Quantitative Assessment of Apnea-Induced Dynamic Blood Pressure Variations

Raichel M Alex¹, Hyung W Chun², Shan Sun-Mitchell², Donald E Watenpaugh³ and Khosrow Behbehani¹*

¹Department of Bioengineering, University of Texas at Arlington, USA
²Department of Mathematics, University of Texas, USA
³Department of Integrative Physiology, University of North Texas Health Science Center, USA

Abstract

Purpose: To characterize obstructive sleep apnea (OSA) induced blood pressure (BP) variations, using quantitative features derived from BP waveform such as area under beat-to-beat pressure cycle, slope of systolic and diastolic time series, and pulse pressure.

Methods: Firstly, to assess the effects of breathing cessation on BP, separate from sleep effects, multiple breath hold maneuvers were performed by 26 volunteer healthy subjects (Age: 26.05±3.2 years, BMI: 24.67±3.45 kg/m²). Effects of apnea severity and posture on BP variations were studied by varying inter-breath hold intervals and subject’s postures. Second study was conducted on 5 OSA patients (Age: 53.60±7.40 years, BMI: 33.66±7.27 kg/m², AHI: 57.94±25.7) during overnight polysomnography, to validate the findings.

Results: Proposed features were sensitive to simulated apnea and OSA effects (p<0.001). Area proved to be responsive to postural changes whereas systolic and diastolic pressures did not. Furthermore, Area and pulse pressure were sensitive to the frequency of simulated apnea.

Conclusion: Dynamics of apnea-induced BP variations can be characterized more thoroughly by the proposed features derived from BP waveform.

INTRODUCTION

Blood pressure (BP) variations elicited by obstructive sleep apnea (OSA) have been explored in both nocturnal (i.e. in OSA patients) and awake (simulated apnea) studies using single-point determinants such as systolic pressure (Systolic), diastolic pressure (Diastolic) and mean arterial pressure (MAP) [1-7]. While these features have been valuable, the ability to record and analyze whole arterial pressure waveform provides an opportunity to explore additional features for improved diagnosis, treatment and monitoring. Pulse pressure (Pulse), area under beat to beat pressure waveform (Area) and rate of rise in systolic (Systole) and diastolic (Diaslope) pressures are examples of such features. These features provide useful information about arterial stiffness, pulse wave reflection, arterial compliance, etc. Pulse pressure is an independent risk factor for predicting myocardial infarction and stroke in middle aged to older adults where OSA is most prevalent [8,9]. Area depends on heart rate, arterial constriction and/or vasodilation [10]. Systole and Diaslope is as an indicator of the progressive rise in BP due to sympathetic and bar reflex activation [11].

Benefits of these features in quantifying OSA effects have not been adequately explored. In this study, we examined the efficacy of Pulse, Area, Systole and Diaslope together with single-point measures (Systolic, Diastolic and MAP) in quantifying apnea induced BP variations. To separate the influence of sleep disruption or other cardiovascular ailments present in OSA subjects, first part of the study explored effects of apnea via multiple breath holds on healthy volunteers. Effects of apnea frequency, postural changes and apnea duration on BP were also determined. Finally, efficiency of proposed BP features during OSA was assessed in an overnight sleep study of OSA patients.

MATERIALS AND METHODS

Data Acquisition

Continuous non-invasive beat to beat BP monitoring was obtained from finger arterial pressure (NetFind HD by BMEYE,
Amsterdam, Netherlands). NetFind accuracy has been compared to intra-arterial and auscultatory pressure measurements, and good agreement has been found: -1±7 mmHg for systolic, 3±6 mmHg for diastolic, 2±6 mmHg for MAP and -3±4 mmHg for pulse pressure [12-14]. BP sensor was placed on the left hand middle finger for all subjects. Data was acquired at 1000 Hz using data acquisition system (DAQ) and Lab VIEW 9.0 (National Instruments, Austin, TX). Digitized data were further imported into MATLAB (Math works Inc. Natick, MA) for feature extraction and analysis.

Area is determined by numerically integrating the pressure waveform between consecutive diastolic troughs (Figure 1a) and is computed for each cardiac cycle separately. Systole and Diaslope are evaluated by fitting a least mean squared error (regression) linear line to the systolic and diastolic pressure values during an apnea event followed by slope computation (Figure 1b).

**Subject Demographics**

First, to determine the effect of apnea (breathing cessation) – independent of possible sleep impact - 26 volunteers (15 Male, 11 Female; Age: 26.05±3.2 years; BMI: 23.02±3.8 kg/m^2) with no known sleep or cardio-respiratory disorders were recruited. Validation study consisted of overnight polysomnography on 5 OSA patients (4 Males, 1 Female; Age: 53.60±7.40 years; BMI: 33.66±17.27 kg/m^2; apnea-hypopnoea index (AHI): 57.94±25.7). Subjects were given complete instructions about the experiments and signed an Institutional-Review-Board-approved consent form.

