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Original Research

The influence of intermittent apnea on aortic hemodynamics in healthy young men

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Abstract

Background: Sleep apnea is known as a high-risk factor for cardiovascular disease (CVD); However, the influence of apnea on aortic blood pressure and augmentation index (AIx), which cardiac load and independent risks for a future CVD event, remains unclear. Therefore, this study aimed to examine the influence of intermittent normoxic apnea on aortic arterial hemodynamics in healthy men. **Methods**: Sixteen healthy young men (23 ± 1.6 years mean ± SD) underwent the repetitive 20-s apnea with a 40 s interval for 20 min. During the interval, each subject maintained a breath pace at 15 breaths/min. Central hemodynamics were evaluated every 5 min by pulse wave analysis from peripheral (radial) arterial pressure waveforms via general transfer function method and compared among three phases defined as "breath" (for 20 s before apnea), "apnea", and "rebreathe" (for 20 s after apnea). The baseline values were calculated from the first breathing cycle and compared with each breathing phase every 5 min. **Results**: Aortic systolic blood pressure and AIx were significantly higher at rebreathe phase than the other phases. Likewise, heart rate and double product (aortic systolic blood pressure × heart rate) were significantly higher in rebreathe phase than the other phases. **Conclusions**: These results suggest that cardiac load is increased by intermittent normoxic apnea, especially during the rebreathing phase.

Keywords: Intermittent apnea; Aortic pressure; Augmentation index

1. Introduction

Sleep apnea syndrome (SAS) is a disorder in which repetitive apnea exposes the cardiovascular system to cycles of intermittent hypoxia [1–3]. SAS is known to involve in the development of arterial stiffness [3,4], cardiac remodeling [5], and left ventricular hypertrophy (LV) [5–7]. In addition, the epidemiologic study showed that SAS has an independent risk factor for stroke and hypertension [2,8]. And hence, SAS is considered a strong risk for cardiovascular disease (CVD). Furthermore, underlying mechanisms have been investigated using the intermittent hypoxia apnea model. Several studies have reported that hypoxia and hypercapnia lead to prolonged muscle sympathetic nerve activity (MSNA) enhancement [9–13].

Recently, aortic hemodynamics has emerged as an essential factor underlying the pathophysiology of CVD [14–18]. For instance, high aortic systolic blood pressure (SBP) and augmentation index (AIx), which indicates augmentation of the aortic pressure in systole derived from the return of pressure waves reflected from the periphery [19–21], predict the development of CVD events and all-cause mortality [18]. Aortic pressure waveform is determined by a forward traveling wave generated by LV ejection and a reflected wave emanating from the peripheral blood vessels that return to the aorta [22]. Even normoxic, intermittent apnea may influence central blood volume and variation in heart rate by switching apnea and rebreathing repeatedly. Then, these responses may alter the timing of the incident wave from the heart and the reflected wave from the periphery. However, it remains to be fully elucidated whether the breathing patterns influence aortic hemodynamics during intermittent apnea. This study aimed to assess the influence of the breathing patterns in intermittent normoxic apnea on aortic hemodynamic. We hypothesized that intermittent apnea raises aortic SBP and AIx.

2. Methods

2.1 Participants

We recruited sixteen healthy young men (23 ± 1.6 year) for the study. Subjects were non-obese (height 173.4 ± 2.5 cm and body mass 66.5 ± 0.5 kg), non-smoking, and free of overt cardiovascular and respiratory disorder. None of the subjects were taking cardiovascular-acting medications. Each subject's habitual physical activity status confirmed initial screening before the experiment via e-mail. We subsequently verified and explored in detail at the experimental visit (by interview and questionnaire).

This study was reviewed and approved by the Institutional Review Board of the National Institute of Advanced Industrial Science and Technology (#2014-495). We have explained to subjects all potential risks and procedures of the study, and they have given their written informed consent to participate in the study.

