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Relation between Arterial Blood Pressure and Cerebral Blood Flow Velocity in Simulated Sleep Apnea

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***Abstract*—Obstructive Sleep Apnea (OSA) is one of the most common breathing disorder, affecting approximately 27% of U.S. adults. Limited data have suggested that OSA causes cerebral autoregulation impairment, thus being an important risk factor to stroke. The objective of this paper is to investigate and measure the relation between arterial blood pressure (BP) and cerebral blood flow velocity (CBFV) in simulated apnea. Sixteen healthy subjects (9 male, 7 female) of 29±4.89 yrs age and body mass index of 24.07±4.84 kg/m^2 participated in the study. Four protocols were used; sitting 30 seconds, 90s, and supine 30s and 90s. Our results showed that systolic BP and peak CBFV were correlated with average r= 0.672 ±0.265. Also, CBFV exhibited a significantly higher percent rise than BP. Thus, our findings suggest that cerebral autoregulation may be impaired during apnea episodes.**

I. Introduction

Obstructive sleep apnea (OSA) is the next most common breathing disorder after asthma affecting approximately 27% of U.S. adults [1]. It is characterized by the cessation of airflow for more than 10 s, caused by repetitive pharyngeal collapse during sleep [2]. The absence of breathing results in hypoxemia and hypercapnia. This alteration leads to increased sensitivity of both peripheral and central chemoreceptors, thus activating the sympathetic outflow and causing an increase in blood pressure [3].One of the major mechanisms of cerebral circulatory control is cerebral autoregulation. Cerebral autoregulation represents the intrinsic ability to maintain a constant blood perfusion during fluctuations in its perfusion pressure. OSA episodes disturb the cerebral circulatory control by the rapid elevation in arterial blood pressure and oxidative stress. This results in both blood pressure and cerebral blood flow velocity rise. Hence the cerebral autoregulation becomes impaired [4] [5].

The purpose of this study is to investigate and measure the relationship between arterial blood pressure and cerebral blood flow velocity in simulated apnea episodes.

II. Materials and Methods

A. Subject Demographics

This study involved 16 healthy volunteer subjects who didn't suffer from any known sleep apnea or cardiac disorders. The subject demography data is shown in Table I. The protocol for the study was approved by our Institutional Review Board informed and consent was signed by all subjects.

TABLE I
SUBJECT DEMOGRAPHICS

Subjects	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Male (9)	30.11±5.11	172±6.86	77.78±17.99	26.14±4.68
Female (7)	27.57±4.54	158±4.89	53.57±10.78	21.4±3.83

B. Arterial Blood Pressure Measurements by the Nexfin HD technique

Noninvasive beat-to-beat arterial blood pressure waveform was measured by Nexfin HD (BMEYE B.V, Amsterdam, Netherlands). The Nexfin HD uses an inflatable finger cuff with a built-in photoelectric plethysmograph to measure the pulsatile unloading of the finger arterial walls [6]. This technique uses the transmural pressure (P_t) equation shown below as the basis:

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

where transmural pressure (P_t) equals to the difference between intra arterial pressure (P_a) and external cuff pressure (P_c). Thus, when P_t equals to zero, the intra arterial pressure, equals the external cuff pressure, P_c. The finger cuff was placed on the left hand middle finger. An integrated heart reference system (HRS) provided by Nexfin HD was used to correct for any change hydrostatic pressure changes resulting from changes in the finger elevation.

C. Cerebral Blood Flow Measurements by Transcranial Doppler

Cerebral blood flow is measured using Transcranial Doppler (TCD) (DWL, Compumedics, Singen, Germany) [7]. TCD measures the blood flow velocity in the Middle Cerebral Artery (MCA). To enable sufficient transmission of ultrasound through the skull, a low frequency transducer (2MHz) was coated with ultrasonic gel and placed on the temple. A special headgear was used to secure the position of the transducer on the temple, after the MCA signal was detected.

