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An Investigation of Simultaneous Variations in Cerebral Blood Flow Velocity and Arterial Blood Pressure during Sleep Apnea

Raichel Alex, *Student Member,* Gauri Bhave, Mohammad A. Al-Abed, *Student Member,* Aditya Bashaboyina, Swathi Iyer, Donald E. Watenpaugh, Rong Zhang, and Khosrow Behbehani, *Senior Member, IEEE*

Abstract— **Obstructive Sleep Apnea (OSA) is a major sleep disorder with a prevalence of about 15 % among US adult population and can lead to cardiovascular diseases and stroke. In this study, we have investigated the OSA-induced concurrent rise in cerebral blood flow velocity and blood pressure in 5 positively diagnosed sleep apnea subjects. The subject population had a mean AHI of 57.94±25.73 and BMI of 33.66±7.27 kg/m^2. The results of this preliminary study yielded a relatively high correlation between rise in blood pressure and rise in cerebral blood flow velocity during apnea episodes (r=0.61±0.16) compared to normal breathing (r=0.28±0.26). These findings suggest that cerebral autoregulation may be less effective during apnea episodes.**

I. Introduction

Obstructive sleep apnea (OSA) is defined as complete cessation of breathing (apnea) or shallow breaths (hypopnea) for 10 seconds or more due to upper airway occlusion during sleep. It is theorized that the airway occlusion occurs because of the loss of muscle tone in the posterior oropharynx. Current estimate is that 15% of the U.S. adult population has sleep disordered breathing, approximately 18 million adults [1]. OSA accounts for an estimated 84% of patient population having sleep disordered breathing [2]. However, only 10% have been diagnosed and treated [3].

Brain requires a consistent blood supply of about 50 to 54 ml of blood per 100 g of tissue per minute irrespective of the fluctuations in arterial blood pressure. If the brain blood flow falls below the range of 8 to 10 ml per 100 g of tissue per minute, brain tissue death occurs. On the other hand, excessive blood flow also results in brain tissue damage by compression resulting from increased intracranial pressure. To avoid brain tissue death, the blood supply to brain is tightly regulated by the cerebral autoregulation mechanism. However studies have shown that during the simulated apnea in awake OSA subjects as well as in healthy volunteer subjects this autoregulation fails during the cessation of breathing.

Studies show that sleep apnea may mediate chronic hypertension in about 45% of patients without any prior history of hypertension within 4 years of the initial diagnosis of apnea [7]. Repetitive short-duration hypoxemia caused by obstructive sleep apnea (OSA) mediates large rise in the blood pressure. Studies (in awake OSA subjects) have shown that cerebral autoregulation is impaired in these subjects [8]. Hence, it is important to investigate the variations in cerebral blood flow during sleep to assess whether cerebral autoregulation can maintain the brain blood flow despite large rise in blood pressure.

Previously, we reported the result of our study of cerebral autoregulation and arterial blood pressure during simulated sleep apnea using a breath hold block design [9]. In that study, we found progressive rise in both blood pressure and cerebral blood flow velocity waveforms during apnea followed by rapid decrease after termination of apnea. Further, we obtained a relatively high correlation between cerebral blood flow velocity variations and changes in blood pressure during simulated apnea (r=0.74 ±0.06), suggesting that cerebral autoregulation may not compensate for the pressure changes during apnea.

This study describes the preliminary result of investigating concurrent changes in cerebral blood flow velocity and blood pressure variations during sleep for five apnea patients. Quantitative measure of the rise in the cerebral blood flow velocity and arterial blood pressure are presented. Further, the level of correlation between the rise in the blood pressure and cerebral blood flow velocity is quantified.

II. Materials and Methods

A. Subject Demographics

Data was collected from 5 sleep apnea patients (4 male subjects and 1 female subject) during an 8-hour sleep study in our accredited laboratory (Sleep Consultants, Inc., Fort Worth, TX). The subjects were given complete instructions

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R. Alex is a Ph.D. student with the Bioengineering Department, University of Texas at Arlington, Arlington, TX 76010 USA (phone: 801-897-8353; fax: 817-272-2251; e-mail: raichelmary.alex@ mavs.uta.edu).

G. Bhave is with University of Texas at Arlington, Arlington, TX 76010 USA (e-mail: gauri.bhave@gmail.com).

M. A. Al-Abed is Ph.D. student with Bioengineering Department, University of Texas at Arlington, Arlington, TX 76010 USA (e-mail: mohammad@uta.edu).