2.2 Instrumentation and data acquisition

Heart rate (HR) was calculated from an electrocardiogram (ECG) (132 Bio Amp, ADInstruments, Colorado Springs, CO, USA). Radial arterial pressure waveforms were recorded by a validated applanation tonometry-based measurement device (Jentow, Colin Medical Technology, Kyoto, Japan) that was connected to an acquisition system (Powerlab/16SP ML795, ADInstruments, Colorado Springs, CO, USA) interfaced with a personal computer equipped with data acquisition software (LabChart6, ADInstruments, Sydney, Australia). Radial arterial pressure waveforms were calibrated with oscillometry-derived brachial blood pressure. Stored radial arterial pressure waveforms were resampled at 128 Hz with data analysis software (AcqKnowledge, BIOPAC Systems, Santa Barbara, CA, USA) [23] and then transferred into aortic pressure waveforms with an arterial waveform analysis software involving a validated generalized transfer function (SphygmoCor Software Version 8.2, AtCor Medical, Sydney, Australia) [24]. To quantify the magnitude of wave reflection from the periphery to the heart, augmented pressure (AP; peak pressure-pressure at the inflection point at the systolic shoulder) was computed from synthesized aortic pressure waveforms. AIx was also calculated as AP divided by aortic pulse pressure. From the blood pressure waveform, ECG, stroke volume (SV), and cardiac output (CO) was calculated using the Model Flow method, which incorporates sex, age, height, and body mass (Beat Scope 1.0 software, TPD-TNO BioMedical Instrumentation, Amsterdam, The Netherlands) [25]. Total peripheral resistance (TPR) was calculated as mean arterial blood pressure (MAP)/CO. Double product was calculated as aortic SBP $\times$ HR. We measured the fraction of end-tidal carbon dioxide ($ETCO_2$) to check the reduction of end-tidal carbon dioxide concentrations during intermittent apnea (AE 280S Aeromonitor, Minato Medical Science Co., Tokyo, Japan). Percutaneous arterial blood oxygen saturation (SpO_2) was measured using the oximeter pod via a finger clip (MLT321, ADInstruments). $ETCO_2$ and SpO_2, two data could not be accurately measured, as mask or sensor was out of the proper position during breathing intervention. These two data were excluded from the analysis.

2.3 Experimental protocol

The subjects were instructed to abstain from alcohol, caffeine, and vigorous exercise for at least 24 h before the experiments. All measurements were conducted after a 3-h fast. Height and body mass were measured (via a digital scale, BWB-200, TANITA, Tokyo, Japan) at the first visit. All measurements were performed in a quiet room and temperature-controlled room (24–26 °C). Hemodynamics and respiratory parameters were conducted at least 10 min of supine rest. Subsequently, these variables were continuously monitored during intermittent apnea trials.

Fig. 1 shows the experimental protocol. Subjects were instructed to perform the breath, apnea, and rebreathe for 20 s each. The breath and rebreathe were controlled by breathing in time to a metronome set at a pace of 15 breaths/min.

All apneas were performed at functional residual capacity. Subjects normally exhaled before apnea to avoid Valsalva and Muller maneuver. We started the 5 s countdown before starting of apnea and rebreathe phase. Subjects performed intermittent apnea maneuvers of the 20 cycles for 20 min.

2.4 Data analysis

The first breathing cycle, 0–1 min, was analyzed for baseline. Then, the 0–1 min (baseline), 4–5 min (5 min), 9–10 min (10 min), 14–15 min (15 min), and 19–20 min (20 min) were analyzed to assess the effect of the repetitive intermittent apnea on hemodynamics. Two-way ANOVA with repeated measures was performed to determine the effects of breathing phase, time course, and the interaction between them on hemodynamic and respiratory variables. The breathing phase was divided and analyzed three-phase that is before the apnea phase (breath) and the apnea phase (apnea), after the apnea phase (rebreathe). A post hoc test using Bonferroni's method identified significant differences among mean values in a significant F value. One tonometry data were excluded from analysis because these could not obtain data by disturbance of electric signal. All data are presented as mean $\pm$ standard deviation. Statistical significance was set a priori with $p < 0.05$.