D. Experimental Protocols

In this study, the simulated apnea response was elicited by series of breath hold maneuvers. It is noted that breath hold is a more appropriate maneuver compared to other popular maneuvers such as Muller or Valsalva maneuvers. This is due to the fact that during obstructive sleep apnea the patient does not do a forced exhalation as is the case in

Muller maneuver. Neither the patient exhales against a resistance. The obstruction occurs during inspiration. The experimental protocols consisted of a baseline of 60s of natural breathing followed by the subject voluntarily holding his/her breath for as long as possible. At the onset of each breath hold, a nose clip was placed on the subject's nose to prevent accidental breathing through nostrils. Two sets of experiments were conducted. For Set 1 experiments, once the subject reached the maximum of his/her ability to a hold breath, he/she breathed naturally for 30s before the next breath hold was initiated. This cycle was repeated five times and these breath holds were named as BH1, BH2, BH3, BH4 and BH5 according to the order of occurrence. At the conclusion of the 5th breath hold, the subject remained in the position and breathed naturally while the data recording continued for another 60s. For Set 2, the same sequence of baseline, five breath holds, and 60s of natural breathing after the 5th breath hold was administered, except that 90s, instead of 30s, of natural breathing between consecutive breath holds was applied. In both Set 1 and 2, the experiments, complete dataset were collected in both supine and sitting positions. Hence, there were four experimental protocols in the session: 1) supine with a 30 s interval between breath holds; 2) sitting with a 30 s interval between breath holds; 3) supine with a 90 s interval between breath holds, and 4) sitting with a 90s interval between breath holds. For ease of reference, these four experimental settings are referred to as protocols. The order of the 4 protocols was randomized to diminish any bias due to the experimental sequence.

E. Data Analysis

Apart from monitoring BP and TCD, vital signs like peripheral oxygen saturation, electrocardiogram and end tidal CO_2 measurements were also made. However for this study, we have considered only the blood pressure dependence of cerebral blood flow velocity. It is important to note that it is not intended to imply that cerebral blood flow changes depend only on changes in blood pressure, instead the aim is to explore if there is a correlation reflecting the degree of breakdown in cerebral autoregulation.

The analog outputs from BP and TCD measuring devices were sampled at 1 kHz and analyzed using Labview (National Instruments, Austin Texas) and Matlab (Mathworks Inc. Natick, MA) software. In order to process the data for periods of breath hold and natural breathing, a custom-designed graphical user interface (GUI) was developed. Further, a peak detection algorithm was developed to detect peaks and valleys of the BP and TCD waveforms [8]. Within the breath hold period, the detected peaks were interpolated using cubic spline. The peaks are then compared to the initial peak value, P_1. A metric, the final percent rise, is proposed and values were calculated as:

$$P_r = [(P_s - P_1)/P_1] * 100 \qquad (2)$$

where P_1 is the first peak value after breath hold commences, P_s is the last peak value at the end of the breath hold, and P_r reflects the total rise in the BP (or TCD) compared to the first peak in the breath hold interval. Figure 1 shows a representative recording of TCD and the detection of the peaks. For each breath hold, the detected peaks were carefully inspected to prevent any incorrect detection of missed peak.

Using detected peaks for BP and TCD, the percentage rise of each peak compared to the first peak is computed as

$$r_i = \frac{P_i - P_1}{P_1} x100$$

where r_i reflects the relative rise in BP (or TCD) for each beat i compared to the first beat peak detected during the breath hold interval, P_1. This metric when plotted for each beat during the breath hold (Figure 3) provides the trend of the relative rise in BP and TCD due to apnea.

The correlation coefficient for the relative rise in BP and TCD (r_i) as well as the total rise P_r values for blood pressure and cerebral blood flow velocity were calculated for all the five breath holds in all four experiments and compared with each other. The correlation coefficient for interpolated waveforms of r_i values (Figure 3) quantifies how BP and TCD vary in tandem.

III. Results

A. Percent Rise of Blood Pressure and Cerebral Blood Flow.

Figure 2 shows the trend of BP and CBFV during a breath hold maneuver.