A. Bashaboyina is with Bioengineering Department, University of Texas at Arlington, Arlington, TX 76010 USA (e-mail: ab86work@gmail.com).

S. Iyer is with Bioengineering Department, University of Texas at Arlington, Arlington, TX 76010 (e-mail: swathi.iyer@gmail.com).

D. Watenpaugh is the Director of Sleep Consultants, Inc. Fortworth, TX 76104 USA (e-mail: dwatenpaugh@texaspulmonary.com).

R. Zhang is with Presbyterian Medical Center of Dallas, Dallas, TX 75231 USA (e-mail: zhangr@wpmail.phscare.org).

K. Behbehani is Professor and Chair of the Bioengineering Department, University of Texas at Arlington, Arlington, TX 76010 USA (e-mail: kb@uta.edu).

about the experiment and signed an informed consent that was reviewed and approved by the institutional review board. The mean Apnea-hypopnea index (AHI) for this group was 57.94±25.73. The subject demographics are as shown in Table I.

TABLE I
SUBJECT DEMOGRAPHICS

Subjects	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
4 M, 1 F	53.60±7.40	166.10±6.60	93.00±23.60	33.66±7.27

B. Blood Pressure and Cerebral Blood Flow Measurements

The noninvasive beat to beat blood pressure (BP) was monitored continuously over the night using Nexfin HD monitor (BMEYE, Amsterdam, Netherlands). This monitor works on the principle of Finapres volume clamp method of dynamic unloading of finger arteries which can be represented using the following equations;

$$P_t = P_a - P_c \quad (1)$$

where P_t is the transmural pressure, P_a is intra arterial pressure and P_c is external cuff pressure [10].

Since the subjects in this study did not have a preference over the hand on which blood pressure measurement was done, left hand middle finger was used for all the subjects. An integrated heart reference system (HRS) is provided with the Nexfin unit that compensates for changes in the elevation of the finger probe relative to the heart. Thus, 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 can be made.

The blood flow velocity in the Middle Cerebral Artery (MCA) is measured since it is one of the major arteries supplying blood to the brain. The velocity of blood flow through the MCA was measured using a Transcranial Doppler (TCD) (DWL, Compumedics, Singen, Germany) [11].

A simplified diagram illustrating the principle of operation of the TCD is shown in Fig 1. The blood flow velocity, *v,* can be calculated using the following equation

$$v = f_d c/[2 f_t Cos(\theta)] \quad (2)$$

where *c* is the velocity of sound in tissue in cm/s , θ is angle of insonation (degrees), f_d is Doppler shift (Hz) and f_t is transmitted beam frequency (Hz) [12].

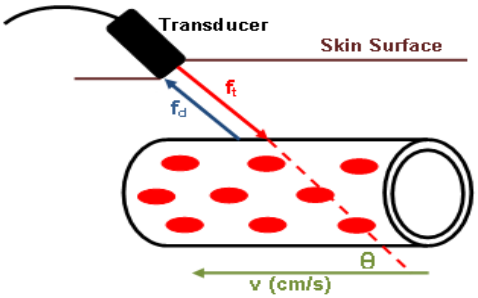

Fig. 1. Principle of Ultrasound Doppler. Here f_d is Doppler shift (Hz) and f_t is transmitted beam frequency (Hz). If a red blood cell is moving with a velocity v (cm/s), with the beam to flow angle θ, the velocity can be calculated by measuring the frequency shift of the reflected wave.

For cerebral blood flow velocity measurement, transtemporal approach was used by attaching a 2MHz transducer on the temporal region of the volunteer's cranium, just in front of the ear. The ultrasonic beam was adjusted to insonate the root of the MCA. To be sure that the signal obtained is from the MCA, specific rules were followed. We checked that the flow was towards the probe and that the strongest signal was found at the depth of about 60mm.

C. Polysomnography

The blood pressure and cerebral blood flow were recorded concurrently with full polysomnography recording. Specifically, polysomnography was conducted on subjects who have been previously diagnosed of having obstructive sleep apnea. Electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), oral and nasal airflow, chest and abdominal movement, leg movements, snoring, blood oxygen and carbon dioxide saturation, blood pressure, cerebral blood flow and a video monitoring of the subject were recorded for the entire polysomnography. Identification of sleep stages and apnea scoring were done by a certified expert sleep lab technician blind to objectives of this study.