3. Results

Table 1 shows the hemodynamic and respiratory parameters. HR, peripheral SBP, DBP, and MAP significantly changed among breath, apnea, and rebreathe phases. Peripheral PP, SV, CO, TPR, and $ETCO_2$ had no significant effects on the time or the breathing phases. SpO_2 showed a significant time-breathing phase interaction, but it was higher than 96% throughout the experiment, suggesting the non-hypoxic condition. Aortic SBP was significantly higher at rebreathe phase compared with the breath and apnea phases, whereas aortic PP did not change significantly (Fig. 2). AP, AIx, and double product were significantly higher at the rebreathe phase compared with the other phases (Figs. 3,4).

4. Discussion

In this present study, we determined the influence of intermittent normoxic apnea on aortic hemodynamics in young men. Aortic SBP, AIx, and double product were

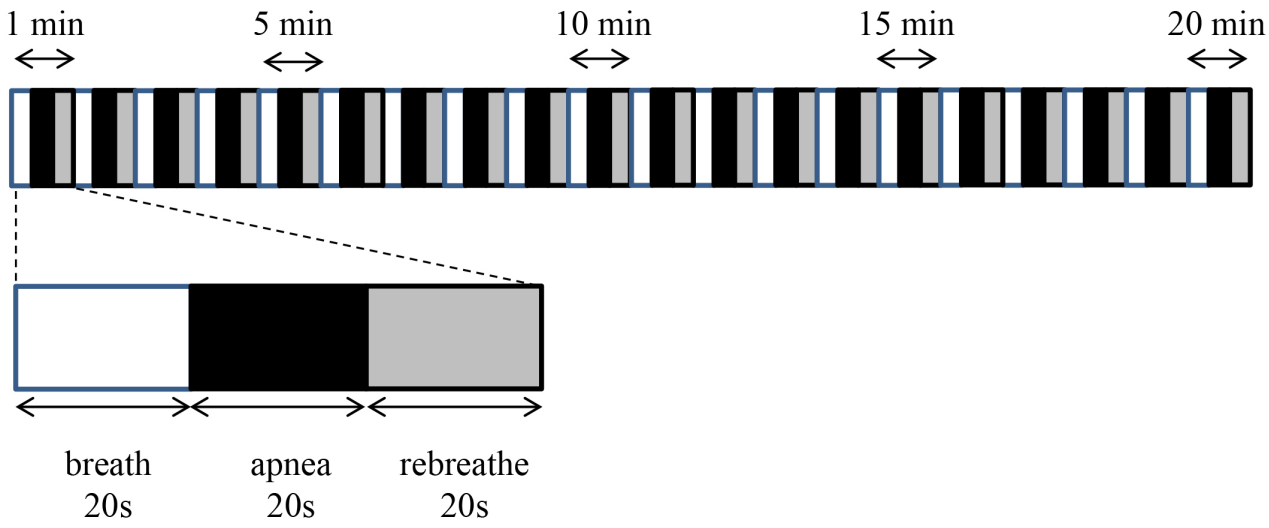

Fig. 1. Diagram of the experimental protocol. The apnea breathing cycle consisted of 20 s of breath, apnea, and rebreathe. Twenty apnea maneuvers were performed over 20 min (one apnea per min). Subjects controlled their "breath" and "rebreathe" in time to a metronome set at a pace of 15 breaths/min.