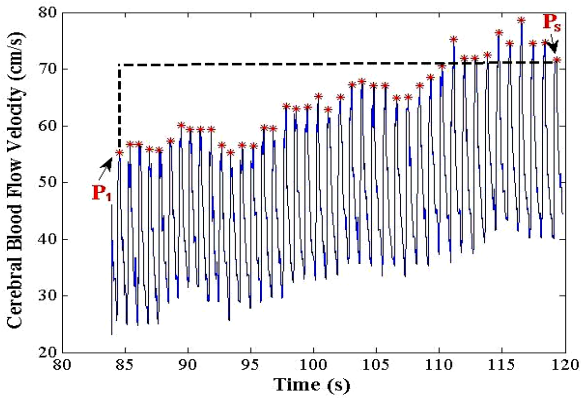

Figure 1. Percent rise calculation. The red asterisks are the detected peaks.

Table II summarizes the percent average rise results for arterial blood pressure and cerebral blood flow velocity.

A. Arterial Blood Pressure and Cerebral Blood Flow Correlation.

The Pearson product moment correlation coefficient (r) was calculated for all five breath holds in all 4 protocols [9]. Figure 3 shows an example of the correlation of percent rise between blood pressure (BP) and cerebral blood flow

velocity (CBFV) during a simulated sleep apnea episode (breath hold) of the protocol with subject sitting and natural breathing period of 30s between breath holds.

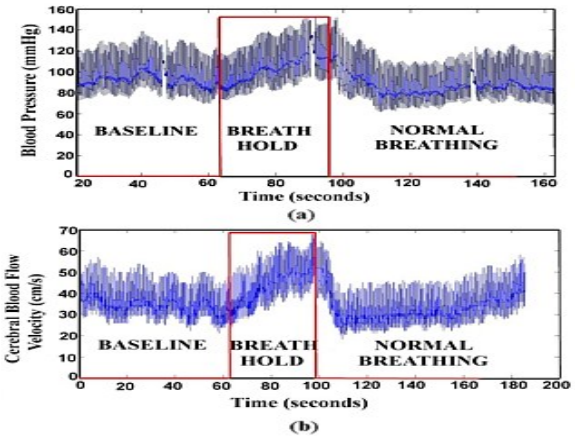

Figure 2. Rise in blood pressure (a) and cerebral blood flow velocity (b) during a first breath hold, a baseline preceding it and followed by natural breathing. The red rectangle marks the simulated sleep apnea episode (breath hold).

TABLE II
AVERAGE AND STANARD DEVIATION OF PERCENT RISE OF BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VELOCITY FOR THE FOUR PROTOCOLS

	Sitting 30s		Sitting 90s		Supine 30s		Supine 90s	
	% BP	% CBFV	% BP	% CBFV	% BP	% CBFV	% BP	% CBFV
BH1	8.52 ±7.92	31.70 ±16.15	11.65 ±6.66	27.54 ±14.51	08.80 ±10.93	20.71 ±13.30	07.10 ±11.27	22.72 ±13.04
BH2	17.55 ±9.00	32.76 ±22.91	12.40 ±9.48	26.49 ±20.88	14.65 ±11.66	23.96 ±15.21	09.16 ±05.36	27.46 ±15.89
BH3	15.84 ±15.60	38.53 ±26.36	12.68 ±8.17	33.24 ±20.15	14.11 ±10.93	34.72 ±16.97	10.35 ±10.17	26.39 ±18.32
BH4	11.53 ±10.52	32.85 ±17.96	09.17 ±8.71	31.85 ±20.76	14.23 ±10.52	33.72 ±18.41	11.24 ±11.00	32.21 ±25.44
BH5	12.35 ±8.50	35.57 ±27.64	10.95 ±9.09	28.67 ±23.65	17.41 ±11.80	31.48 ±16.53	06.45 ±12.33	19.85 ±23.22

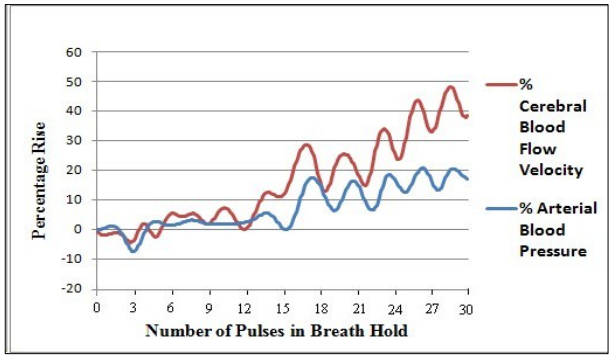

Figure 3.Percentage rise in blood pressure and cerebral blood flow velocity. This figure shows the correlation between them.