D. Data Analysis

The analog outputs from TCD and BP measurement systems were sampled at 1 kHz and analyzed using a custom designed Labview software (National Instruments, Austin Texas). 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 separate apnea and normal breathing segments. In this preliminary study we have used 75 normal breathing and 80 apnea clips from all the five subjects. Custom made peak detection algorithm was used to detect the peaks and valleys during for each of these clips [13]. Once the peaks are detected, all the subsequent peaks are compared to the initial peak value and percentage rise of the peaks compared to the first peak is calculated as follows

$$D_i = \frac{P_i - P_1}{P_1} \text{x} 100 \qquad (3)$$

where D_i is the percent change in the peak value between the i[th] peak (P_i) and the first peak, P_1, at the beginning of the apnea / normal breathing epoch. Fig 2 illustrates the peak detection and delta (D_i) calculation. For clarity, we designate the values of D_i computed for BP as D_i^b and for TCD as D_i^t.

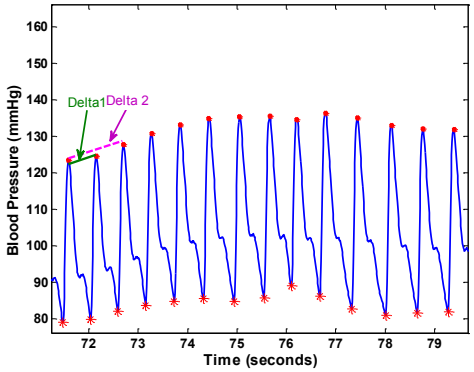

Fig. 2. Peak Detection and Delta Calculations. Delta 1 represents the difference between initial peak and the succeeding peak where as delta 2 is the difference between initial peak and the third peak.

The output of peak detection algorithm was visually inspected to correct any errors in detecting the peak values. The delta and percentage rise for both cerebral blood flow velocity and blood pressure were calculated for all the normal breathing and apnea episodes and was compared with each other.

III. Results

A. Apnea Effect on Pressure and Cerebral Hemodynamics

Fig 3 shows the trend of cerebral blood flow velocity and blood pressure during apnea and post apnea period.

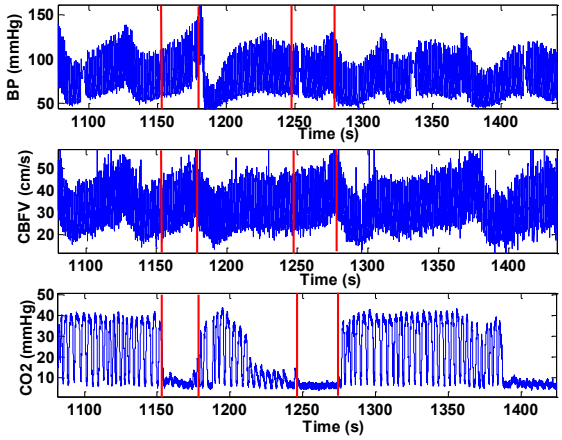

Fig. 3. Rise in Blood Pressure and Cerebral Blood flow Velocity. Apnea episodes indicated by red markers, induced simultaneous rise in both blood pressure (BP) and cerebral blood flow velocity (CBFV). Carbon dioxide (CO_2) waveform is shown for the ease of visual identification of apnea.

As seen from Fig. 2, the decline in breathing during apnea episodes resulted in an elevation of both blood pressure and cerebral blood flow velocity.

Correlation of Blood Pressure (D_i^b) and Cerebral Blood Flow(D_i^t)

The percentage rise for both blood pressure and cerebral blood flow velocity were calculated during normal breathing and apnea episodes using the equation (3). Fig. 4 shows an example of percentage rise in both waveforms during a single apnea episode.