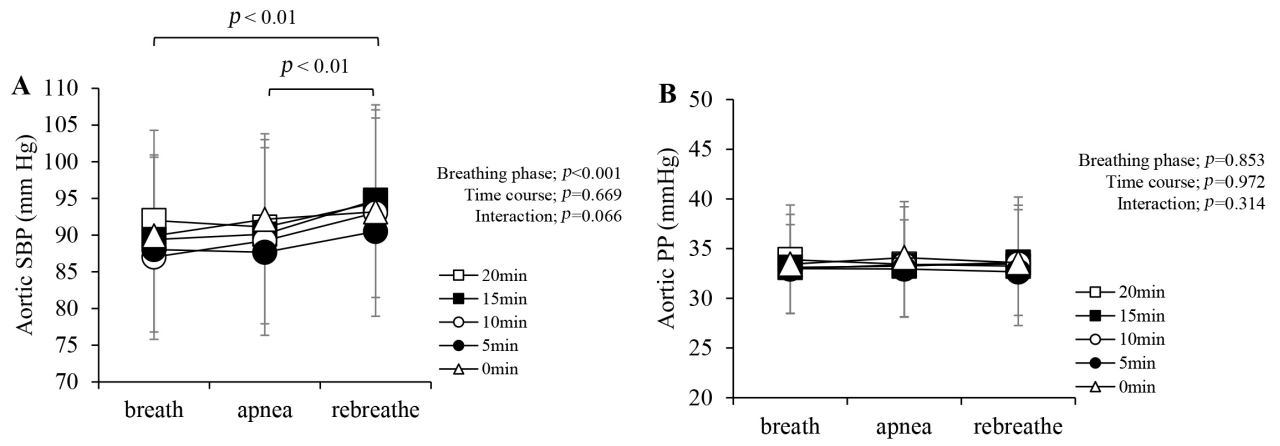

Fig. 2. Response of aortic systolic blood pressure (SBP; A) and aortic pulse pressure (PP; B) at the phase of breath, apnea, and rebreathe during intermittent apnea in 20 min. Error bars represent standard deviations.

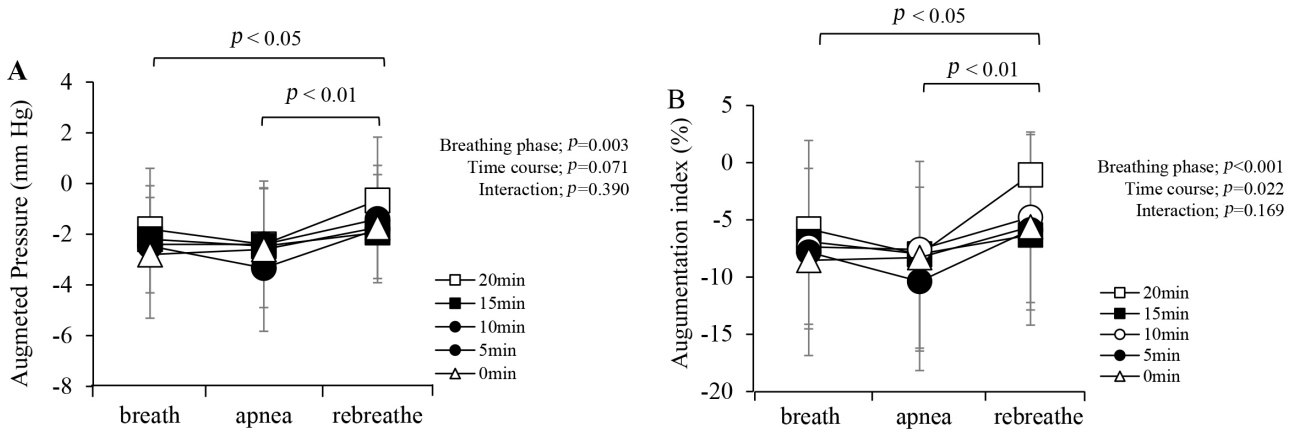

Fig. 3. Response of augmentation pressure (A) and augmentation index (B) at the phase of breath, apnea, and rebreathe during intermittent apnea in 20 min. Symbols represent mean values, and error bars represent standard deviations.

Table 1. Hemodynamic and respiratory variables during the intervention.