**SIMULATED APNEA STUDY**

**Experimental Protocol**

Subjects were asked to avoid caffeinated drinks at least 6 hours prior to the study. To investigate the effect of apnea frequency, two protocols, A and B, were devised. Both protocols started with baseline (BL) recording for 60, with subject breathing normally. At the end of BL, subjects were instructed to exhale completely and hold their breath as long as they can. A nose clip was placed to prevent any accidental breathing. Breath hold (BH) was followed by an inter-BH interval of 90s in Protocol A and 30s in Protocol B. This sequence was repeated for five times (BH1, BH2, BH3, BH4 and BH5). Upon the completion of BH5, a post BH period of 60s was given. Further, in order to investigate whether the subject position – supine or sitting – had any influence on BP response, both Protocol A and B were conducted in sitting and supine posture of the subject. Hence, 4 sets of data were generated: sitting A, sitting B, supine A and supine B. Each subject randomly selected a posture, followed by randomization of the order of protocols within each posture.

**Data Analysis**

Using custom designed graphical user interface (GUI) [16], BP features were extracted as illustrated in (Figure 1a, 1b) along with duration, for BH and BL events. It was hypothesized that BP features, both proposed and single-point metrics, show significant dynamic changes due to apnea. We also hypothesized that temporal separations between apnea episodes or apnea frequency (Protocol A vs B) as well as subject’s posture (sitting vs. supine) significantly affect BP. Following statistical analyses were carried out using SAS 9.2 (Cary, NC) with α = 0.05 and were corrected for multiple comparison errors. Normality of features was tested using Kolmogorov-Smirnov (K-S) D statistics.

a. **Effect of Breath Hold:** Repeated measures ANOVA with “CONTRAST” option was used to test whether the extracted BP features are responsive to BH. CONTRAST option compares mean of the features during each BH with BL.

b. **Effect of Apnea Frequency:** Analysis of covariance (ANCOVA) with BH duration as a covariate on a 2x2 cross-over design was used.

This design was chosen since each subject repeated ‘BH – normal breath’ five times within a protocol and underwent both Protocol A and B for each posture [17,18].

c. **Effect of Posture:** As explained earlier, in due consideration of subject’s comfort, each subject selected either sitting or supine posture at will, followed by randomization of protocols within the assumed posture. Therefore, both protocol A and B were applied in the selected posture before the posture was changed.
precluding the application of crossover design analysis. Hence to determine postural effect, average of both protocols A and B was taken in a given posture and paired t-test was conducted.

d. Effect of Breath Hold Duration: In order to explore the relation between apnea duration and BP response, we used linear regression model with BP features as dependent variables and BH duration as independent variable.

**SLEEP APNEA STUDY**

**Experimental Protocol**

In addition to continuously recording BP, polysomnography data was recorded on sleep diagnostic system integrated with Sandman Elite software (Embla, Broomfield, CO). Data from Sandman and DAQ were synchronized to ensure that there is no time delay.

**Data Analysis**

Identification of sleep stages and apnea scoring were done by a certified sleep technician blind to objectives of this study. Custom designed GUI was utilized for segmentation of BP waveform into normal breathing and OSA events, followed by feature extraction. A t-test with unequal variance (α=0.05) was used to analyze the efficacy of BP features in reflecting physiological responses to OSA.

**RESULTS**

Upper panels of (Figure 2a) show an example of BH-induced elevation of BP. Detectable and fairly repeatable BP elevation during all five BH episodes, followed by recovery to baseline during inter-BH intervals was observed in both protocols during supine and sitting posture. (Figure 2b) shows representative cyclical variations in BP during OSA episodes, comparable to the results obtained during BH.

**Simulated Apnea Study**

a) Effect of Breath Hold: BP features extracted from each of the five BH’s during all four experiments were pooled together (BH Aggregate). Overall Mean±SD values were (in mmHg): Systolic: 131.52±12.99, Diastolic: 77.31±10.13, MAP: 95.32±10.62, Pulse: 54.03±7.03, Area: 8346±1757, Systole: 0.51±0.48 mmHg/s and Dias lope: 0.46±0.35 mmHg/s. Further, two-tailed t-test with unequal variances on BH Aggregate vs BL, were significant (p<0.0001; α=0.05) for all these features. Afterwards, BH1, BH2, BH3, BH4 and BH5 from all four experiments were independently compared against BL. Results from repeated measures ANOVA (p<0.0001; α=0.05) showed that, all BP features are significantly different during any BH period compared to BL.