Table III shows the average and standard deviations for *r* values for BP and CBFV for all 4 protocols. The correlation coefficients for breath holds, r, are grouped according to the breath hold order for all subjects and the values are computed for each breath hold.

TABLE III
AVERAGE AND STANDARD DEVIATION OF PEARSON PRODUCT MOMENT CORRELATION COEFFICIENT (r) FOR BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VELOCITY

Protocols	Sitting 30s	Sitting 90s	Supine 30s	Supine 90s
	r (avg±std)	r (avg±std)	r (avg±std)	r (avg±std)
BH1	0.710 ± 0.163	0.676 ± 0.247	0.650 ± 0.234	0.601 ± 0.259
BH2	0.607 ± 0.308	0.649 ± 0.338	0.695 ± 0.236	0.748 ± 0.207
BH3	0.662 ± 0.271	0.701 ± 0.233	0.660 ± 0.281	0.690 ± 0.291
BH4	0.667 ± 0.288	0.645 ± 0.288	0.684 ± 0.276	0.663 ± 0.359
BH5	0.697 ± 0.233	0.716 ± 0.185	0.687 ± 0.268	0.635 ± 0.349

B. Statistical Analysis

In order to examine whether the order of breath holds had any effect on the results, one way Analysis of Variance (ANOVA) by IBM SPSS Statistics (International Business Machines Corporation, NY) was done.

The values used were percent rise values and correlation coefficients for the 5 breath holds for all subjects in the four protocols. The analysis showed there was not any significant difference.

To further examine whether the different protocols have any effect on percent rise and correlation values, one way ANOVA followed by post hoc analysis were done. Table IV, V, and VI summarize the results.

TABLE IV
ANOVA ANALYSIS FOR EFFECT OF DIFFERENT PROTOCOLS ON PERCENT RISE OF BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VELOCIY

	Source of Variation	Sum of Squares	df	Mean Square	F	Sig.
% BP	Between Groups	1170.38	3	390.12	3.72	.012
	Within Groups	32292.40	308	104.84		
	Total	33462.79	311			
% CBFV	Between Groups	2879.74	3	959.91	2.47	.062
	Within Groups	119570.34	308	388.21		
	Total	122450.08	311			

df = degree of freedom, F= F test, Sig. = significance; value < 0.05 is considered significantly different.

Also, a Student's t Test was performed on the mean percent rise values of arterial blood pressure and cerebral blood flow velocity. The p values represent the probability that random sampling would lead to a difference between sample means larger than observed. Having a p-

value smaller than 0.05 indicates that there is a significant difference. The Student's T-Test for sitting 30s and 90s, supine 30s and 90s yielded the following results: p=0.004, 0.004, 0.008, and 0.006 respectively.

TABLE V
ANOVA STATISTICS FOR EFFECT OF DIFFERENT PROTOCOLS ON BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VELOCITY CORRELATION

Source of Variation	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	0.223	3	0.074	0.868	0.458
Within Groups	26.665	311	0.086		
Total	26.888	314			

df = degree of freedom, F= F test, Sig. = significance; value < 0.05 is considered significantly different.

TABLE VI
POST HOC ANALYSIS FOR EFFECT OF DIFFERENT PROTOCOLS ON PERCENT RISE OF BLOOD PRESSURE

Group1	Group 2	C.I lower	C.I upper	Sig
Sitting 30s	**Sitting 90s**	-2.5063	6.0486	0.708
Sitting 30s	**Supine 30s**	-4.9357	3.5667	0.976
Sitting 30s	**Supine 90s**	0.0385	8.5668	0.047
Sitting 90s	**Supine 30s**	-6.6644	1.7531	0.434
Sitting 90s	**Supine 90s**	-1.6904	6.7534	0.410
Supine 30s	**Supine 90s**	0.7919	9.1824	0.012

C.I lower=lower limit of 95% confidence interval; C.I upper=upper limit of 95% confidence interval; Sig= significance; value < 0.05 is considered significantly different.