Breath		Baseline	5 min	10 min	15 min	20 min	Time	Breath	Interaction
Heart rate (beats/min)	B	52.2 ± 5.3	52.8 ± 5.4	53.0 ± 4.8	52.0 ± 5.7	53.1 ± 6.4	0.81	<0.01	0.64
	A	51.7 ± 5.8	51.0 ± 5.3	51.0 ± 5.4	50.4 ± 5.9	52.1 ± 6.9			
	R	54.5 ± 6.2	53.7 ± 6.1	55.0 ± 6.7	53.5 ± 5.9	55.0 ± 7.5			
Peripheral SBP (mmHg)	B	110.4 ± 13.5	108.0 ± 13.2	108.7 ± 14.7	109.4 ± 12.5	113.2 ± 15.0	0.72	<0.01	0.02
	A	113.8 ± 13.2	108.2 ± 12.8	109.6 ± 12.1	109.9 ± 13.4	111.7 ± 15.0			
	R	115.0 ± 14.0	110.1 ± 13.0	113.3 ± 15.0	114.9 ± 13.8	113.4 ± 14.8			
Peripheral DBP (mmHg)	B	57.4 ± 9.4	55.8 ± 10.1	56.3 ± 10.9	57.0 ± 9.8	59.0 ± 9.4	0.61	<0.01	0.19
	A	58.6 ± 9.4	55.4 ± 10.5	56.5 ± 10.0	57.3 ± 9.8	58.2 ± 9.0			
	R	59.5 ± 8.5	57.8 ± 8.9	59.4 ± 9.8	61.2 ± 10.0	61.2 ± 7.7			
MAP (mmHg)	B	73.2 ± 9.6	71.5 ± 10.4	72.2 ± 11.5	72.9 ± 10.6	76.3 ± 11.0	0.42	<0.01	0.05
	A	75.0 ± 10.1	70.9 ± 10.4	72.5 ± 10.0	73.3 ± 10.4	74.5 ± 10.0			
	R	76.7 ± 10.3	74.2 ± 9.9	76.6 ± 11.8	78.2 ± 11.3	78.9 ± 9.5			
Peripheral PP (mmHg)	B	53.1 ± 8.0	52.2 ± 7.8	52.3 ± 8.0	52.4 ± 6.1	54.2 ± 8.6	0.80	0.23	0.01
	A	55.2 ± 7.9	52.8 ± 7.1	53.1 ± 6.8	52.7 ± 6.9	53.6 ± 9.2			
	R	55.5 ± 9.4	52.4 ± 7.7	53.9 ± 9.0	53.7 ± 7.5	53.4 ± 9.4			
SV (mL)	B	83.3 ± 17.3	82.7 ± 16.9	81.8 ± 16.7	82.8 ± 15.9	84.8 ± 17.1	0.06	0.26	0.38
	A	82.8 ± 17.2	82.2 ± 16.9	82.0 ± 16.1	82.3 ± 16.4	83.1 ± 17.5			
	R	83.3 ± 16.5	81.4 ± 15.2	81.2 ± 14.0	81.6 ± 15.8	83.2 ± 16.9			
CO (L/min)	B	4.2 ± 0.8	4.3 ± 0.9	4.3 ± 1.0	4.3 ± 0.9	4.5 ± 1.1	0.03	0.26	0.52
	A	4.3 ± 0.9	4.3 ± 0.9	4.2 ± 1.0	4.2 ± 0.9	4.5 ± 1.2			
	R	4.4 ± 1.0	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 1.0	4.6 ± 1.1			
TPR (a.u)	B	1.09 ± 0.3	1.05 ± 0.3	1.09 ± 0.3	1.09 ± 0.3	1.06 ± 0.3	0.42	0.96	0.41
	A	1.09 ± 0.3	1.04 ± 0.2	1.08 ± 0.3	1.09 ± 0.3	1.09 ± 0.3			
	R	1.05 ± 0.3	1.06 ± 0.3	1.08 ± 0.3	1.11 ± 0.3	1.06 ± 0.3			
SpO_2 (%)	B	97.0 ± 0.3	96.8 ± 0.4	96.7 ± 0.2	96.5 ± 0.3	96.9 ± 0.3	0.03	0.48	0.04
	A	97.0 ± 0.2	97.2 ± 0.1	97.2 ± 0.2	97.2 ± 0.2	97.4 ± 0.2			
	R	97.0 ± 0.2	96.8 ± 0.2	96.7 ± 0.3	96.8 ± 0.2	96.9 ± 0.3			
$ETCO_2$ (%)	B	5.50 ± 0.1	5.42 ± 0.1	5.39 ± 0.1	5.44 ± 0.1	5.38 ± 0.1	0.24	0.30	0.70
	A	5.48 ± 0.1	5.39 ± 0.1	5.38 ± 0.1	5.42 ± 0.1	5.39 ± 0.1			
	R	5.51 ± 0.1	5.40 ± 0.1	5.41 ± 0.1	5.42 ± 0.1	5.38 ± 0.1			

