< 0.0001*	0.5125

* = significant; α = 0.05

IV. Discussion

Previously we have shown that during an apnea episode there is a progressive increase in both the cerebral blood flow velocity and blood pressure followed by a rapid decrease after the apnea termination [12]. In this study, we investigated whether the duration of apnea plays a role in the apnea-induced rise in CBFV and BP.

Fig 2 shows that as the duration of apnea increased from 10s to greater than 30s, there is an increase in the mean percentage rise for both CBFV and BP. Further, The ANOVA analysis showed that there is a significant difference ($p=0.05$) between the values of the metrics for various durations of apnea. Post hoc analysis ascertained that the percentage rise in amplitude for both CBFV and BP is significantly different across all the three duration intervals. Moreover, percentage rise in area of blood pressure was found to be significant for Group1apneas (lasting10-20s) vs. Group 2 apneas (lasting 21- 30 s) and Group1 vs. Group 3 apneas (lasting >30s). % Area CBFV was found to be significantly different only for Group 1 (10-20 s) vs. Group 3 (>30s). Considering this statistical significance and computed mean values for the metrics, the results suggest that the degree of rise in CBFV and BP increases with the increase in apnea duration.

One possible explanation for the observed relationship between BP, CBFV and apnea duration is that, for a longer duration apnea, the amount of CO_2 accumulated in the body and the amount of oxygen desaturation will be higher compared to that of a shorter duration apnea. Further, it has been reported that combined effects of hypoxia and hypercapnea synergistically increase sympathetic nerve activity [13]. Hence, for a longer duration apnea, the degree of sympathetic activation may be higher which in turn can lead to more elevated levels of blood pressure. These combined effects of hypoxia, hypercapnea and elevated blood pressure may lead to the rise in the cerebral blood flow velocity. This points to a possible conclusion that, for prolonged apnea episodes cerebral autoregulation may fail to compensate for the rise in blood pressure.

It is interesting to note that the percentage rise in area was found to be lower than the percentage rise in amplitude for apnea duration of $\geq$ 30s. It has been observed that for longer apnea duration, the temporal distance between adjacent diastolic troughs of the last few pulses was reduced, suggesting an increase in heart rate due to increased sympathetic activity in spite of what must be strong baroreflexive chronotropic inhibition from the rise in systolic pressure [14]. This may be a reason for the reduced percentage rise in area compared to the amplitude of blood pressure.

V. Conclusion

This study investigated the effect of apnea duration on arterial blood pressure and cerebral blood flow during obstructive sleep apnea. The results indicate that, rise in both of these variables during apnea episodes are sensitive to the increase in the duration of the episodes.

VI. Acknowledgment

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