b) Effect of Apnea Frequency: During K-S test, Area (p=0.02), Systole (p=0.015) and Dias lope (p=0.021) in supine posture, and BH duration (p=0.034) in sitting posture did not follow Gaussian distribution, requiring data transformation and outlier removal with Mean±2SD as threshold. Outliers were removed from Area (p=0.15) and Systole (p=0.27); and for BH duration (p=0.15) and Dias lope (p=0.43), outlier removal was followed by log transformation.

c) Effect of Posture: BP features from all five BHs during Protocol A and B were pooled for sitting and supine postures. Only Area proved to be significantly different for sitting vs supine (p=0.04, α=0.05).

d) Effect of Breath Hold Duration: Average BH durations were: 29.79±10.99s (Supine A), 30.09±10.66s (Supine B), 30.63±12.90s (Sitting A) and 28.67±8.83s (Sitting B). Log transformation was performed on Area and Systole in supine posture prior to regression analysis. Slope of regression line was positive for all features in both postures (Table 2a,2b). Statistically significant slope was obtained for Systolic, Diastolic, and MAP in sitting posture.

**Sleep Apnea Study**

Subjects were tested for 6.7±2.94 hours. Random samples of 117 OSA (duration=31.23±15.36s) and 107 normal breathing (duration=35.87±10.33s) episodes, were selected. Each subject contributed at least 20 OSA and normal breathing events. Two tailed t-test with unequal variances showed that the proposed BP features during OSA were significantly different from normal breathing (p<0.001).
We further noticed that, while mean AHI was 57.94±25.7, major contributing factor was hypopneas (59% of all events). Average OSA events/hour was found to be 24.88±25.22. Hence, on an average, subjects experienced an OSA event at every 144s.

Further, BP features during BH maneuvers were compared against OSA using t-test with unequal variance (Table 3).

### DISCUSSION

This study aimed to obtain a more detailed quantitative characterization of BP variations during apnea by examining measures derived from continuous BP waveform as well as single point measures. Effects of apnea severity and posture were also explored. Lastly, OSA induced BP changes were compared with that of voluntary BHs.

Comparison of BP variations during BH and OSA events (Figure 2) reveals a repeatable and significant BP rise during breathing cessation. All BP features exhibited sensitivity to apnea (p<0.001), hence can be considered for quantifying apnea effects on blood pressure. Increase in pulse pressure may be due to temporary increase in arterial stiffness resulting from sympathetically mediated vasoconstriction, or increased cardiac stroke volume driven by isotropic effects of sympatho excitation, or both. Moreover, central arterial stiffness increases with aging - an OSA hallmark - can result in more prominent rise in systolic than in diastolic pressure resulting in increased baseline pulse pressure [8]. The combined effect may lead to elevated pulse pressure during apnea episodes, as suggested by the findings of Logan et al [19] that women affected by drug resistant hypertension and OSA exhibited a higher pulse pressure than those without OSA.

Our results showed an increase in Area under beat to beat BP waveform. This can be attributed to the increase in either pressure amplitude or temporal length of pressure pulse. During initial stages of breathing cessation, heart rate slows down due to increased vagal tone thereby increasing duration of pressure pulse, leading to rise in Area [20]. As apnea prolongs, sympathetic nerve activation causes significant rise in pressure amplitude and heart rate (i.e. lower duration). An overall increase in Area suggests that, shorter pulse (i.e., increased heart rate) is offset by the degree of rise in pressure amplitude.

Absence of ventilation reduces arterial $O_2$ and elevates $CO_2$, resulting in sympathetic outflow. Further, breathing against occluded airway leads to negative intra-thoracic pressure thereby removing sympathetic inhibition from pulmonary stretch receptors and carotid sinus bar receptors [21,22]. This sympathetic outflow increases arterial resistance and stroke volume, thereby increasing BP. Our results -significant rise of Systole and Diastole during apnea – are in agreement with findings by Aardweg et al [7] and Morgan et al [23] who have shown that repetitive hypoxias – induced by breath-hold – can cause periodic hypertensive episodes. Similar swings in BP have also been observed in OSA [21,24,5].

Effect of apnea frequency was examined by choosing protocols such that in Protocol B, BH occur every 30s which is three times faster compared to 90s in Protocol A. Results (Table 1) suggest that apnea frequency had significant effect on Systolic pressure and MAP in both sitting and supine postures (i.e., irrespective of subject’s posture); Diastolic pressure and Area in sitting posture; and Pulse pressure in supine position. Possible explanation is that an inter-BH interval of 90s provides adequate time for BP to return to baseline values, while an inter-BH interval of 30s does
not, thus leading to cumulative effect. However, rate of rise in pressures was insensitive to these temporal separations.