Data are means ± SD. B, breath; A, apnea; R, rebreathe; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; SpO_2, percutaneous arterial blood oxygen saturation; $ETCO_2$, end-tidal carbon dioxide.

raised at the rebreathe phase during intermittent apnea, while SpO_2 remained normoxic. These results showed that during intermittent apnea, breathing maneuvers *per se* might elevate cardiac load without hypoxic stimuli.

The mechanism of sleep apnea had been examined by the hemodynamic responses to the intermittent hypoxic apnea model [9–13]. For instance, Culter *et al.* [10] reported that muscle sympathetic nerve activity in intermittent apnea persisted beyond the duration of the apnea trials, which resulted in the elevation of peripheral blood pressure. However, impacts of intermittent hypoxic apnea on aortic hemodynamics have not been elucidated. Besides, the effects of intermittent normoxic apnea on aortic hemodynamics remain unknown. Accordingly, we focused on the influence of the aortic hemodynamics during the 20 min intermittent normoxic apnea, which consisted of 20 s apnea and 40 s control breathing. To best our knowledge, this is the first study to clarify the influence of intermittent apnea on aortic hemodynamics.

Aortic hemodynamics, such as aortic SBP and AIx, has emerged as an essential factor underlying the pathophysiology of CVD [14–18]. For instance, the increase in left ventricular (LV) afterload potentiates an increase in LV mass [14], an independent risk for heart failure and coronary heart disease mortality [26]. Of note, we found that aortic SBP, AIx, and double product (calculated as aortic SBP × heart rate) were elevated at the rebreathe phase following the apnea. We calculated a double product from aortic SBP and HR, associated more strongly with the cardiac load. Notably, during the 20-min intervention, SpO_2 did