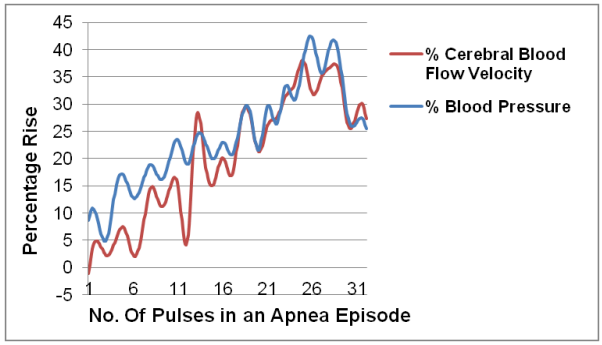

Fig. 4. Representative plot of D_i^b in blood pressure and cerebral blood flow velocity D_i^t. This figure shows that the rise in CBFV occurs as BP rises during an apnea episode.

For each subject, the percentage of rises in blood pressure and cerebral blood flow velocity were grouped as normal and apnea. Then, the average of Pearson product moment correlation coefficients (r) for each mode of respiration (i.e. normal and apnea) is calculated. Table II provides summary of the result.

TABLE II
AVERAGE PEARSON PRODUCT MOMENT CORRELATION COEFFICIENT (R) ALONG WITH STANDARD DEVIATION FOR D_i^b AND D_i^t FOR ALL SUBJECTS

Subjects	Normal	Apnea
1	0.26±0.08	0.56±0.11
2	0.18±0.05	0.55±0.20
3	0.16±0.03	0.69±0.14
4	0.48±0.06	0.67±0.15
5*	0.23±0.08	0.33±0.11

* See discussion section for an explanation of the low average correlation coefficient for subject 5.

TABLE III
AVERAGE CORRELATION COEFFICIENT (R) ALONG WITH STANDARD DEVIATION FOR PERCENTAGE RISE IN BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VELOCITY DURING RESPIRATORY STAGES

Respiratory Stages	R value
Normal*	0.28±0.26
Apnea*	0.61±0.16

* Average excludes data from subject 5, as TCD recordings showed no rise while BP rose measurably for this subject. If the result for subject 5 is included, the average values will be 0.27±0.26 and 0.57±0.18 respectively.

To obtain mean correlation coefficients for normal breathing and apnea events, the correlation coefficients for all the subjects are pooled together based on the respiratory stages and the average value is found out for each stage. Table III gives the mean correlation coefficient during each respiratory stage.

A t-test of the means of correlation coefficients of D_i^b and D_i^t for apnea and normal breathing across all subjects was conducted. T-test yielded a p-value of 0.008. The level of significance was set a priori at α=0.05. Hence the results indicate that there is a significant difference in the mean correlation during apnea episodes compared to normal breathing.

IV. Discussion

The result of this preliminary investigation showed that in all five subjects tested, apnea mediates a rapid and significant rise in the instantaneous blood pressure as the cession of breathing progresses. The blood pressure then drops when apnea episode ends. As seen by the typical result in Fig 3, the results confirm highly similar results that we have previously reported based on simulated sleep apnea [9].

Recent studies have examined variations in cerebral blood flow velocity to quantify impaired cerebral auto regulation in awake sleep apnea subjects [8]. In this study, we have used the peak values of CBFV to detect the maximum rise in brain blood flow resulting from an apnea episode. The results showed that concomitant with the rise in BP, there is a measurable rise in cerebral blood flow velocity in 4 out of five subjects, confirming similar observation in simulated sleep apnea. One subject, as indicated in Table III, showed remarkably stable cerebral autoregulation that did not rise as the blood pressure rose during apnea episodes. While additional investigation is needed to ascertain the possible reasons for such difference, it is to be noted that the subject had normal body mass index (24.4kg/m^2), by far the lowest in the subject pool. Also, the subject's apnea index was low; only 27 apneas in 7 hours of test were recorded. However, the subject had a large number of hypopneas.

The percentage rise graph shown in Fig 4 indicates that the rate of rise in cerebral blood flow velocity is comparable to the rate of rise in arterial blood pressure. The average correlation of BP and TCD during apnea is significantly larger than the correlation during normal breathing: from 0.57 to 0.61 versus from 0.27 to 0.28 respectively. Since both the arterial blood pressure as well as the cerebral blood flow rises significantly during apnea compared to normal breathing, it suggests that the cerebral autoregulation becomes ineffective during apnea.

V. Conclusion

This study investigated the concurrent rise in arterial blood pressure and cerebral blood flow during sleep apnea and has found reasonable correlation between the rises of both physiological signals during apnea episodes. The results suggest that the autoregulation mechanism may not be able to compensate for the effect of apnea-induced blood pressure rise.

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