Postural effect on apnea induced BP variations was examined since it has been shown that supine posture worsens OSA severity [25], while sleeping in 60 degree upright posture significantly reduces AHI and improves SaO₂ [26]. However, BP features proved to be insensitive to postural changes except Area. Area is the only parameter which depends on both heart rate and BP. Heart rate is dependent on body position [27] and might explain why Area is sensitive to posture. This illustrates that multi-parameter characterization of BP may reveal differences which are not discernable through use of single-point parameters. Magnitude of BP rise induced by Systolic, Diastolic and MAP were sensitive to BH duration (Table 2a,2b) in sitting posture. This hints that while longer duration pressure rise result in higher level of BP, the rate of BP rise may not vary based on duration. All BP features proposed in this study, were responsive to OSA events as well. Further, Systolic during BH and OSA were not significantly different from each other (Table 3). Hence, Systole during simulated apnea might be useful in estimating OSA induced rate of rise in systolic pressure. It is noteworthy that, Dias lope for protocol A – in both supine and sitting – was not significantly different from Dias lope during OSA (Table 3). Similarly, MAP for Sitting A was not significantly different from MAP during OSA. This may be attributed to comparable average time of 144s between OSA events (Results: 2. Sleep Apnea Study) and 120s between BHs in protocol A (90s inter-BH interval+30s average BH duration).

A point of consideration about the findings is physiological conditions and responses of subjects recruited for simulated apnea study may be different from OSA subjects, due to age differences. Nonetheless, this study demonstrated that even in young healthy subjects, apnea induces significant BP variations. Further, it has been suggested that voluntary BHs may not completely mimic OSA, due to absence of negative intra-thoracic pressure [15]. However, it is reasonable to expect chemoreceptor stimulation to be more dominant in generating apnea induced neuro circulatory response than intra-thoracic pressure since it has been shown [23] that BHs and sustained Mueller maneuvers cause similar chemoreceptor stimulation and sympathetic activation. Moreover, our results indicate that, BP features responsive to BH in younger healthy subjects were also sensitive to OSA events in older sleep apnea patients.

**CONCLUSIONS**

This study showed that apnea-induced rapid and spontaneous BP changes can be more accurately quantified when traditional single-point BP features are complemented with features derived from BP waveform. Using these measures, it was demonstrated that rate of systolic rise is similar for awake subjects voluntarily holding breath and OSA events. Apnea severity, subject’s posture and apnea duration influence the level of variations in one or more BP features. In short, all the proposed features are useful markers for quantification of apnea effects on BP.

**REFERENCES**


---

Table 3: Average Blood Pressure Features During Simulated and Sleep Study.

<table>
<thead>
<tr>
<th>Experimental Protocols</th>
<th>Systolic Pressure (mmHg)</th>
<th>Diastolic Pressure (mmHg)</th>
<th>MAP Pressure (mmHg)</th>
<th>Pulse Rate (mmHg)</th>
<th>Area (mmHg)</th>
<th>SysSlope (mmHg/s)</th>
<th>DiaSlope (mmHg/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated Sitting A</td>
<td>133.19±14.18</td>
<td>78.62±10.55</td>
<td>96.75±11.22</td>
<td>54.40±7.98</td>
<td>8288±1755</td>
<td>0.52±0.44</td>
<td>0.47±0.35</td>
</tr>
<tr>
<td>Simulated Sitting B</td>
<td>130.59±13.13</td>
<td>77.13±10.77</td>
<td>94.88±11.09</td>
<td>53.29±6.91</td>
<td>8082±1604</td>
<td>0.47±0.49</td>
<td>0.46±0.38</td>
</tr>
<tr>
<td>Study Supine A</td>
<td>131.02±11.63</td>
<td>76.74±9.11</td>
<td>94.78±9.48</td>
<td>54.12±6.67</td>
<td>8463±1800</td>
<td>0.48±0.49</td>
<td>0.39±0.33</td>
</tr>
<tr>
<td>Sleep Supine B</td>
<td>131.17±12.63</td>
<td>76.64±9.82</td>
<td>94.74±10.38</td>
<td>54.29±6.31</td>
<td>8559±1823</td>
<td>0.57±0.49</td>
<td>0.49±0.32</td>
</tr>
<tr>
<td>Study OSA</td>
<td>137.57±21.37</td>
<td>75.66±10.75</td>
<td>96.29±13.54</td>
<td>61.90±14.45</td>
<td>8152±1751</td>
<td>0.60±0.79</td>
<td>0.36±0.47</td>
</tr>
</tbody>
</table>

*=significantly different compared to OSA; α=0.05