IV. DISCUSSION

Our findings showed that there is a reasonable correlation between the level of rise in blood pressure and cerebral blood flow velocity in simulated apnea episodes, as exemplified in Figure 3. Table III shows a correlation R value $\geq$ 0.65 for most of the breath holds in all protocols. Figure 2 shows the general trend that not only are they correlated, they both elevate rapidly at the beginning of the breath hold and keep rising as the simulated apnea episode continues, then decrease dramatically when natural breathing is resumed.

The data was further analyzed for any dependence of percent rise in BP and CBFV and their correlation on the order of breath holds. One-way ANOVA results showed that there is no significant difference in the correlation among different breath holds in the four protocols. Thus, the order of breath holds does not have any effect on the BP- CBFV relation. This finding suggests that at the apnea frequencies tested in this study (i.e., once every 30s or ever 90s), there is no significant change across the five simulated episodes.

The effect of the four protocols was also examined. One-way ANOVA results shown in table VI indicated that there is a significant difference in the BP percent rise among the experiments. The post hoc analysis in Table V showed that this difference involves sitting 30s vs. supine 90s, and supine 30s vs. supine 90s, with supine 90s having significantly lower percent rise in both cases. This suggests that experiencing apnea in supine position may result in less of a rise in blood pressure compared to sitting position.

The student's T-Test results show that cerebral blood flow velocity rises significantly higher than arterial blood pressure. This suggests that cerebral autoregulation cannot effectively compensate for the rise in the blood pressure.

V. CONCLUSION

The study results show that a strong, concurrent elevation in blood pressure and cerebral blood flow velocity occurs during apnea. This suggests that cerebral autoregulation becomes impaired or less effective during apnea episodes. These findings together suggest that studying cerebral blood flow changes in sleep apnea patients is important to assess the degree of absence cerebral blood flow regulation during sleep apnea and its possible consequences.

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REFERENCES

[1] Tishler PV, Larkin EK, Schluchter MD, Redline S, "Incidence of sleep-disordered breathing in an urban adult population: The relative importance of risk factors in the development of sleep-disordered breathing," *JAMA* 2003; Vol. 7, pp. 289-2230.

[2] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S, "The occurrence of sleep-disordered breathing among middle-aged adults," *N Engl J Med.* 1993;328:1230–5

[3] Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK, "Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea," *Circulation* 1998;97:943-5

[4] Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK, "Altered cardiovascular variability in obstructive sleep apnea," *Circulation* 1998;98:1071-7.

[5] [8] F. Urbano, F. Roux, J. Schindler, and V. Mohsenin, "Impaired cerebral autoregulation in obstructive sleep apnea," *J Appl Physiol*, vol. 105, pp. 1852-7, 2008

[6] Sipkens LM, Treskes K, Ariese-Beldman K, Veerman DP, Boer C, " Application of Nexfin noninvasive beat-to-beat arterial blood pressure monitoring in autonomic function testing," *VU University Medical Center*. 2011; 16(5):246-51.

[7] Jose´ Manuel Valdueza, Jorn Oliver Balzer, Arno Villringer, Thomas Josef Vogl, Raphael Kutter, and Karl Max Einha¨upl, " Changes in Blood Flow Velocity and Diameter of the Middle Cerebral Artery during Hyperventilation: Assessment with MR and Transcranial Doppler Sonography," *AJNR Am J Neuroradiol* 1997; 18:1929–1934.

[8] R. Alex, "Quantitative variation of Blood Pressure dynamics during sleep apnea," *M asters Thesis*, University of Texas Arlington, Texas, 2010.

[9] Toby Segaran, "Programming Collective Intelligence," *O'Reilly Media, In.* 2007.