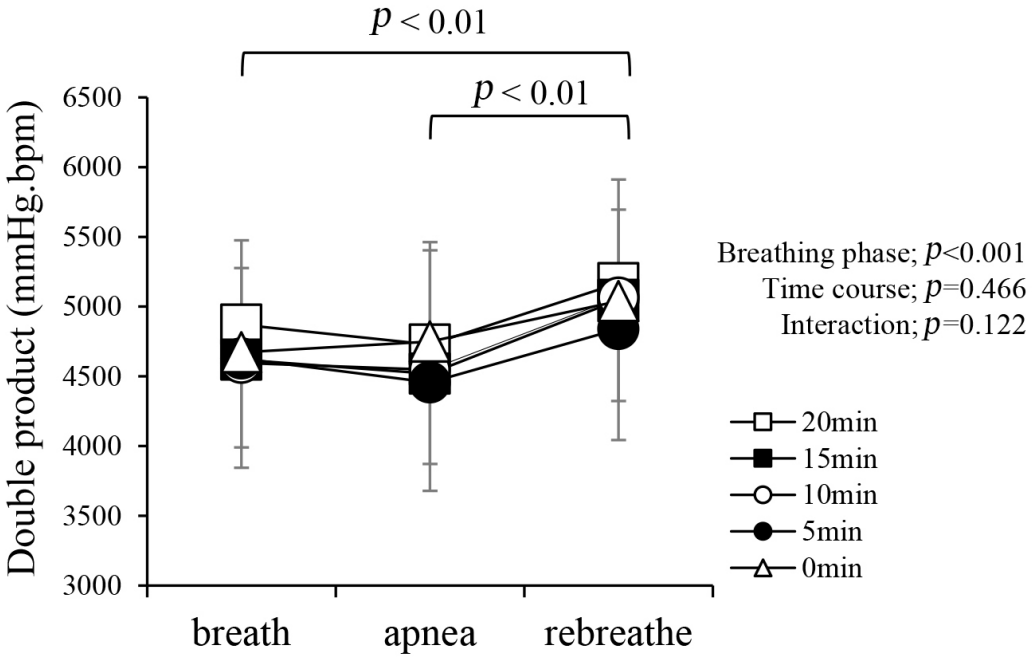

Fig. 4. Response of double product at the phase of breath, apnea, and rebreathe during intermittent apnea in 20 min. Double product multiplied aortic peripheral pressure by heart rate.

not decrease more than 3%, indicating a normal level [27]. These results demonstrate that repetitive apnea augments cardiac load even in non-hypoxic conditions.

The influence of breathing on HR is known as respiratory sinus arrhythmia (RSA): the HR increases with inspiration and decreases with expiration [28]. The intermittent apnea occurred tachycardia following apnea for a few seconds in the rebreathe phase. This switching from apnea to rebreathe accompanies changing HR variability, which may cause a fluctuation of AIx at rebreathe phase. The tachycardia at the rebreathe phase accelerates left ventricle ejection time. These variations disturb the timing of the reflected wave from the periphery to the heart, which may raise the AP, and hence AIx.

Jouett *et al*. [29] examined MSNA and peripheral arterial pressure responses to a 20 s, voluntary, end-expiratory apnea. They demonstrated that MSNA peaks abruptly shut off at end-apnea. In contrast, arterial pressure peaks within the first few breaths after apnea termination, and bradycardia at end-apnea resolved shortly after apnea termination. In the present study, similar hemodynamic responses were observed during the rebreathe phase. In particular, elevations of aortic SBP and AIx might be explained by the increased wave reflection from the periphery, which was attributed to the MSNA-related increase in vasoconstrictor tone [30].

Sleep apnea causes a closed upper away by snoring, generating substantial negative pressure in the chest cavity [31]. This excessive negative pressure in the chest cavity increases the venous return [32]. In this study, as subjects normally exhaled before apnea, the effect of negative pressure in the chest cavity on venous return appeared to be minor. Thus, SV did not change with the breathing maneuver.

There are a few critical study limitations that need to be mentioned. First, in this study, we studied healthy young men only. For generalizability, further studies need to investigate the elderly, etc. Second, we did not investigate the impact of prolonged intermittent apnea. On the other hand, we confirmed that intermittent apnea of short duration affects aortic hemodynamics in healthy young. Even just breathing disturbance during sleeping may potentially be the risk of developing CVD in the future.

5. Conclusions

Aortic SBP, AIx, and double product were raised at the rebreathe phase during intermittent apnea, while SpO_2 remained normoxic. These results showed that during intermittent apnea, breathing maneuvers *per se* might elevate cardiac load without hypoxic stimuli.

Abbreviations

SAS, sleep apnea syndrome; CVD, cardiovascular diseases; AIx, augmentation index; MSNA, muscle sympathetic nerve activity; HR, heart rate; AP, augmentation pressure; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MAP, mean arterial pressure; $ETCO_2$, a fraction of end-tidal carbon dioxide; SpO_2, percutaneous arterial blood oxygen saturation; SBP, systolic blood pressure.

Author contributions

JS, SO conceived and designed the experiments; JS, TT, TI performed the experiments; JS, TI analyzed the data; TI wrote the paper.

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board of the National Institute of Advanced Industrial Science and Technology (#2014-495). All study potential risks and procedures have been explained to the subjects, and they gave their written informed consent to participate in the study.

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Conflict of interest

The authors declare no conflict of interest.

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